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ACC Expert Consensus Guidance on Tobacco Cessation

The American College of Cardiology (ACC) has issued an expert consensus decision pathway that outlines and standardizes tobacco-cessation treatment. The document is published online December 6 in the *Journal of the American College of Cardiology*.

Doctors should take a front-line approach in delivering smoking-cessation therapy to patients who come to their clinic or who are in the hospital because they have had a cardiac event, because we know these are times that offer a teachable moment when patients are more primed and open to these discussions. In a recent study, roughly 23% received at least one smoking-cessation pharmacotherapy during hospitalization, most commonly a nicotine patch.

Smoking is a "chronic relapsing substance use disorder", which requires clinicians to adopt a chronic disease-management strategy, monitoring progress over time and making repeated efforts to encourage and facilitate smoking cessation. Most smokers who attempt to quit will have "repeated cycles of abstinence followed by relapse to smoking" before they achieve long-term abstinence.

Current evidence strongly supports combining pharmacotherapy with behavioral interventions to help smokers attain and to maintain abstinence. The pharmacologic component helps smokers adjust to the absence of nicotine after cessation of smoking by lessening the symptoms of nicotine withdrawal, whereas the behavioral treatments are based on principles of behavioral and cognitive psychology that attempt to bolster smokers' self-control over their smoking.

The consensus document has also addressed electronic cigarettes or e-cigarettes, as they are commonly referred to, which differ from cigarettes and other combustible products in that they do not produce smoke by burning tobacco. Approximately one-half of the committee felt e-cigarettes are associated with less short-term harm than combustible cigarettes and may be of benefit for smokers.

All patients should try to quit smoking using the standard therapies, but those who are failing and want to try e-cigarettes have to recognize that the long-term health risks are largely unknown at this time. They should also recognize that the e-cigarette should be discontinued as soon as the target is achieved, and they should set a specific date for that quitting as well.

ABOUT E-CIGARETTES AND EXCERPTS FROM THE CONSENSUS STATEMENT

Also known as electronic nicotine delivery systems (ENDS), e-cigarettes do not produce smoke by burning tobacco; this is how they differ from the traditional cigarettes and other combustible tobacco products. Instead, they heat a solution (e-liquid) that usually contains nicotine, propylene glycol or vegetable glycerin, and flavorings to generate an aerosol that the user inhales.

E-cigarette devices vary considerably in design. First-generation products are disposable devices that

mimic the appearance and experience of smoking a combustible cigarette. Second-generation devices are larger and have rechargeable batteries and/or replaceable cartridges of e-liquid. Third-generation e-cigarettes allow the user to customize the devices by manipulating features such as batteries, temperature and dose of nicotine.

Recently, a novel vaping device emerged that differs from previous e-cigarettes in its technology, product design and marketing. Exemplified by JUUL, the device is designed to resemble a computer flash drive and encapsulates nicotine, flavorings and other contents in small replaceable cartridges called "pod-mods". The device's battery, rechargeable via a USB port, heats the liquid to produce vapor. The product differs from the earlier e-cigarettes in the chemical formulation of nicotine used in the product. Pod-mod devices use nicotine salts, which produces more protonated nicotine at a lower pH than the free-base form of nicotine used in other e-cigarettes, which has a higher pH and activates nicotine sensory receptors. Therefore, the nicotine in the newer devices is less irritating when inhaled.

Additionally, these devices can deliver a higher concentration of nicotine to the user. A higher dose of nicotine might benefit adult smokers who are seeking to quit cigarettes but might also promote nicotine dependence among nonsmoking adolescents and young adults.

E-cigarettes have the potential for large public health benefit if they help smokers to quit smoking combustible cigarettes, especially smokers who have not been willing or able to quit using current treatments. This potential benefit must be balanced against e-cigarettes' own long-term health risks, which are largely unknown at this time, and against the potential for e-cigarettes to attract youth and young adults who might not otherwise smoke to take up their use and perhaps increase the uptake of cigarettes.

In August 2016, the FDA gained regulatory authority over e-cigarettes, allowing it to enforce laws preventing the sale of e-cigarettes to persons under the age of 18 years, ban provision of free product samples, and regulate the labeling and content of e-cigarettes. A 2018 systematic evidence review by the National Academies of Sciences, Engineering and Medicine (NASEM) concluded that while scientific evidence is insufficient to allow reliable conclusions to be made about the long-term health effects of e-cigarettes (including cardiovascular outcomes or measures of subclinical atherosclerosis), such risks could be less than those associated with smoking, because toxicants and carcinogens present in cigarette smoke are absent or present at much lower concentrations in e-cigarette aerosols (*2018. NASEM. Public Health Consequences of E-Cigarettes. ed. The National Academies Press, Washington, DC*).

The NASEM report concluded that completely switching from combustible tobacco products to e-cigarettes should reduce short-term adverse health effects of continued smoking, indicating e-cigarettes' potential for harm reduction.

Dual use of both cigarettes and e-cigarettes is bad. Smoking even one cigarette daily increases cardiovascular disease (CVD) risk in epidemiological studies. The NASEM report found only limited evidence that e-cigarettes are effective as cessation aids when compared with no treatment or current FDA-approved cessation therapies, but it found moderate evidence that e-cigarettes may be more likely to lead to smoking cessation when used more frequently as compared to infrequent or intermittent use.

Despite gaps in the evidence base about the effectiveness of e-cigarettes for smoking cessation, many smokers are asking physicians in clinical practice for guidance about e-cigarettes.

Writing committee members were unanimous on 3 points:

1. The clinician's role is to encourage and support a smoker's efforts to stop using cigarettes and other combustible tobacco products.
2. Given the uncertainties of the long-term effects of e-cigarettes on health, a clinician should advise cigarette smokers seeking to quit to use evidence-based, FDA-approved, safe and effective smoking cessation pharmacotherapies as first-line treatments in preference to e-cigarettes.
3. Clinicians should be prepared to discuss the risks and benefits with patients who ask about or are already using an e-cigarette. If a smoker decides to use e-cigarettes, the committee felt that the clinician should play a supportive role, helping the patient to use the product in a way that minimizes risk to themselves and others and indicating that the eventual goal is complete abstinence from all products, including e-cigarettes.

Approximately one-half of the committee felt e-cigarettes are associated with less short-term harm than combustible cigarettes and may be of benefit for smokers who have been unable to quit smoking after

multiple attempts using FDA-approved medications and behavioral support or for smokers who are unwilling to quit but seek to reduce tobacco-related health harms. In these situations, e-cigarette use is likely to minimize risk if smokers switched completely to e-cigarettes, avoided dual use, and used e-cigarettes temporarily as an aid to cessation of both cigarettes and e-cigarettes. Other committee members felt that the limited evidence of benefit of e-cigarettes for cessation of combustible tobacco products and the insufficient evidence regarding long-term health effects outweighed any potential benefits of e-cigarettes at this time.

Like smokers using conventional cessation therapies, those using e-cigarettes should be followed regularly by the clinician or smoking cessation professional. Although there are no data yet to show that behavioral support enhances the potential effectiveness of e-cigarettes for cessation, it is reasonable to encourage e-cigarette users to use the standard resources for behavioral support. "Heat-not-burn" (HNB) devices are also alternative tobacco products that, like e-cigarettes, do not burn tobacco. Unlike e-cigarettes, which heat a nicotine-containing liquid, HNB products heat tobacco itself. A pen-like device heats a tobacco stick to a temperature lower than that required for combustion but high enough to release an aerosol that users inhale.

Studies funded by the manufacturers have reported that HNB products produce lower levels of harmful chemicals compared with conventional cigarettes.

Little is known about the health effects of HNB products. Novel HNB products are not currently approved for sale in the United States, but one tobacco company has applied to the FDA for approval to market its product as a modified-risk tobacco product.

Should e-cigarettes be introduced in India under NRT? The answer is yes.

Source: 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment. A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. Published online December 6, 2018.

■■■■

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Medications for Chronic Asthma

NATHAN P. FALK, SCOTT W. HUGHES, BLAKE C. RODGERS

ABSTRACT

Chronic asthma is a major health concern for children and adults worldwide. The goal of treatment is to prevent symptoms by reducing airway inflammation and hyperreactivity. Step-up therapy for symptom control involves initiation with low-dose treatment and increasing intensity at subsequent visits if control is not achieved. Step-down therapy starts with a high-dose regimen, reducing intensity as control is achieved. Multiple randomized controlled trials have shown that inhaled corticosteroids are the most effective monotherapy. Other agents may be added to inhaled corticosteroids if optimal symptom control is not initially attained. Long-acting beta$_2$ agonists are the most effective addition, but they are not recommended as monotherapy because of questions regarding their safety. Leukotriene receptor antagonists can be used in addition to inhaled corticosteroids, but they are not as effective as adding a long-acting beta$_2$ agonist. Patients with mild persistent asthma who prefer not to use inhaled corticosteroids may use leukotriene receptor antagonists as monotherapy, but they are less effective. Because of their high cost and a risk of anaphylaxis, monoclonal antibodies should be reserved for patients with severe symptoms not controlled by other agents. Immunotherapy should be considered in persons with asthma triggered by confirmed allergies if they are experiencing adverse effects with medication or have other comorbid allergic conditions. Many patients with asthma use complementary and alternative agents, most of which lack data regarding their safety or effectiveness.

Keywords: Chronic asthma, airway inflammation and hyperreactivity

Approximately 25.7 million persons in the United States, including 7 million children, had the diagnosis of asthma as of 2010.[1] It is reported that 4.1 million children experienced at least one asthma exacerbation in 2011.[2] Between 1995 and 2010, exacerbations accounted for one-third of all hospital admissions for children younger than 15 years.[3] Asthma caused 3,345 U.S. deaths in 2011,[4] and it accounts for $50.1 billion annually in direct health care costs.[5] The management of asthma involves care plans, chronic medications, and monitoring and self-care for acute exacerbations. Therapeutic agents used in the chronic management of asthma aim to prevent symptoms by controlling airway inflammation and hyperreactivity. This article reviews the currently available medications and complementary agents for chronic asthma management. A previous article in *American Family Physician* discussed the management of acute exacerbations.[6]

ASSESSMENT

To provide appropriate long-term medication, physicians should assess asthma severity and symptom control at diagnosis and at each subsequent visit using one of several validated tools, such as the Asthma Control Test (https://www.asthma.com/additional-resources/asthma-control-test.html).[7-9] The 2007 National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) recommends classifying disease severity based on level of impairment and risk of adverse events (Figure 1, eFigure A, and eFigure B).[10] Once disease severity is determined, the physician must then decide on medication and self-care management options.

STEP-UP AND STEP-DOWN THERAPY

Two general approaches when choosing asthma medication regimens are step-up and step-down therapy (Figure 2, eFigure C, and eFigure D).[10] Step-up therapy involves initiating treatment at a low dose and assessing symptom control at subsequent visits (every two to four weeks), increasing the intensity of therapy as needed if control is not initially achieved. Step-down

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Source: Adapted from Am Fam Physician. 2016;94(6):454-462.

therapy starts with patients receiving a high-dose regimen, the intensity of which is reduced as control is achieved. The latter approach could be preferred, for example, to obtain rapid control in a patient who has significant symptoms at the time of diagnosis. Steps 4 and 5 within the EPR-3 Stepwise Approaches, which recommend the use of a medium- or high-dose inhaled corticosteroid plus a long-acting beta$_2$ agonist (LABA), are common starting points in step-down therapy.

A small randomized trial found that patients with moderate persistent asthma who were started on a high-dose corticosteroid followed by the step-down approach experienced a more prompt improvement in respiratory function and asthma symptoms, as well as a lower maintenance dose of inhaled corticosteroids, compared with patients treated with a step-up approach.[11] The EPR-3 guidelines advise that treatment generally be maintained at a high-dose level with patients experiencing good symptom control for three months before stepping down in intensity; reliable patients with well-controlled asthma may be able to step down earlier. Physicians should monitor symptom control in the period after a step down in therapy because patients may have increased symptoms, particularly when an LABA is discontinued.[12-14] Medications commonly used in these two approaches are listed in Table 1, with additional information on dosing and adverse effects for these drugs available in eTable A.

Table 1. Common Asthma Medications

Short-acting bronchodilators
Albuterol DPI
Albuterol HFA
Albuterol nebulized
Ipratropium/albuterol inhaled
Ipratropium/albuterol nebulized
Levalbuterol HFA
Levalbuterol nebulized
Inhaled corticosteroids
Beclomethasone HFA
Budesonide DPI
Budesonide nebulized
Ciclesonide HFA
Flunisolide HFA
Fluticasone furoate DPI
Fluticasone propionate DPI
Fluticasone propionate HFA
Mometasone DPI
Mometasone HFA
Long-acting beta$_2$ agonists
Budesonide/formoterol
Fluticasone/salmeterol DPI
Fluticasone/salmeterol HFA
Fluticasone/vilanterol
Leukotriene receptor antagonists
Montelukast
Zafirlukast
Leukotriene inhibitor
Zileuton
Methylxanthines
Theophylline
Cromolyn
Monoclonals
Omalizumab

DPI = Dry powder inhaler; HFA = Hydrofluoroalkane.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids are the most effective long-term medication for asthma.[10,15-18] They have been shown to reduce symptom severity, systemic steroid use, emergency department visits, hospitalizations, and deaths caused by asthma, and improve asthma control, quality of life, and objective measures of lung function.[10,15-18] Adverse effects of inhaled corticosteroids are limited, with only a slight effect on linear growth of approximately 0.5 cm per year noted in children. The effect on linear growth lessens after the first year of medication use and seems to be independent of patient age or the type of corticosteroid, dose, or delivery mechanism. It is unclear if inhaled corticosteroid use has an impact on final adult height.[19] Other adverse effects, such as dysphonia, are generally self-limited or may be improved by changing the delivery mechanism of the inhaled corticosteroid.[20] There are clinically significant differences in patient response to corticosteroids that are associated with age, race, and risk factors such as smoking. Black children and smokers have an increased risk of corticosteroid insensitivity.[21,22] In general, delivery mechanism and type of steroid have little impact on the clinical effectiveness of corticosteroids, with the notable exception of a spacer device, which can result in a 20% to 30% increase in the amount of medication that is deposited in the lungs.[23] Dosing of inhaled corticosteroids should be managed in a step-up or step-down fashion based on an assessment of symptom control and severity (Figure 2, eFigure C,

and eFigure D).[10] Whereas abrupt cessation of inhaled corticosteroids predisposes patients to acute asthma exacerbations, changing the dosage of an inhaled corticosteroid does not increase exacerbation risk.[24,25]

LONG-ACTING BETA$_2$ AGONISTS

LABAs are effective for the control of persistent asthma symptoms. They initially have an action of more than 12 to 24 hours. Available non-combination LABAs include salmeterol and formoterol. Duration of action decreases to less than five hours with chronic regular use of LABAs,[10] excluding those that contain vilanterol which currently lack data regarding duration of action decrease. The addition of an LABA to inhaled corticosteroid therapy is superior to the addition of leukotriene receptor antagonists (LTRAs) to inhaled corticosteroids in reducing asthma exacerbations requiring oral corticosteroid use, as well as improving quality-of-life measures and the effects and frequency of rescue inhaler use.[26] Current evidence shows no clear difference in the risk of fatal adverse events between LABA monotherapy and combination therapy with inhaled corticosteroids. The risk of nonfatal adverse events is increased with salmeterol monotherapy, but it is not significantly increased with either formoterol monotherapy or combination therapy with inhaled corticosteroids and either LABA option.[27] Current recommendations discourage the use of LABA monotherapy for long-term control of asthma.[10]

COMBINATION THERAPY

The combination of an inhaled corticosteroid and an LABA is considered a preferred therapy by the EPR-3 for the control of moderate persistent asthma in children five to 11 years of age and those 12 years and older.[10] Combination therapy offers the best prevention of severe asthma exacerbations.[28] A 2013 study confirmed the overall safety of combination inhaled corticosteroid and LABA therapy, especially compared with LABA monotherapy.[29] Combination therapy dosing should be managed in a step-up or step-down approach similar to the management of inhaled corticosteroid therapy. Slight differences in when to start combination therapy are noted between the EPR-3 and Global Initiative for Asthma (GINA) guidelines.[10,30] For example, according to step 3 of the EPR-3 stepwise approach for patients 12 years and older, either a low-dose inhaled corticosteroid plus an LABA, or a medium-dose inhaled corticosteroid alone is appropriate (Figure 2).[10] The GINA guidelines recommend a low-dose inhaled corticosteroid plus an LABA as the preferred selection in this age group, with a medium-dose inhaled corticosteroid considered the secondary option.

LEUKOTRIENE MODIFIERS

Leukotriene modifiers include LTRAs and leukotriene inhibitors, which both act as anti-inflammatory medications. LTRAs block leukotriene receptors, whereas leukotriene inhibitors block the production of 5-lipoxygenase. The two LTRAs licensed in the United States are montelukast and zafirlukast. LTRAs may be used as monotherapy for mild persistent asthma, but are considered second-line agents based on the EPR-3[10] and GINA guidelines.[30] For mild to moderate asthma, the risk of exacerbation is approximately 50% less in patients prescribed an inhaled corticosteroid compared with those prescribed an LTRA.[15] A 2014 Cochrane review found an LABA plus inhaled corticosteroid to be modestly superior to an LTRA plus inhaled corticosteroid in adults with inadequately controlled asthma.[26] LTRAs are best used to improve pulmonary function in patients with aspirin-sensitive asthma[31] and to decrease symptoms in exercise-induced bronchospasm.[32,33] They should also be considered in patients with mild persistent asthma who prefer not to use inhaled corticosteroids. Although LTRAs generally have few adverse effects, physicians should be aware of rare case reports of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), psychiatric symptoms, hypertriglyceridemia, angioedema, urticaria, and glomerulonephritis.[34]

Leukotriene inhibitors, such as zileuton, are a more recent addition to the treatment of asthma. Limited data show some improvement in peak flows with zileuton compared with montelukast.[35] However, zileuton is extremely expensive and has not been shown to improve symptom scores.

METHYLXANTHINES

Theophylline, the most commonly used methylxanthine in asthma patients, acts as a bronchodilator at high serum concentrations (10 to 20 mcg per L [56 to 111 μmol per L]), but has an anti-inflammatory effect at lower serum concentrations (5 to 10 mcg per L [28 to 56 μmol per L]).[36,37] Theophylline administered with inhaled corticosteroids decreases exacerbations,[38] but it has similar effects to increasing the dosage of the inhaled corticosteroid.[39,40] The EPR-3 specifies that theophylline is a nonpreferred alternative to inhaled corticosteroid.[10] The GINA guidelines recommend a trial of increased dosage of inhaled corticosteroid before considering theophylline, unless steroid sparing is necessary, such as in patients with severe glaucoma or active tuberculosis infection.[30] Patients in developing

countries are more likely to use low-dose theophylline than inhaled corticosteroids because it is a cheaper option.[39,40] Although theophylline is considered safer at lower serum concentrations, care of patients who use theophylline should be comanaged with an asthma subspecialist because of the narrow therapeutic range of this drug and the risk of death from an overdose.[36,40] Theophylline is metabolized in the liver and is susceptible to drug-drug interactions through cytochrome P450 1A2 (Table 2).[37,41]

CROMOLYN

Cromolyn decreases bronchospasm through an anti-inflammatory effect.[42] A 2008 Cochrane review found insufficient evidence of benefit of cromolyn over

Table 2. Common Drug-Drug Interactions with Theophylline

Medication or substance	Approximate effect on serum levels of theophylline
Alcohol	30% increase
Ciprofloxacin	40% increase
Diltiazem	Increase or no effect
Erythromycin	35% increase
Oral contraceptives	30% increase
Phenytoin	40% decrease
Propranolol	100% increase
Verapamil	20% increase

Information from references 37 and 41.

Table 3. Select Complementary and Alternative Asthma Treatments

Name	Comments	Effectiveness for treatment
Black seed (*Nigella sativa*)	One small RCT showed improved pulmonary function testing and decreased symptoms compared with placebo.[59] Effect on pulmonary function testing was less than with theophylline.[60]	Possibly effective
Butterbur	Traditionally used in Taiwan to treat asthma. Has anti-inflammatory properties.[61] A small non-randomized open trial showed 48% decrease in exacerbations, and 40% of patients were able to reduce their dosage of inhaled corticosteroids, but results potentially biased due to study design. Blinded RCT is needed to determine true benefit and adverse effects.[62]	Possibly effective
Caffeine	Improves airway function for up to four hours and may impact pulmonary function testing. No evidence that results have clinical or quality-of-life significance.[63]	Not effective
Fish oil (omega-3)	Theoretically acts to decrease inflammation. Studies of its effectiveness have inconsistent results and are poorly designed. A large, well-designed RCT is needed to determine if there is any benefit.[64]	Effectiveness unknown
Ginkgo	No clinical evidence available. Effect on asthma is theoretical via anti-inflammatory effect in an animal model.[65] Increases metabolism of theophylline by four times via cytochrome P450 1A2.[66]	Effectiveness unknown
Homeopathy	A 2004 Cochrane review found no evidence of benefit, citing a lack of quality studies.[67]	Not effective
Magnesium	Associated with bronchodilatory and anti-inflammatory effects. Small, blinded RCT showed improved peak expiratory flow and quality of life and decreased bronchial activity with 340 mg of supplementation per day. Larger RCT is needed.[68]	Possibly effective
Pycnogenol	Small, blinded RCT showed improved peak expiratory flow and decreased use of rescue medication compared with placebo group.[69] A 2012 Cochrane review concluded insufficient evidence is available.[70] Larger RCT is needed.	Possibly effective
Soy	Small RCT showed no significant difference compared with placebo.[71]	Not effective
Vitamins C and E	Associated with anti-inflammatory effects. A 2014 Cochrane review found insufficient evidence due to limited small studies and lack of clinically important end points.[72]	Effectiveness unknown
Vitamin D	Used to treat deficiency associated with severe asthma,[73] however, an RCT showed vitamin D_3 supplementation had no effect on exacerbation rate in vitamin D–deficient patients with asthma.[74]	Not effective

RCT = Randomized controlled trial.

Information from references 59 through 74.

placebo.[43] Because cromolyn is less effective and less cost-effective than an inhaled corticosteroid, its use should be limited to patients who cannot tolerate inhaled corticosteroids.[44] Cromolyn is beneficial for exercise-induced bronchospasm but is considered second-line therapy.[44,45]

MONOCLONAL ANTIBODIES

Omalizumab is currently the only monoclonal anti-immunoglobulin E (IgE) antibody with a U.S. Food and Drug Administration indication for asthma.[46] It binds the free IgE antibodies, decreasing the release of inflammatory mediators from mast cells. In a randomized trial, omalizumab reduced the rate of exacerbations in inner-city children from 48.8% to 30.3%, resulting in decreased reliance on an inhaled corticosteroid.[47] A 2014 Cochrane review found omalizumab effective in reducing exacerbations, decreasing the dosage of inhaled corticosteroid used, and improving health-related quality of life.[48] Because of its high cost and the risk of anaphylaxis, omalizumab should be considered only for adults and children 12 years and older with confirmed IgE-dependent allergic asthma that is uncontrolled with conventional medications.[49,50]

IMMUNOTHERAPY

Subcutaneous and sublingual immunotherapies involve repeated patient exposure to antigens to desensitize the patient to the antigen. Immunotherapy is effective in reducing exacerbations, need for medication use, and overall cost of care in patients with allergic asthma.[51-53]

A 2010 Cochrane review found a number needed to treat of 4 to avoid one deterioration in asthma symptoms, but it could not determine the size of effect compared with other therapies.[54] Immunotherapy should be considered in patients with asthma triggered by confirmed allergies who are experiencing adverse effects from medication or have other comorbid allergic conditions.

ALTERNATIVE TREATMENTS

The rate of complementary and alternative medicine (CAM) use in children and adolescents with asthma is as high as 71% to 84%, but 54% of parents do not disclose the use of these methods.[55,56] CAM use is more common among children with poorly controlled asthma and those with barriers to treatment.[57,58] However, data indicate that CAM treatment is typically not used as a substitute for conventional medicine.[57] Patients who are receiving CAM substances should be cautioned that there is little regulation to ensure the consistency and purity of the contents and that CAM is never a substitute for rescue medication. Common CAM treatments and their effects on asthma symptoms are listed in Table 3.[59-74]

Note: For complete article visit: www.aafp.org/afp.

eTable A. Common Asthma Medications

Drug	Dosage	Adverse effects
Short-acting bronchodilators		
Albuterol DPI	Age > 11 years: 180 mcg every 4 to 6 hours as needed	Same as albuterol nebulized
Albuterol HFA	Age 4 to 11 years: 180 mcg every 4 to 6 hours as needed Age > 11 years: 180 mcg every 4 to 6 hours as needed	Same as albuterol nebulized
Albuterol nebulized	Age < 2 years: 0.05 to 0.15 mg per kg every 1 to 6 hours as needed, max 1.25 mg per dose Age 2 to 5 years: 0.1 to 0.15 mg per kg every 4 to 6 hours as needed, max 2.5 mg per dose Age 5 to 11 years: 2.5 mg every 4 to 6 hours as needed, max 10 mg per day Age > 11 years: 2.5 to 10 mg every 1 to 4 hours as needed	Angina, arrhythmia, bad taste, cough, dizziness, headache, hyperglycemia, hypertension, hypokalemia, nausea, nervousness, palpitations, tachycardia, throat irritation, tremor
Ipratropium/albuterol inhaled	Age < 13 years: 80 mcg/400 mcg to 160 mcg/800 mcg every 20 minutes as needed for up to 3 hours Age ≥ 13 years: 160 mcg/800 mcg every 20 minutes as needed for up to 3 hours	Same as ipratropium/albuterol nebulized

continues

eTable A. Common Asthma Medications *(continued)*

Drug	Dosage	Adverse effects
Ipratropium/albuterol nebulized	Age < 13 years: 0.25 mg/1.25 mg to 0.5 mg/2.5 mg every 20 minutes for three doses, then as needed for up to 3 hours Age ≥ 13 years: 0.5 mg/2.5 mg every 20 minutes for 3 doses, then as needed for up to 3 hours	Angina, arrhythmia, cardiac arrest, glaucoma, hyperglycemia, hyperlactatemia, hypertension, hypokalemia, hypotension, pharyngitis
Levalbuterol HFA	Age 4 to 11 years: 90 mcg every 4 to 6 hours as needed, max 540 mcg per day Age > 11 years: 90 mcg every 4 to 6 hours as needed, max 540 mcg per day	Same as albuterol nebulized
Levalbuterol nebulized	Age 6 to 11 years: 0.31 to 0.63 mg three times a day as needed, max dose 0.63 mg Age > 11 years: 0.63 to 1.25 mg three times a day as needed	Same as albuterol nebulized
Inhaled corticosteroids		
Beclomethasone HFA	Age 5 to 11 years: 40 to 160 mcg per day Age > 11 years: 40 to 640 mcg per day	Adrenal suppression, cataracts, cough, dysmenorrhea, dysphonia, eosinophilia, glaucoma, hypercorticism, growth suppression, Churg-Strauss syndrome, oral candidiasis, osteoporosis
Budesonide DPI	Age 6 to 11 years: 180 to 720 mcg per day Age > 11 years: 180 to 1,440 mcg per day	Same as beclomethasone HFA
Budesonide nebulized	Age 1 to 8 years: 0.25 to 1.0 mg daily	Same as beclomethasone HFA
Ciclesonide HFA	Age > 11 years: 80 to 640 mcg per day	Same as beclomethasone HFA
Flunisolide HFA	Age 6 to 11 years: 160 to 320 mcg per day Age > 11 years: 160 to 640 mcg per day	Same as beclomethasone HFA
Fluticasone furoate DPI	Age > 11 years: 100 to 200 mcg per day	Same as beclomethasone HFA
Fluticasone propionate DPI	Age 4 to 11 years: 100 to 200 mcg per day Age > 11 years: 100 to 1,000 mcg per day	Same as beclomethasone HFA
Fluticasone propionate HFA	Age 4 to 11 years: 88 to 176 mcg per day Age > 11 years: 88 to 880 mcg per day	Same as beclomethasone HFA
Mometasone DPI	Age 4 to 11 years: 110 mcg per day Age > 11 years: 220 to 440 mcg per day	Same as beclomethasone HFA
Mometasone HFA	Age > 11 years: 400 to 800 mcg per day	Same as beclomethasone HFA
Long-acting beta$_2$ agonists		
Budesonide/formoterol	Age > 11 years: 320 mcg/18 mcg to 640 mcg/18 mcg per day	Adrenal suppression, angina, arrhythmia, cardiac arrest, cataracts, cough, dysmenorrhea, dysphonia, eosinophilia, glaucoma, growth suppression, hypercorticism, hyperglycemia, hypertension, hypokalemia, hypotension, oral candidiasis, osteoporosis, palpitations, Churg-Strauss syndrome, tremor

continues

eTable A. Common Asthma Medications *(continued)*

Drug	Dosage	Adverse effects
Fluticasone/salmeterol DPI	Age 4 to 11 years: 200 mcg/100 mcg per day Age > 11 years: 200 mcg/100 mcg to 1,000 mcg/100 mcg per day	Same as budesonide/formoterol
Fluticasone/salmeterol HFA	Age > 11 years: 180 mcg/84 mcg to 920 mcg/84 mcg per day	Same as budesonide/formoterol
Fluticasone/vilanterol	Age ≥ 18 years: 100 mcg/25 mcg to 200 mcg/25 mcg per day	Same as budesonide/formoterol
Leukotriene receptor antagonists		
Montelukast	Age 1 to 5 years: 4 mg every evening Age 6 to 14 years: 5 mg every evening Age ≥ 15 years: 10 mg every evening	Cough, dyspepsia, fatigue, gastroenteritis, headache, nasal congestion, Churg-Strauss syndrome, rare elevations of LFTs, rash[A1]
Zafirlukast	Age 5 to 11 years: 10 mg twice a day Age ≥ 12 years: 20 mg twice a day	Diarrhea, headache, nausea, Churg-Strauss syndrome, rare elevations of LFTs[A2]
Leukotriene inhibitor		
Zileuton	Age > 12 years: 600 mg four times a day	Abdominal pain, dyspepsia, headache, myalgia, nausea; rare sleep disorders and behavior changes[A3]
Methylxanthines		
Theophylline	300 to 600 mg by mouth, divided, twice a day	Serum level < 20 mg per L (111 µmol per L): Headache, insomnia, nausea, vomiting Serum level > 20 mg per L: Arrhythmias, seizures[A4]
Cromolyn	20-mg inhalation nebulizer four times a day	Cough, nasal congestion, nausea, sneezing, wheezing[A5]
Monoclonals		
Omalizumab	Age > 12 years: 150 to 375 mg subcutaneously every 2 to 4 weeks	Headache, injection site reaction, pharyngitis, sinusitis, upper respiratory tract infection, viral infections[A6]

DPI = Dry powder inhaler; HFA = Hydrofluoroalkane; LFT = Liver function tests.

Information from:

[A1]Montelukast [package insert]. Whitehouse Station, N.J.: Merck; 2016. https://www.merck.com/product/usa/pi_circulars/s/singulair/ singulair_pi.pdf. Accessed July 28, 2016.

[A2]Zafirlukast [package insert]. http://druginserts.com/lib/rx/meds/accolate-2/. Accessed August 20, 2015.

[A3] Zileuton [package insert]. http://druginserts.com/lib/rx/meds/zyflo-1/. Accessed August 20, 2015.

[A4]Theophylline [package insert]. http://druginserts.com/lib/rx/meds/theophylline-8/. Accessed August 20, 2015.

[A5]Cromolyn sodium [package insert]. http://druginserts.com/lib/rx/meds/cromolyn-sodium-8/. Accessed August 20, 2015.

[A6]Omalizumab [package insert]. East Hanover, N.J.: Novartis; 2016. http://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed July 25, 2016.

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Practice Guidelines

LOW BACK PAIN: AMERICAN COLLEGE OF PHYSICIANS PRACTICE GUIDELINE ON NONINVASIVE TREATMENTS

Low back pain occurs in most persons living in the United States and has been shown to have high costs, health care–related and indirect (e.g., missed work days, reduced efficiency at work and home), totaling about $100 billion in 2006. Often, management is based on how long symptoms have persisted, possible etiologies, occurrence of radicular symptoms, and abnormalities found on physical examination or radiography. The American College of Physicians has released a guideline, which partially updates its 2007 guideline, to provide recommendations for noninvasive treatment of acute (duration less than four weeks), subacute (duration of four to 12 weeks), and chronic (duration longer than 12 weeks) low back pain. It does not address topical or epidural therapies.

Recommendations

It should be noted that any improvements in pain or function with medication or other nonpharmacologic options have been found to be minimal based on the literature, and did not show well-defined differences vs. control treatments; therefore, treatment decisions should be based on patient preference, availability, possible harms, and cost. Persons with any type of low back pain should be encouraged to remain as active as pain allows.

Acute and Subacute Pain

Because acute and subacute low back pain often resolve spontaneously with time, superficial heat, massage, acupuncture, and spinal manipulation are all appropriate treatment options to try initially. Harms that have been reported with these treatments are sparse and not severe. Based on evidence of moderate quality, heat wraps result in moderate improvement of pain and disability compared with placebo. Based on evidence of low quality, massage results in moderate improvement in pain and function in the short term compared with sham therapy in persons with subacute pain, and acupuncture results in minimal improvement in pain compared with sham acupuncture but does not appear to improve function. Also based on evidence of low quality, spinal manipulation results in minimal improvement in function compared with sham manipulation; data were insufficient to make conclusions about how it affects pain.

If the patient or physician chooses medication, a nonsteroidal anti-inflammatory drug (NSAID) or skeletal muscle relaxant can be considered; the decision between the two medication classes should be based on patient preference and the risks associated with each. Compared with placebo, NSAIDs result in a minor improvement in pain and function based on evidence of moderate and low quality, respectively. Based on evidence of moderate quality, muscle relaxants improve pain in the short term compared with placebo.

Physicians should discuss with patients the typically encouraging prognosis associated with acute low back pain, such as the high probability of the pain improving considerably within one month, so that they do not have to undergo tests or treatments that can be expensive and possibly harmful.

Chronic Pain

For chronic low back pain, exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercises, progressive relaxation, electromyography biofeedback training, low-level laser therapy, operant therapy, cognitive behavior therapy, and spinal manipulation are first-line options and have fewer harms compared with medication; therefore, they should be tried initially. Evidence of moderate quality indicates that exercise results in minimal improvement in pain and function compared with no exercise, and that mindfulness-based stress reduction successfully treats pain, with one trial indicating a minimal improvement in pain and function compared with standard treatment.

The evidence for the following interventions is of low quality. Multidisciplinary rehabilitation results in moderate improvement in pain in the short term and minimal improvement in disability compared with no rehabilitation, and Iyengar yoga results in moderate improvement in pain scores and improvement in function compared with standard treatment. Motor control exercises result in moderate improvement in

Source: Adapted from Am Fam Physician. 2017;96(6):407-408.

pain scores and minimal improvement in function compared with nominal treatment. Compared with sham therapies, acupuncture results in moderate improvement in pain for up to three months after it is performed, but it does not appear to improve function; low-level laser therapy results in minimal improvement in pain; and spinal manipulation does not result in a difference in pain. Compared with a wait-list control group, tai chi resulted in moderate improvement in pain; progressive relaxation therapy resulted in moderate improvement in pain and function; and operant therapy, cognitive behavior therapy, and electromyography biofeedback training resulted in minimal improvement in pain, but not a difference in function.

If these nonpharmacologic treatments are ineffective, an NSAID would be considered a first-line treatment option, with tramadol and duloxetine being second-line options. NSAIDs result in minimal to moderate improvement in pain compared with placebo and no to minimal improvement in function based on moderate- and low-quality evidence, respectively. Based on evidence of moderate quality and compared with placebo, tramadol results in moderate improvement in pain in the short term and a minimal improvement in function, and duloxetine results in a minimal improvement in pain and function. Traditional opioids should be considered for treatment only if these other treatments do not help and the benefits of their use outweigh the risks, which are discussed with the patient.

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Photo Quiz

A PERSISTENT RASH ON THE BACK, CHEST, AND ABDOMEN

A 62-year-old woman presented with an erythematous, pruritic, expanding rash on her back, chest, and left lower abdomen (Figures 1 and 2). It appeared two months earlier and did not improve with conservative home treatment, including application of skin lotion, petroleum jelly, and an over-the-counter topical steroid cream. There was no pain or drainage from the affected area. The patient was diagnosed with breast cancer three years earlier, for which she underwent right simple mastectomy and left modified radical mastectomy.

She was afebrile on physical examination. The rash was a large, erythematous plaque with discrete borders. There was some slight edema noted in the lower portion of the back. There was no tenderness or warmth. A punch biopsy was performed.

Question

Based on the patient's history and physical examination findings, which one of the following is the most likely diagnosis?

A. Inflammatory breast cancer.

B. Mycosis fungoides.

C. Radiation dermatitis.

D. Tinea corporis.

Discussion

The answer is A: inflammatory breast cancer. Inflammatory breast cancer is a rare subtype of locally advanced primary breast cancer, accounting for roughly 2.5% of breast cancers in the United States.[1] It is characterized by the disruption of dermal lymphatics with tumor emboli, leading to diffuse skin erythema, ulceration, and edema.[2] It is commonly high grade, estrogen receptor negative, and progesterone receptor negative, and it often affects younger patients.[3] Onset of symptoms can be rapid over days to weeks. Erythema and edema can appear overnight, and the breast may swell to two to three times its normal size within weeks.

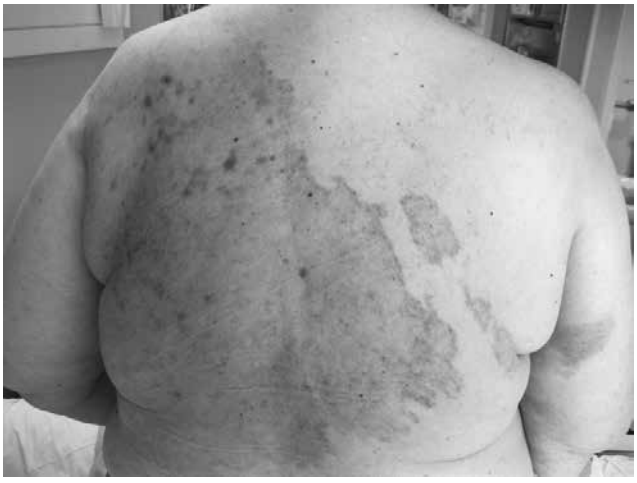

Figure 1.

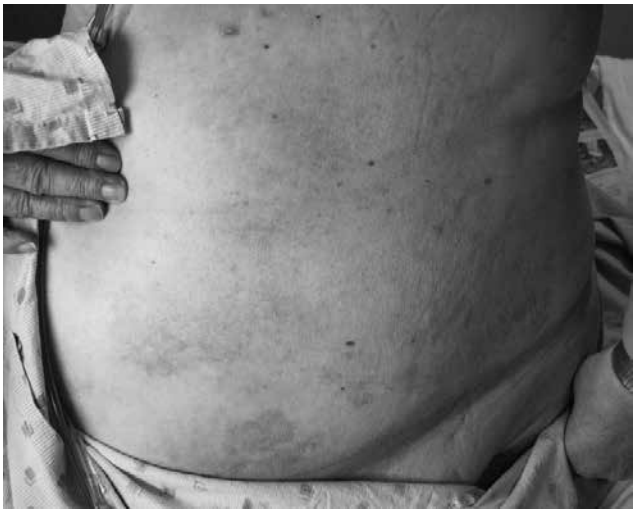

Figure 2.

Recurrent inflammatory breast cancer appears with the same skin and microscopic characteristics as the original primary breast cancer biopsies.

Inflammatory breast cancer is an aggressive carcinoma with a five-year survival rate of roughly 50% even with multimodal therapy.[1] Poor prognostic factors include metastasis to lymph nodes, extensive erythema, estrogen receptor–negative disease, and the *TP53* gene mutation.[4] This highly malignant cancer is often misdiagnosed as a benign infectious or inflammatory process and can also mimic other tumors, such as sarcomas.[5]

Mycosis fungoides is the most common form of cutaneous T cell lymphoma. It has a variable

Source: Adapted from Am Fam Physician. 2017;96(6):390-392.

Summary Table

Condition	Characteristics
Inflammatory breast cancer	Skin erythema, ulceration, and edema; punch biopsy shows breast tumor pathology
Mycosis fungoides	Rash-like patches or lesions that may be pruritic; biopsy shows cutaneous T cell lymphoma
Radiation dermatitis	Recent radiation exposure; acute: blisters, erythema; chronic: atrophic indurated plaques that are typically white or yellow
Tinea corporis	Red, scaly, pruritic rings that appear raised and dry

presentation, including rash-like patches or lesions that may be pruritic. Diagnosis is based on clinical presentation and histopathology.

Radiation dermatitis can be acute or chronic but is always associated with recent radiation therapy. Blisters and erythema are typically observed in the acute phase. Chronic radiation dermatitis presents as atrophic indurated plaques that are typically white or yellow.

Tinea corporis is a fungal infection that causes red, scaly, pruritic rings that are raised and dry. It can appear anywhere on the body but is more common in warm, moist areas, such as under the breasts or in the groin.

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Thyroid, Obesity and Thyromimetic Compounds

PRAGATI KAPOOR*, PANKAJ KUMAR†, AK KAPOOR‡

ABSTRACT

Obesity is one of the most important health risks of our times especially owing to modern lifestyle. An association between hypothyroidism and weight gain is well-documented and that thyroid hormones (THs) play a key role in regulating energy homeostasis. An inverse relationship between obesity and energy expenditure (EE) is also well-known. An increase in EE has long been considered for treating obesity. Hence, increasing EE with thyromimetic drugs constitutes an important line of management of obesity. Moreover, TH receptor activation has beneficial effects including lowering of low-density lipoprotein cholesterol and a reduction in whole body adiposity and weight. Selective thyromimetic compounds, though not clinically approved as yet, may be a big leap forward in this direction, because of a close association between THs and EE. The review encompasses the influence of TH in obesity, body mass index, dyslipidemia and thermogenesis. Besides, therapeutic potential of thyromimetic compounds in the treatment of obesity and dyslipidemia as well as their harmful effects have been outlined.

Keywords: Obesity, thyroid hormones, thyromimetic compounds

Obesity is defined as an excessive accumulation of body fat. Recent years have visualized an unprecedented increase in the prevalence of obesity world over, especially in industrialized nations.[1] The enhanced prevalence is basically due to dietary changes associated with modern lifestyles. Obesity is one of the most important health risks of our time[2] because of its association with an increased risk of diabetes, dyslipidemia, kidney disease, cardiovascular disease, all-cause mortality and cancer.[3] Obesity, especially central obesity is linked to many endocrine abnormalities[4] including thyroid dysfunction.[5] Thyroid hormones (THs) are the prime regulators of metabolism and play a pivotal role in regulating energy homeostasis[6] and a definite relationship exists between TH and obesity.[5] Moreover, tri-iodothyronine (T3) regulates energy metabolism and thermogenesis, and plays a critical role in glucose and lipid metabolism, food intake and oxidation of fatty acids.[5] Further, an association between TH and energy expenditure (EE) as well as an inverse relationship between obesity and EE are well-known. Thus, by increasing EE, obesity can be controlled.

Hypothyroidism represented by a higher prevalence of overt and subclinical hypothyroidism (~20%) in morbid obese subjects,[7] is generally associated with increased weight, decreased thermogenesis and metabolic rate. Studies support the clinical evidence that mild thyroid dysfunction is linked to significant changes in body weight and likely represents a risk factor for overweight and obesity.[2] Moreover, subclinical and overt hypothyroidism correlated with higher body mass index (BMI) and higher prevalence of obesity in both smokers and nonsmokers.[8] Conversely, thyroid hyper function leads to weight loss, which could be reversed by proper treatment.[9] This partially justifies involvement of thyroid in obesity. Hence, the role of thyromimetic drugs have been explored because of the influence of TH in obesity and that these agents may provide an opportunity for the treatment of obesity or for weight loss.

THYROID FUNCTION AND RELATIONSHIP BETWEEN TSH AND BODY WEIGHT IN EUTHYROID INDIVIDUALS

Thyroid function is primarily determined by serum thyrotropin (TSH) concentration despite wide fluctuations in TSH levels among healthy individuals,

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although variability exists regarding definition of normal thyroid function.[10,11] Factors like ethnicity, age, sex, health status and probably, BMI may influence TSH normal range.[12] First, the methods for measurement of TSH are highly different in terms of specificity, sensitivity, accuracy and confounding influences such as heterophilic antibodies, second, reference populations used as the basis for a normal range are highly different in terms of e.g., iodine intake, age, gender and presence of thyroid autoantibodies, and should not be confused with cut-off limits.[13] Overt hypothyroidism is diagnosed when serum concentration of TSH is at or above 10 mU/liter with a low serum thyroxine (T4) level, while patients with TSH levels between 4 and 10 mU/liter, and serum T3 and T4 within the normal population-based reference range are defined as having mild (or subclinical) hypothyroidism. However, a consensus on the exact limits for cut-off between normal and subclinical hypothyroid individuals is not around an immediate corner.[10] Interestingly, thyroid dysfunction is more common in older persons. A low metabolic rate, which is associated with high TSH level, denotes longevity. Thus, mild hypothyroidism may be harmless or perhaps beneficial for elderly individuals.

Studies suggest that even slight variations in thyroid function, lead to the development of regional obesity and tendency to gain weight.[14,15] Besides, BMI has been negatively associated with serum free T4 (FT4), and fat accumulation has been associated with lower FT4,[14,16] and higher TSH levels among slightly overweight euthyroid individuals, thereby resulting in a positive correlation between TSH and the progressive increase in weight with time.[5,14-16]

The correlation between TSH and BMI could be mediated by leptin produced by adipose tissue.[17,18] TSH stimulates leptin secretion by human adipose tissue. Leptin physiologically regulates energy homeostasis and also affects thyroid deiodinase activities with activation of T4 to T3 conversion.[5,19] These observations support the concept of an inverse relationship between TH and leptin. There are still surprising gaps and uncertainties regarding cardiac morbidity and mortality, since evidences are based on surrogate markers such as adverse lipid profile, endothelial dysfunction, increased arterial stiffness and cardiac performance.[20]

THYROID FUNCTION IN OBESE INDIVIDUALS

Workers in the field have observed that in euthyroid obese individuals, the baseline serum TSH levels are generally in the upper limit (or slightly over it) of the normal range.[7,21,22] Further, increased TSH levels are positively correlated with elevated waist circumference and BMI and related to the degree of obesity.[15,21] Further, a positive correlation has also been observed between serum leptin and serum TSH levels in obese individuals,[21] which could reflect the positive association between TSH and BMI.[14-16] Moreover, a moderate increase in total T3 or FT3 levels has been observed in obese individuals.[23,24] Progressive fat accumulations have been associated with a parallel increase in TSH and FT3 levels irrespective of insulin sensitivity and metabolic parameters.[23] A positive association has been reported between FT3 and FT4 ratio and both waist circumference and BMI in obese patients.[23] This suggests a high conversion of T4 to T3 in patients with central fat obesity due to increased deiodinase activity.[23] Interestingly, inspite of high plasma TSH levels, TSH receptors are less expressed on adipocytes of obese versus lean individuals, thus further elevating plasma TSH and FT3 levels.[24] This sequence of events would be reversed by weight loss, which restores the size and function of mature adipocytes.[24] Weight loss leads to significant decrease in both TSH and FT3,[23-25] thereby increasing reverse T3 (rT3) due to reduced 5′-deiodination. The observations that increased TSH, FT3 and leptin levels in obese patients are decreased with weight loss supports the hypothesis that the alteration in thyroid function observed in obese subjects may be reversed by losing weight.[26]

It may be emphasized that evaluation of thyroid structure by ultrasound does not help to diagnose hypothyroidism in obese patients. It may be noted that hypothyroidism should be suspected in obese individuals with slightly increased TSH levels only after measuring plasma levels of THs and thyroid autoantibodies. A link between obesity and risk of autoimmune thyroid dysfunction (AITD); which is the main cause of hypothyroidism in adults, and TSH increase, leptin increase and thyroid morphology alteration have been noted as high levels of leptin increases susceptibility to AITD by regulating immune process, which in turn may facilitate development of subclinical or overt hypothyroidism.[27] Though some authors have found that autoimmunity is not a major cause sustaining the high rate of subclinical hypothyroidism in morbid obese subjects. Morbid obese subjects with higher TSH concentrations have shown regularly higher levels of T3 and in some studies a high T4 levels as well.[25] Further, an Italian study has reported that an increase in FT3 and TSH levels were also associated with BMI, waist circumference and fat accumulation.[23]

One of the major functions of T3 is to control thermogenesis. T3 raises basal metabolic rate and promotes thermogenesis by inducing an increase in the mitochondrial respiratory chain activity.[22] Conditions associated with a lack of physical activity exhibit an increase in serum rT3 levels that denotes an elevated thyroxine 3,5-deiodinase enzyme (D3) activity, which converts T3 to the inactive metabolite rT3.[28] Resting EE (REE) depends on obligatory and adaptive thermogenesis. THs are important for adaptative thermogenesis characterized by an uncoupling of oxidative phosphorylation in cold exposed brown adipose tissue.[29] Around 30% of obligatory thermogenesis depends on TH and this fraction is essential for temperature homeostasis.[22]

PATHOPHYSIOLOGY

The possible mechanism that can unfurl the relation between obesity and thyroid gland activity are being actively explored, since there are conflictive data in the literature regarding relationship between obesity and TH. The positive association between TSH and BMI may be due to changes in TH activity or due to alterations in the regulation of hypothalamic-pituitary thyroid (HPT) axis.[22] A direct effect of TSH may be responsible as TSH receptor is expressed in adipose tissue. Besides, there are a number of factors that contribute to FT3 levels in obese subjects. Moreover, a number of authors reported a direct relationship between FT3 and BMI.[22]

TSH seems to be positively related to degree of obesity.[21] Further, a raised TSH levels in obese individuals may be the result of neuroendocrine dysfunction leading to an abnormal secretion rate of TSH. D2 is the main pituitary deiodinase isoenzyme and its activity is a prime factor to release TSH under T3 control, but it does not work properly or is damaged in obese subjects. Some investigators have suggested that there may be certain TH resistance, as well as decreased T3 receptors in obese individuals. Whereas, other authors have suggested presence of partially bioinactive TSH in obese subjects. Additionally, direct and indirect effects of decreased serum leptin contribute to a decreased activity of thyroid-releasing hormone (TRH) neurons in paraventricular nucleus.[22]

SALIENT FEATURES RELATED TO THYROID HORMONE AND OBESITY

Insulin Resistance

The link between thyroid disease and glucose metabolism is well-documented. Insulin sensitivity can be affected by thyroid function. Insulin resistance with hyperinsulinemia are main features of metabolic syndrome and usually accompany obesity.[30] Insulin resistance noted in hypothyroidism is due to decreased tissue sensitivity to insulin, hence reduced glucose disposal. Though, insulin resistance in hypothyroidism is counterbalanced by a reduction in gluconeogenesis.

Thyroid and Adipokines

Fat cells produce leptin are thus considered an active endocrine organ.[5] Leptin physiologically regulates energy homeostasis. Relationship and modulatory role of leptin on the pituitary-thyroid axis has been investigated.[22,31] A leptin regulatory effect on TSH secretion and BMI has been visualized though reasons for this relationship are not clear. Hypothyroidism has been associated with serum leptin levels below,[32] above[33] or in the normal[34] range. Authors observed a significant positive correlation between circulating leptin and TSH levels in obese men and women, whereas correlation between leptin and age was negative.[17,22]

Leptin directly stimulates TRH secretion[29] and subsequently TSH and TH. Besides, leptin has been shown to have a direct inhibitory effect on several components involved in TH production from thyrocytes,[31] and, leptin may directly affect the sensitivity of thyrotroph or the thyrocytes. Leptin modulates the neuroendocrine and behavior responses to overfeeding thereby regulating food intake and energy expenditure. Leptin also effects thyroid deiodinase activities with activation of T4 to T3 conversion.[5,19] This supports the concept of an inverse relationship between TH and leptin. Additionally, serum ghrelin levels are reversibly increased by 32% in hypothyroid patients and that a relationship between ghrelin levels and thyroid function exist.[35]

THYROMIMETIC COMPOUNDS AND OBESITY

A reduction in body weight can be achieved by a negative caloric balance though caloric deprivation usually results in reduction of both fat tissue (desirable) and fat-free mass. However, a reduction in fat-free mass is not desirable as loss of fat-free mass due to reduction in muscle tissue is partly responsible for a reduction in resting EE (REE), which contributes to frequent phenomenon of weight regain. Intense caloric deprivation is usually associated with a decrease in plasma leptin, T3 and sometimes T4 concentrations, and a rise in rT3 as an adaptation process to reduce metabolic needs.[36] A number of trials have been carried out to promote weight loss and avoid weight regain with TH supplementation. Selective modulation

of TH actions is an important therapeutic tool for the treatment of obesity and some of its complications. The purpose of thyroid hormone supplementation is to increase fat loss by increasing oxygen consumption and fatty acid oxidation without having either TSH suppression or side effects on muscle, central nervous system (CNS), bone or cardiac function.[22]

Several animal experimental studies as well as recent human clinical trials strongly point out that thyromimetics are an important group of pharmacological agents that can modify serum lipids without affecting heart rate and causing other major adverse events. Attempts have been made for rational drug designing of synthetic structural analogs of TH that may avoid the adverse cardiac effects of TH, while maintaining its calorogenic, thermogenic activity. It is well-known that TH receptor agonist has beneficial effects including lowering of low-density lipoprotein (LDL) cholesterol and a reduction in whole body adiposity and weight for this reason, TH agonists are among the first antiobesity agents. In a nutshell, they will be useful for the treatment of both obesity and hypercholesterolemia.

THYROID HORMONES

Thyroid hormones are the prime hormones for normal development and are major modulator of metabolic efficiency, EE and thermogenesis. Thyroid dysfunction is associated with changes in body weight and composition, body temperature, and total and REE independent of physical activity. Both subclinical and overt hypothyroidism are frequently associated with weight gain, decreased thermogenesis and metabolic rate.[2] However, the mode of action of TH in promoting mitochondrial uncoupling, which reflects to TH-induced calorigenesis and thermogenesis still remained elusive.

Obesity and thyroid dysfunction are quite common yet TH have been inappropriately and frequently used to induce weight loss in obese euthyroid subjects; there is no indication for their administration to control body weight except in obese hypothyroid subjects. In fact, long-term treatment with TH does not significantly improve weight loss in obese subjects without thyroid dysfunction and may cause adverse effects.[37] Moreover, TH have a plethora of physiological effects/targets hence their therapeutic usefulness in dyslipidemia and obesity is fairly limited. Lomenick et al[38] investigated short-term and long-term changes in weight with T4 treatment of hypothyroidism in children. The authors did not support the view that hypothyroidism as a cause of obesity, and observed that one should not expect significant changes in weight following treatment in most children with hypothyroidism.

In a recent review exhibiting results observed in 14 studies with TH treatment (T3 administration) in obese patients submitted to caloric deprivation failed to draw any firm conclusions owing to heterogeneity in the quality and designs of these trials. No studies evaluated body composition vis-a-vis changes in fat tissues or fat-free mass components. Besides, only a few studies measure REE, nitrogen balance, protein breakdown and 3-methylhistidine urinary excretion, with no consistent results. No clear variations in heart rate were seen. Moreover, these studies did not demonstrate any sustained benefit on weight loss despite T3-induced subclinical hyperthyroidism.[37]

Thyroid extract were quite popular for treating obesity throughout the 20th century but were later abandoned due to severe side effects consisting of cardiac dysrhythmias, osteoporosis, electrolyte and loss of lean body mass.

Thyroid Hormone Receptors and Molecular Basis of Thyroid Hormone Action

TH genomic action is mediated by binding of the hormone to nuclear TH receptors (THRs). Binding affinity is higher for T3 hormone than its T4 precursor. THRs are members of the family of nuclear receptors that regulate the expression of genes. THRs are encoded by the α and β C-erbA genes located on chromosomes 17 and 3, respectively, and are expressed as several spliced isoforms. The C-erbA α gene encodes the TH-binding receptor THR α_1 and two spliced variants that do not bind hormone (THR α_2 and THR α_3), whereas the C-erbA β gene encodes the THRβ_1, THRβ_2 and THRβ_3 isoforms. The three β isoforms differ in their aminoterminal domains. Both THRα_1 and THRβ_1 are expressed ubiquitously. However, THRα_1 has its highest expression in skeletal muscles and cardiac muscle, bone and brown fat, whereas THRβ_1 is highly expressed in liver, brain and kidney.[39] Additionally, TH genomic action may be complemented by TH nongenomic action which require high dose.

Dextrothyroxine and TRIAC

Thyroid hormone analogs have been used in past for reduction of fat mass or control of hyperlipidemia and weight loss while avoiding side effects on bone, brain and heart. A large number of TH analogs were synthesized and tested on experimental animal models for their lipid-lowering activity. Dextrothyroxine was

the first such compound. Analogs may cause weight loss by increasing EE as well as improving lipid profiles in obese patients with low T3 during continued caloric deprivation, though use of dextrothyroxine for hyperlipidemia therapy has been unsuccessful.[40] Tri-iodothyroacetic acid, a natural TH metabolite has shown thermogenic capacity in brown adipocytes in culture,[41] yet no clinical studies demonstrated its efficacy in obesity treatment. The pace of development of thyroid analogs was slowed down firstly, because of associated mortality with use of analogs, and secondly, because of introduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, usually referred to as 'statins' into clinical practice to lower plasma cholesterol.

Selective Thyroid Hormone Receptor Activation

Presence of selectivity has led to the resurgence of this novel class of drugs. The existence of distinct isoforms of THRs and the knowledge of their tissue distribution, regulation and crystal structure has given impetus for the development of selective thyromimetics. More recently agents with specific liver selectivity (affinity to THRβ isoforms) have been developed based on the so called HepDirect liver targeting approach. Thus, selective THRβ analogs have been designed to target liver by adding substituents that promote hepatic first-pass, rather than systemic distribution.

Selective modulation of TH actions represents a promising therapeutic tool for the treatment of obesity and some of its complications. Mechanisms of TH action at the cellular level have shown that selective applications of different THR forms are responsible for tissue-specific responses to TH.

There are two THR isoforms (α and β) that are encoded by two genes. Thus, THRα mostly present in brain and heart regulates cardiac function; while THRβ present in liver controls effects of TH on lipid metabolism.[42] Further, THRβ_1 is the systemic form, while THRβ_2 is the pituitary form which controls TSH secretion.

Investigators have opined that selective THR activation may be beneficial for therapeutic application in some diseases namely dyslipidemia and obesity. Thus, selective thyroid receptor activation for obesity treatment may bring about a rise in REE, a reduction in fat mass, an improvement in insulin sensitivity and lipid profile though, TH overexposure may cause adverse events such as muscle wasting, bone loss, nervousness, hypertension and cardiac dysfunction (arrhythmias, heart failure).[22] Hence, development of THRβ-selective modulators which preferentially have an effect on liver metabolism will be a step in the right direction.

Thus, selective compounds are synthetic structural analogs of TH having tissue-specific TH actions i.e., they bring about lowering of LDL cholesterol and fat loss by an effect on THRβ_1 isoforms in the liver. They do not alter the heart rate mediated through THRα_1 isoforms in the heart.[43] Presently liver selective, cardiac-sparing TH analogs (THRβ-selective compounds) as lipid modifying agents have been developed and have been tested on different animals. A few such compounds are in various phases of human clinical trials.

THRβ Agonists

The first liver-selective, cardiac-sparing thyromimetics were produced by substitution of iodine moieties by arylmethyl groups at the 3' position. Other structural TH analogs such as 3,5-diiodothyropropionic acid (DITPA) followed soon thereafter.

Sobetirome

A selective thyromimetic compound, GC-1 (3,5-dimethyl-4-(4-hydroxy-3-isopropylbenzyl) phenoxy acetic acid - sobetirome) has 10 times more selective action on THRβ_1 than over THRα_1. Since, affinity of GC-1 for THRα_1 is 10 times lower than T3 hence less stimulation of heart rate in relation to increase in energy expenditure. The compound caused an increase in EE of 5-10% and mild tachycardia in mice.[44] In a phase 1 clinical trial on 24 patients over 2 weeks. LDL cholesterol was reduced up to 41% at 100 μg/day.[45] Further GC-1 administration to primates causes increase in oxygen consumption and reduction of body weight and minimal effect on skeletal muscle mass.[46] Animal studies have shown that GC-1 may have a promising role as an antiobesity agent, since it reduces fat mass without increasing food intake and controls dyslipidemia, without causing a deleterious effects on heart or bone mass.[45] It increases fatty acid oxidation, decreases inflammatory markers and reduction of liver steatosis and reduction in TSH. Sobetirome is generally well-tolerated and exhibits a promising role as an antiobesity agent. It causes no changes in heart mass, and skeletal mass is minimally affected and induces 20% reduction in fat mass without increasing food intake.

KB-141

KB-141 is another THRβ agonist, is 10 times more selective for stimulating metabolic rate and 30 times more selective for cholesterol-lowering than for increase

in heart rate. Besides, KB-141 has been shown to cause weight reduction as well as reduction of cholesterol and lipoprotein(a).[22] Increase in EE, reduction of fat mass, increase LDL receptor expression has been observed.

GC-24

GC-24 again a THRβ agonist having 40-100 times preference for THRβ over THRα.[47] It also reduces body fat accumulation and increases EE.[48] These effects are noted without any change in food intake or a significant effect on myocardium. Besides, this compound reduces glucose response to glucose load, improves insulin sensitivity and normalizes the previous hypertriglyceridemia. Total cholesterol is marginally affected and there is no effect on free fatty acids or interleukin (IL-6) levels. Additionally, the compound has significant thermogenic effects as well as effects on EE.[22] It prevents increase in fat mass, there reduction in cholesterol and triglycerides, reduction in TSH, T3 and T4 and it has no effect on heart.

Eprotirome

Chemically eprotirome (KB-2115) is 3-((3,5-dibromo-4-(4-hydroxy-3-(1-methylethyl)-phenoxy) phenyl)amino)-3-oxopropanoic acid. It is also THRβ selective compound that has been administered to human beings. It has seven times greater affinity for the β isoforms of TH receptor than does T3.[49] The tissue uptake of eprotirome is highly liver selective; uptake in nonhepatic tissues is minimal.[50] KB2115 compound leads to 40% reduction in total and LDL cholesterol after 14 days treatment probably owing to an increase in bile acid synthesis. Also, there is a dose-dependent reduction in total and FT4 levels without any affect on TSH concentrations.[51]

In human data from a clinical trial of 98 hyperlipidemic patients, eprotirome caused 25% reduction in LDL apolipoprotein B, along with 37% decrease in lipoprotein A at 100 μg/day after 16 weeks. There was 40% decline in hyperlipidemia. No cardiac, bone or muscle effects were observed, though mild transient elevation in liver enzymes was noted.[50] In phase II trial, eprotirome in combination with atorvastatin or simvastatin caused additional lipid reduction. However, phase III trials to evaluate eprotirome safety and efficacy profile was terminated because of cartilage damage.[49] No changes in metabolic rate, body weight, EE or heart have been observed.

3,5-Diiodothyropropionic Acid

DITPA chemically is 3,5-diiodothyropropionic acid. It is an early but less selective thyromimetic agent. The compound has low THR selectivity. In animal experimentations, DITPA did increase the cardiac output by reducing the end-diastolic pressure but was without any positive chronotropic effects on the heart.[49] A pilot study on DITPA in 19 patients led to increased cardiac index and decreased vascular resistance index.[49] After 24 weeks, it reduced serum LDL cholesterol by 30% and increased cardiac index by 18%, but there was no evidence of symptomatic benefit in congestive heart failure (CHF).[52] DITPA was poorly tolerated in a phase II clinical trial of 86 patients with CHF. DITPA was also associated with a significant reduction in body weight of 5.7 kg and an increased bone turn over.[53] The compound caused suppression of the hypothalamic pituitary thyroid axis and increased bone turnover. Cardiac symptoms are unaffected.[53,54] Reduction in TSH, T3 and T4 and increase in heart rate have been observed.

MB07811

This prodrug undergoes first pass hepatic extraction and cleavage of prodrug generates the negatively charged active THR agonist (3,5-dimethyl-4-(4′hydroxy-3-isopropyl benzyl) phenoxy) methylphosphonic acid (MB07344) in liver microsomes, which gets poorly distributed in most tissues and is rapidly eliminated into the bile.[55] This is essential in limiting the extra hepatic side effects associated with this class of agents. In rats and mice, MB07811 reduces not only cholesterol and triglycerides levels but also hepatic steatosis. Further, in combination with atorvastatin it has additive effects on LDL cholesterol-lowering in animal models. The human phase 1b clinical trial also noted a reduction in LDL cholesterol and triglyceride levels. The main mechanism underlying MB07811 effects seems to be an increased metabolic rate in liver and specifically an increased rate of mitochondrial β-oxidation. Further, in therapeutic doses it is devoid of measurable extra hepatic effects.

Bile Acids

Administration of bile acids can modulate EE as well as TH activation via changes in D2 expression, an enzyme involved in BAT thermogenic pathways that regulate EE.[56,57] Kaempferol may increase skeletal myocyte oxygen consumption by increasing cAMP generation and inducing protein kinase A activation. Besides, the agent may influence expression of genes involved in thermogenesis, such as UCP-3, and to upregulate D2 gene expression; prolonging its half-life.[58] These pathways may be targeted for the treatment of obesity and other metabolic disorders.

USE OF THYROMIMETICS IN DYSLIPIDEMIA

THRβ-selective thyromimetics serve as an important pharmacological tool to modify serum lipids and to treat dyslipidemia. The mechanism of lowering of LDL cholesterol by thyromimetics is different from that of statins, which are first-line drugs for the treatment of hypercholesterolemia. Interestingly, thyromimetics have synergistic action when combined with statins.[53] Following are several mechanisms through which thyromimetics act in dyslipidemia.[49]

- The anti-atherogenic effects of selective thyromimetic is primarily due to upregulation of the LDL receptor in the liver, which leads to a strong reduction in plasma LDL particles, associated with a significant reduction in plasma total cholesterol and triglycerides.
- Inhibition of hepatic transcription factor, sterol regulatory element-binding protein 1 (SREBP-1), leading to reduced very LDL assembly.
- Facilitation of the reverse cholesterol transport, which describes the transport of cholesterol from extra hepatic tissues, for example plaque macrophages, back to liver for fecal excretion.
- Increase hepatic expression of the HDL receptor, scavenger receptor B-1 (SRBI), which increases the clearance of HDL cholesterol without affecting the HDL particle number, thus promoting the delivery of HDL cholesterol derived from atherosclerotic macrophages.
- In human beings, HDL cholesterol can be transferred to LDL particles through the cholesterylester transfer protein (CETP) and then cleared through hepatic LDL receptor. Hepatic cholesterol is than excreted into bile either directly by the transporters ABCG5 and ABCG8 or gets converted into bile acids by cholesterol 7 α-hydroxylase (CYP7A1). Both these mechanisms are facilitated by selective thyromimetics.
- Thyromimetics probably reduce intestinal absorption of dietary sterols due to competition with sterols of biliary origin.

Moreover, selective thyromimetics may have additive LDL cholesterol-lowering when used in combination with statins in animal models.[59]

USE IN OBESITY AND HEPATIC STEATOSIS

THs reduce body fat by increasing basal metabolic rate without muscle wasting and effect on heart rate.[45,60] Loss of weight was observed in the phase II clinical trial with DITPA.[53]

Sobetirome reduces body fat in animal studies by increasing fatty acid β-oxidation and increasing oxygen consumption and body temperature. Besides, development and progression of hepatic steatosis is prevented owing to increased mitochondrial and peroxisomal fatty acid β-oxidation and reduced levels of inflammatory marker.[54,61] Sobetirome is also less effective than THs in promoting weight loss.[49]

Similarly, MB07811 reduced hepatic steatosis through increased fatty acid oxidation in animal models. A reduction of hepatic and body fat may be beneficial for glucose homeostasis and type 2 diabetes.[62] It may be emphasized, that long-term human clinical trials are required to prove whether thyromimetics will be of use in the treatment of obesity and hepatic steatosis.

Potential Harmful Effects

Since, the selectivity of thyromimetics for THRβ and/or the liver is not absolute, but a relative one, hence high doses still activate THRα resulting in adverse events related to positive chronotropic and inotropic cardiac effects as well as enhance bone resorption and muscle catabolism.[63] However, muscle and bone catabolism are fairly less common in therapeutic dose.[49,50]

Less selective DITPA has shown increased bone turnover in human trials.[53] Landenson et al,[53] in phase II study with DITPA, also noted poor tolerability profile in patients with pre-existing CHF. Development of positive chronotropic effect is deleterious in cases of CHF.

Selective THRβ agents may influence regulation of HPT axis as this receptor is also expressed in the pituitary gland and regulates the feedback loop over TSH.[49] In human being, eprotirome reduced serum T4, although TSH and serum T3 levels are not significantly affected.[50,53] Besides, patients receiving eprotirome may also be watched for mild reversible increases in the levels of serum alanine aminotransferase and potential hepatic toxicity.[53]

Potential Limitations

THRβ-selective thyromimetics may result in novel nongenomic effects, hence the safety of THRβ-selective thyromimetic have to be screened particularly in subjects suffering from CHF or coronary heart disease (CHD).[52]

Some potential limitations of a liver-specific antisteatotic agent such as MB07811 are, firstly burning hepatic fat may not be sufficient for patients with nonalcoholic steatohepatitis (NASH) (those who really need

therapy) because the metabolic imbalance, in particular peripheral insulin resistance, will continue and the beneficial effect of thyromimetics could be counteracted by increased lipogenesis in the liver or lipolysis in adipocytes, secondly burning hepatic fat may not be appropriate in a liver, which already has some degree of damage, thirdly systemic fibrogenic stimuli, such as hyperinsulinemia pathways may remain unaffected by thyromimetic agents.

CONCLUSION

TH-induced calorigenesis and thermogenesis have been shown to reflect uncoupling of mitochondrial oxidative phosphorylation though the mechanism remained elusive. Future therapy of obesity, fatty liver, type 2 diabetes, dyslipidemia, etc. needs designing of new compounds, which selectively modify different metabolic pathways. Till date, therapeutic usefulness of selective thyromimetics in the treatment of dyslipidemia, obesity and atherosclerosis is still hanging in balance at least till the final outcome of long-term phase III clinical trials.

However, animal studies have shown that they are quite effective as lipid-lowering agents with minimal effects on heart rate and bone catabolism. Further, more knowledge and clinical trials are required to decipher mechanisms of action, safety and tolerability profile of newer agents. Moreover, newer thyromimetic agents should be safe to heart, bone, HPT axis and CNS. At the moment, the major indication of this novel class of drugs seems to be the treatment of dyslipidemia which is a major cardiovascular risk factor, and they have limited prospects in treating human obesity.

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Enlarged Ovaries Following IVF/ICSI as an Etiology of Obstructive Uropathy Resulting in Acute Renal Failure: A Case Report

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ABSTRACT

In vitro fertilization (IVF) is one of the most comprehensively registered interventions in clinical medicine. IVF is regarded as safe with very few complications. We report a woman who developed acute renal failure due to compression of both ureters from enlarged stimulated ovaries. The condition was diagnosed using magnetic resonance imaging. It was treated with insertion of double-J stents in both ureters and dialysis. Compression of the ureters due to enlarged ovaries should be considered if a patient especially with pre-existing endometriosis develops acute renal failure following IVF.

Keywords: Acute renal failure, *in vitro* fertilization, ovarian hyperstimulation syndrome, ultrasound

During the last 35 years, *in vitro* fertilization, (IVF) has become an important treatment option in patients with infertility. Following hormone stimulation, the oocytes are collected from the ovaries transvaginally using ultrasound guidance. The procedure is regarded as safe. The most common complications are hemorrhages, pelvic abscesses and pain. There are also some reports of ureteric damage after puncture by the collecting needle.[1,2] We report a case, where a woman with pre-existing endometriosis developed acute renal failure due to compression of both ureters from enlarged stimulated ovaries.

CASE REPORT

A 28-year-old woman married for 8 years, with two previous first trimester miscarriages presented to us for treatment of secondary subfertility. She had history of 2 laparoscopies elsewhere suggestive of bilateral tubal block and extensive adhesions between tubes, ovaries and uterus suggestive of stage IV endometriosis. She had regular cycles with a body mass index (BMI) of 20. She had a past history of surgically corrected atrial septal defect at 5 years of age, asymptomatic; since then with good left ventricular ejection fraction. She had ureteric calculi diagnosed on both sides on ultrasound done outside with no renal changes 3 years back, for which she underwent conservative management.

Her follicle-stimulating hormone (FSH) was 12.3 mIU/L and luteinizing hormone (LH) was 14.2 mIU/L, antimullerian hormone (AMH)-1.2 pmol/L with reduced antral follicle count with 2 cm endometriotic cyst on both ovaries. Kidneys were normal. Husband's semen analysis was normal. Hysteroscopy and trial transfer was done as pre-IVF evaluation. She was counseled for therapeutic trial and a flexible antagonist protocol was followed. Recombinant FSH was used for stimulation. Five oocytes were retrieved under ultrasound guidance after 35 hours of human chorionic gonadotropin (hCG) trigger. Three embryos were fertilized and three 8 cell Grade A embryos were transferred without any difficulty.

Six days following embryo transfer, she reported with loin pain and high-grade fever and reduced urinary output. There was no tenderness on abdominal examination. Investigations revealed normal leukocyte count with more than hundred pus cells on routine urine analysis. Renal function test revealed a picture of pre-renal failure with a serum urea of 100 mg/dL and

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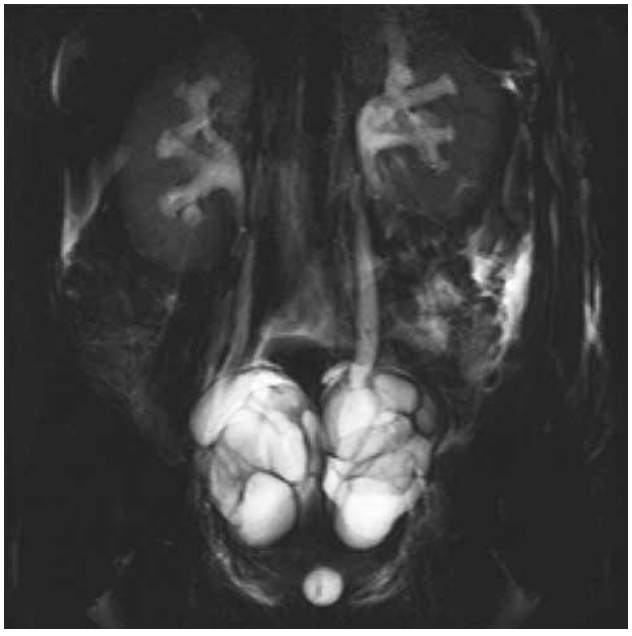

Figure 1. Ultrasound showing bilateral stimulated enlarged ovaries compressing both ureters resulting in bilateral hydronephrosis.

creatinine of 7.9 mg/dL. Serum electrolytes showed hyperkalemia. Investigations to rule out other causes of pyrexia were normal. Ultrasound showed bilateral enlarged ovaries measuring right 5 × 6 cm and left 6 × 7 cm and bilateral hydronephrosis (Fig. 1). Magnetic resonance imaging (MRI) scan showed bilateral hydronephrosis and enlarged ovaries, which led to compression of ureters. She was catheterized and her urine output was only 300 mL/24 hours. Nephrologist's and urologist's opinion were taken. Injection carbapenem following sensitivity to Klebsiella and extended-spectrum beta-lactamase (ESBL) growth on culture was started. Patient was transferred to Nephrology department and dialysis was done as her creatinine showed increasing trend and persistent oliguria. Serum creatinine started to decline following dialysis. Double-J (DJ) stent was inserted. The postoperative course was uneventful and her creatinine level showed declining trends. Oral progesterone was continued as luteal support and on Day 16 of embryo transfer, β-hCG was positive. Her β-hCG showed an increasing trend. Renal sonogram was repeated and it was normal. The patient was asymptomatic and urine culture was negative.

At 6 weeks from last menstrual period (LMP), ultrasound showed evidence of echogenic ring and presence of yolk sac with no cardiac activity and fluid collection was seen in the right adnexa suggestive of right ectopic pregnancy. She was posted for an emergency laparoscopy as she was hemodynamically stable, which needed conversion to laparotomy in view of frozen pelvis.

Approximately, 1 liter of blood and clots were removed along with necrotic and hemorrhagic tissue scattered in the abdominal cavity. Right tube was the seat of rupture and salpingectomy was done. Right ovary was stuck to the back of uterus, and left ovary stuck to lateral pelvic wall. Abdomen was washed with saline and a drain was placed. Two units of packed cells were transfused postoperatively. Histopathology confirmed ruptured ectopic gestation in the right tube. She was discharged in a stable condition. DJ stent was removed 6 weeks later.

DISCUSSION

Transvaginally, ultrasound-guided oocyte retrieval has become the gold standard for IVF therapy. It is considered as a well-tolerated, cost-effective and safe procedure.[3,4] A few cases of ureteral damage due to puncture of the ureter by the collecting needle have been described. In one case, the ureter was compressed by a stimulated ovary in a patient with a transplanted pelvic kidney.[5] The diagnosis of ureteral compression was confirmed by MRI scan, a procedure without ionizing radiation and which should not cause any harm to fertilized embryos.[6] Severe pelvic adhesions may have worsened the situation by limiting the normal movement of the ovaries. Ovarian hyperstimulation syndrome (OHSS) is a common complication in assisted reproductive technologies. In spite of frequent occurrence of abdominal compartment syndrome and oliguria in OHSS, acute renal failure secondary to obstructive uropathy is uncommon in OHSS.[7] Acute renal failure due to a hypovolemic state following production of protein-rich ascites in patients with OHSS has been reported,[8] but in this case, no ascites and only slight hemoconcentration was noted. The most pronounced finding was the huge enlargement of the ovaries and bilateral hydronephrosis.

To date, there have been just two case reports of obstructive uropathy associated with OHSS.[9] The patient was diagnosed earlier as having stage 4 endometriosis and frozen pelvis. Even though the complication risk related to IVF is low, one should be aware of a possible compression or damage to the ureters with subsequent development of acute renal failure. Injury, either by direct puncture or extrinsic compression, compromised ureteral function, but did not completely halt urination—a testimony to the resilient nature of this structure and an intimation of

more frequent, unrecognized injury. We, therefore, suggest that obstructive uropathy should also be considered as a possible etiology in patients with enlarged ovaries who develop oliguria or acute renal failure.

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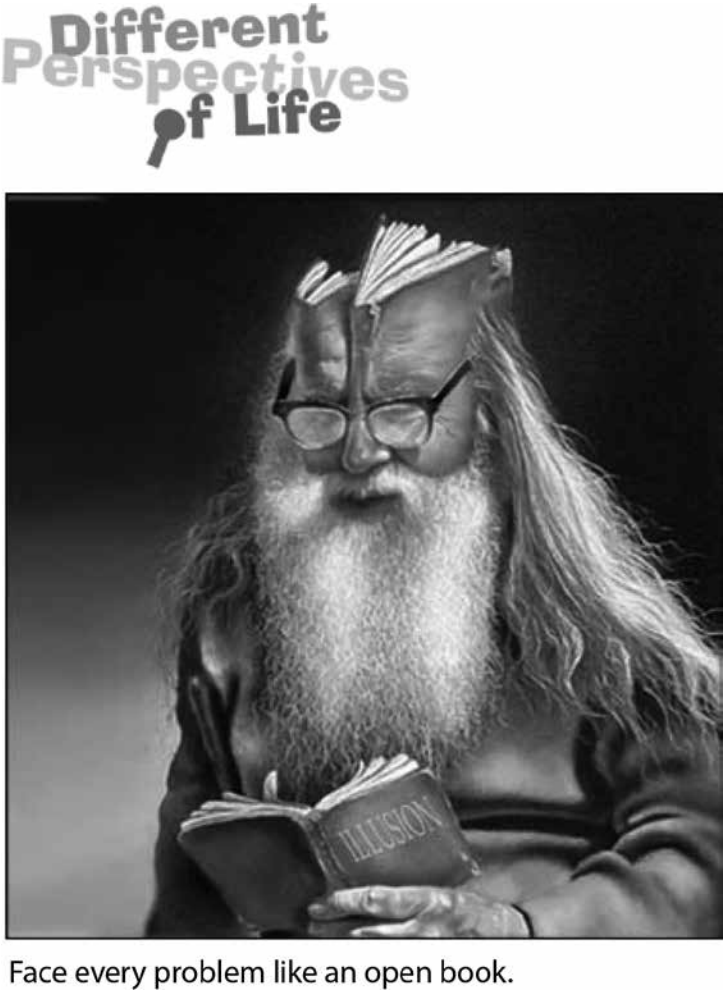

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Psychosocial Impacts as Predictors of Compliance in Celiac Disease

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ABSTRACT

Celiac disease is an immune-mediated disease due to gluten and related prolamins in genetically susceptible individuals. The only option of treatment is lifelong gluten-free diet (GFD). Strict adherence to GFD may be difficult in children and adolescents due to psychosocial factors. A study evaluated the impact of celiac disease and GFD on social interactions of children with celiac disease and their families, in the backdrop of aim to identify predictors of barriers affecting compliance to GFD. Three types of psychosocial impacts as predictors of barriers to compliance were noted - those caused by effect of celiac disease on feelings of children suffering from celiac disease; barriers derived from parent's attitude; and those derived from child's attitude.

Keywords: Celiac disease, gluten-free diet, psychosocial impact, barriers, predictors, compliance, adherence

Celiac disease is an immune-mediated disease due to gluten and related prolamins in genetically susceptible individuals and characterized by variable combination of gluten-dependent clinical manifestations, celiac disease-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy. Celiac disease is a global disease with continuously increasing incidence, particularly in Western countries. This rise is related to increase of autoimmune diseases (Rheumatic, Endocrinological, Gastrointestinal and Neurological) whose incidences and prevalences are on significant rise over the past 30 years. The frequency of celiac disease in general population is reported to be approximately 1% with regional differences. Higher rate is mentioned in females, concrete ratio is 2:1. Celiac disease is also prevalent in India with rates of 1 in 96 in North India. The patient may initially present with nonspecific symptoms but unpleasant complaints, such as diarrhea, flatulence, cramps, fatigue causing difficulties to patient and sometimes even limiting daily activities may be there. Weight loss, decreased bone density, unexplained iron deficiency and infertility are also noted in celiac disease.

Neuropsychiatric symptoms such as ataxia, neuropathy, headache, epilepsy, depression and anxiety are also frequent in celiac disease. The only option of treatment is lifelong gluten-free diet (GFD). Although a well-planned GFD may provide adequate nutrition, it may be restrictive. Strict adherence to GFD may be more difficult in children and adolescents than in adults due to psychosocial factors. Compliance to GFD varies from 45% to 81% in children as reported by the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition.

Noncompliance is a major problem and the greatest challenge, which the pediatricians face is in predicting the compliance to GFD in children. Noncompliance may occur due to factors like temptation and not liking the taste of GFD and alternative food grains. In adolescents, peer pressure, unclear labeling on ready-to-eat food and nonavailability of GFD at party, marriages and so forth have contributed to noncompliance. An increasingly hectic lifestyle of teenagers has contributed to a greater reliance on packaged foods which often contain gluten, and thus making it inconvenient for them to adhere to restrictive diet.

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According to Urban-Kowalczyk (2015) depression is one of the main psychiatric disorders related with celiac disease (besides anxiety, psychosis and anorexia nervosa). Many children experience psychological reactions to being placed on a restrictive diet (e.g., feeling deprived, depressed, angry and anxious), which have been found to further decrease compliance. This study evaluates the impact of celiac disease and the GFD on social interactions of the children with celiac disease and their families, in the backdrop of aim to identify predictors of barriers affecting compliance to GFD. This study is significant and will contribute to better understand education techniques for dietary instruction as well as provide an insight in the psychosocial effects of the disease.

MATERIAL AND METHODS

The present study was conducted by Dept. of Pediatrics, SMS Medical College and Attached Hospitals, Jaipur, Rajasthan, India. One hundred fifty children and their parents visiting the gastroenterology superspecialty clinic for growth monitoring and compliance assessment, aged between 2 years and 15 years, diagnosed with celiac disease as per revised European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria for diagnosis of celiac disease 1990, on GFD for more than 6 months, were enrolled in the study after getting the requisite clearance from the Institute Research Review Board. Children less than 2 years and more than 15 years of age, those who did not have a documented positive serology and/or biopsy suggestive of celiac disease as per revised ESPGHAN criteria 1990, those on GFD for less than 6 months, and those children whose parents refused consent were excluded.

All children enrolled in the study after signing of the written informed consent form were evaluated for dietary compliance based on a 5-day dietary recall form. A child who had taken even one food article containing gluten in last 5 days was considered noncompliant and those who had strictly taken no gluten in their diet in that period were considered compliant. Diet recall was done by parents for children in preschool age up to 5 years since parents were the only one giving the eatables to these children. Children, above 5 years of age, going to school and interacting with peers, were actively involved in the dietary recall along with the parents. Parents and children in the study group were assessed for dietary compliance followed by a questionnaire based interview. Psychosocial parameters were assessed by standard Pediatric Symptom Checklist (PSC). Dietary compliant and noncompliant groups were compared and assessed for factors affecting the dietary compliance. Predictability of all of these factors was assessed using binary logistic regression analysis with backward elimination to find out the best predictors of compliance.

RESULTS AND DISCUSSION

Three types of psychosocial impacts as predictors of barriers to compliance were noted- those caused by effect of celiac disease on feelings of children suffering from celiac disease, barriers derived from parent's attitude and those derived from child's attitude. All percentage data are rounded off for purpose of easy understandability.

Predictors Related to Child's Feelings

In the present study, about 48% of the compliant children never felt left out of the activities at school, while only 23% of noncompliant children never felt left out of the activities at school. Also, 15% of noncompliant children and 8% of compliant children believed that their teacher and friends didn't understand the disease all or most of the time. Forty-six percent of noncompliant children felt different from other kids because of disease as compared to 3% of compliant children; 72% of children in compliant group were not having any problem in bringing GFD to school parties, while in noncompliant group this was true for 28% only; 63% felt embarrassed to bring GFD at parties. While inquired about their social life and asked to grade it, 9% children in compliant group believed that they were left out of activities at school or friends' home due to their disease all or most of the time while 48% children in noncompliant group believed that they were left out of activities at school or at friends' home. In noncompliant group, 3% felt different from others all the time while 43% felt different most of the times as compared to 0% and 3%, respectively in the compliant group. Due to their disease, feeling of embarrassment of bringing GFD to parties was higher in noncompliant group in comparison to compliant group i.e., 80% and 28%, respectively (Table 1).

Feeling of anger for following special diet was also higher in noncompliant group as compared to compliant group i.e., 91% and 78%, respectively. Twenty-two percent never felt angry to follow GFD in compliant group in comparison to 9% in non-compliant group who never felt angry to follow GFD. In compliant group, 66% of children understood the importance of following a GFD and never felt that they can be healthy without following a special diet while in noncompliant

Table 1. Predictors Related to Child's Feelings

	Compliant Group (%)					Noncompliant Group (%)					P value
	A	B	C	D	E	A	B	C	D	E	
Feel left out of activities at school or friends home	0 (0.00)	9 (9.23)	40 (41.54)	45 (47.69)	2 (1.500)	2 (2.86)	24 (45.71)	15 (28.57)	13 (22.86)	0 (0.00)	<0.001
Felt different from other kids	0 (0.00)	3 (3.08)	36 (36.92)	58 (60.00)	0 (0.00)	2 (2.86)	22 (42.86)	16 (28.57)	13 (25.71)	0 (0.00)	<0.001
Felt embarrassed to bring gluten-free foods to parties	2 (1.54)	10 (9.23)	14 (16.92)	70 (72.31)	0 (0.00)	5 (8.57)	22 (42.86)	6 (11.43)	15 (28.57)	6 (8.57)	<0.001
Felt angry about following a special diet	0 (0.00)	18 (18.46)	58 (60.00)	21 (21.54)	0 (0.00)	21 (40.00)	12 (22.86)	15 (28.57)	5 (8.57)	0 (0.00)	<0.001
Felt their teacher and friends didn't understand the disease	0 (0.00)	7 (7.69)	20 (20.00)	62 (64.62)	7 (7.69)	4 (5.71)	5 (8.57)	18 (34.29)	22 (42.86)	5 (8.57)	<0.001
Felt that they can be healthy without following a special diet	2 (1.54)	2 (1.54)	35 (30.77)	66 (66.15)	0 (0.00)	10 (17.14)	12 (22.86)	21 (40.00)	111 (20.00)	0 (0.00)	<0.001
Avoid restaurants	47 (50.77)	25 (26.15)	9 (9.23)	9 (9.23)	5 (4.62)	27 (51.43)	13 (22.86)	3 (5.71)	4 (5.71)	8 (14.29)	0.171
Avoid traveling	33 (35.38)	49 (50.77)	12 (12.31)	2 (1.54)	0 (0.00)	34 (57.14)	7 (14.29)	5 (8.57)	8 (20.00)	0 (0.00)	<0.001
Found difficult to determine which food is gluten-free	12 (12.31)	25 (26.15)	48 (49.23)	12 (12.31)	0 (0.00)	24 (45.71)	15 (28.57)	9 (17.14)	4 (5.71)	1 (2.86)	<0.001
Felt they were not invited out	2 (1.54)	10 (9.23)	12 (13.85)	60 (61.54)	12 (13.85)	6 (11.43)	2 (2.86)	4 (8.57)	28 (51.43)	14 (25.71)	0.002

A = All the time; B = Most of the time; C = Some of the time; D = Never; E = Not answered.

group only 20% understood this. Seventy-four percent children in noncompliant group had problems all or most of the times in identifying the gluten-free food stuff as compared to 38% in compliant group who had this problem all or most of the time. Seventy-two percent in compliant group believed that their teachers and friends understood the nature of their disease compared to 51% in noncompliant group. Eleven percent in compliant group always or most of the time felt that they were not invited in parties because of the disease, while 14% in noncompliant group believed so all or most of the time. Most questions depicted perception of the child about the disease and GFD significantly affected compliance ($p \leq 0.001$).

Psychological Impacts of School Environment

Only 42% of compliant patients found it difficult to maintain compliance at school in contrast to 74% of noncompliant patients. Olsson et al in 2008 showed that for adolescents, school was the most difficult place to comply with GFD. Other children bringing mainly gluten containing foods and peer pressure about taking packed food items containing gluten were responsible for difficulty in maintaining compliance at school.

Psychological Impacts of Family Party and Marriages

Noncompliant children also found it more difficult to maintain GFD at family party/marriages (80%), compared to 36.92% in the compliant group. Gluten containing food as the main dietary item served at above places was a problem for both compliant and noncompliant groups who had problems in maintaining diet at such places. Greater negative impact of celiac disease on patients was perceived in social activities. This effect was more apparent among women - more women said that they have avoided some social situation (such as eating in a restaurant. Rose and Howard (2014) describe social anxiety that comes from the violation of social rules of decency - patients are afraid that others will negatively perceive their non-conformist behavior. People that are

nervous about eating outside of the home are changing their strategy towards lowering their social activities. Strategies of avoiding eating in restaurants or traveling are also described in other studies.

Psychological Impact Related to Taste of Gluten-free Diet

In response to question related to taste of GFD, 66% of compliant patients graded taste of GFD to be very good or good, while only 11% in noncompliant group graded it good or very good. Taste liking of GFD is significantly associated with compliance ($p \leq 0.001$). Butterworth et al (2004) have also reported better compliance in patients who were frequently explained and educated by dieticians regarding selection and preparation of gluten-free meals to improve the taste of the meals. These results highlight importance of counseling and education of parents and children in selecting and preparing gluten-free foods. Parents should be taught palatable, easily available gluten-free food preparations for their children.

In our study, 18% compliant and 63% noncompliant children felt angry about having to follow a special diet all or most of the time. Sixty-six percent of compliant and only 20% of noncompliant children never believed that they can be healthy without following a special diet. We noted that majority of both compliant (86%) and noncompliant children (71%) avoided traveling because of difficulty in availability of GFD. Rashid et al (2005) also studied the effect of child's feeling on compliance to GFD. In their study 13% of compliant children felt left out of school activities due to their disease and 11% of compliant children felt that their teacher did not understand their disease. While 18% children felt themselves different from other kids, 23% were embarrassed to bring gluten-free food to parties. In their study, 23% children felt angry about having to follow a special diet.

These results indicate that these dietary restrictions have significant impact on child's social activities including school and extracurricular events. It affects their participation in school, parties and enjoyable social activities such as birthday parties. Nonavailability of gluten-free items in restaurants and during travel is further disastrous.

Psychosocial Problem Related to Noncompliance

In our study, the mean score increased as the age increased in the children suffering from celiac disease in both compliant and noncompliant patients. Hence, an older child is at more risk of noncompliance.

Sixty-three percent of children in compliant group found it easy to keep compliance to GFD. Fifty-seven percent of children in noncompliant group found it fairly difficult to maintain GFD. In noncompliant group, 74% children found it difficult to maintain GFD at school; 80% found it difficult to maintain GFD at family parties and marriages; 63% found it difficult to comply to diet when with friends. Sixty-nine percent in compliant group compared to 86% in noncompliant group found difficulty in complying with diet while traveling.

When they were assessed regarding sharing of responsibility in maintaining GFD, 66% of compliant children were found to be sharing responsibility of keeping the diet, in contrast to 29% of noncompliant children who shared responsibility of keeping the diet. Forty-three percent of noncompliant children reported the taste of gluten-free food as bad while 66% of children in compliant group found it very good or good and only 3% of compliant children reported food as bad. A statistically significant difference was observed in these results. In the present study, the questionnaire included questions related to child's attitude in response to the disease and GFD. While 63% of children in compliant group found maintaining GFD easy, only 20% of noncompliant children found it easy to maintain a GFD. Fifty-seven percent of noncompliant children found it fairly difficult and 23% children found it difficult to maintain the diet. Our study also found that 66% of compliant patients were fairly responsible in maintenance of GFD as compared to 29% in noncompliant group. Active involvement of child is significantly related ($p \leq 0.001$) to compliance in our study; as in study by Chauhan et al in 2010. In the study by Anson et al (1990), 71% of compliant children's mothers and 44% of noncompliant children's mothers thought that the children shared responsibility in keeping diet.

Celiac disease patients usually experience relief after diagnosis. Experienced relief decreases with time; however, the acceptance of diet itself gradually increases. Experiencing most of the negative emotions also decreases with time, for example, those who live with GFD for more than 5 years experience difficulties and negative emotions less often. However, frustration and feeling of isolation that most people suffering from celiac disease experience often persist even several years after diagnosis. In first months after diagnosis, the same is true – women experience negative feelings more than men.

Psychosocial Impact on Parents

Twenty-five percent of parents of children in compliant group hardly felt a burden on their budget; 94% of parents with children in noncompliant group felt a fairly heavy or heavy burden on their budget and 75% of parents with children in compliant group felt a fairly heavy or heavy burden on their budget. Eighty-eight percent of parents of children in compliant group cooked more than once for their children as compared to 71% of parents of children in noncompliant group. In compliant group, 72% of parents believed that special diet was hardly a burden to the family, whereas in noncompliant group 57% parents felt it as a burden. Thirty-seven percent of parents of children in compliant group were not hesitant to discuss the child's condition and were interacting with other parents; these parameters were significantly lower in noncompliant group i.e., 14%. Sixty-five percent parents of compliant children and 72% parents of noncompliant children believed that the disease will interfere with their child's marriage.

Ninety-four percent of parents of children in noncompliant group and 75% of parents of children in compliant group also felt a financial burden by GFD. Seventy-one percent parents with children in noncompliant group cooked more than once for their children as compared to 88% of parents with children in compliant group. All these parameters had a significant correlation ($p \leq 0.001$) with compliance and show that noncompliance was most common in parents who consider special diet a burden to budget and family and hence they avoided cooking fresh meals for the children. Hence, cheap and easy to cook food will help these disease bearing families.

A study by Lee et al in 2007 also shows that financial burden of gluten-free food may affect compliance. Anson et al in 1990 also showed that 50% of noncompliant group parents considered diet a burden on family's budget. However, this did not significantly affected compliance in their study. In the study, 56% of compliant parents considered special diet a burden; however, compliant and noncompliant parents did not differ significantly with regard to this parameter. In study by Chauhan et al in 2010, 60.7% of compliant parents believed that special diet was hardly a burden; 84.6% in noncompliant group felt it as a burden. Olsson et al in 2008 and Lee et al in 2007, both have shown that availability of cheap gluten-free food was a significant factor affecting compliance. Increased availability of food items is needed for celiac patients.

Thirty-seven percent of parents of children in compliant group were not hesitant to discuss the condition with others and were able to interact with other parents in the clinic. This was significantly lower (14%) in noncompliant group. Rashid et al (2005) reported compliance rates of 95% in those children whose families were a part of celiac support group, Canadian Celiac Association (CCA). These families regarded CCA as the best source for the information provided to them about their child's disease.

CONCLUSIONS

These results will contribute to the current body of research by providing healthcare practitioners with a framework for better dietary instruction to ensure maximum adherence to GFD as well as psychosocial impact of celiac disease on parents and children suffering from celiac disease. Psychosocial aspects of celiac disease are not well-studied. Knowledge of psychological aspects and interventions can improve the acceptance and compliance concerning GFD.

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CHAT WITH DR KK

Kaun sa Stent?

Giant Mucocele Appendix: A Hybrid Laparoscopic Approach

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ABSTRACT

Appendicular mucocele is a rare but well-described clinicopathological diagnosis. It denotes dilatation of the appendix due to luminal obstruction by mucinous secretions. We report a case of a 71-year-old male patient with chronic kidney disease on regular hemodialysis with lump in right iliac fossa since 4 months with no history of pain abdomen. Ultrasonography abdomen followed by contrast enhanced computed tomography of abdomen suggested a diagnosis of mucocele appendix. Patient was taken up for laparoscopic appendectomy which revealed appendix that was hugely dilated with wide base impinging into the cecal wall. In order to prevent intraoperative rupture of mucocele and keeping malignancy as a differential, procedure was converted into open and cecum was repaired at the site of wide appendicular base. Surgery is the definitive treatment for mucocele and laparoscopic assist provides precision of dissection and minimizes injury to surrounding viscera. The aim of this publication is to demonstrate that laparoscopic surgery is as safe as traditional open approach. Also, surgeon should never hesitate to convert the procedure to open if there is risk of peritoneal spillage and doubt of malignancy in mind.

Keywords: Appendix, mucocele, malignancy, hemodialysis

Rokitansky was the first one to describe mucocele of appendix in 1842. It is an obstructive distention of the appendix due to mucoid secretions in the lumen, which can be either neoplastic or non-neoplastic. It is a rare entity with an incidence of 0.2-0.3% of all appendectomies and 8-10% of all appendiceal tumors. The clinical presentation ranges from asymptomatic to appendicitis like symptoms.

It can rarely present as intestinal obstruction. Four types of appendiceal mucocele have been explained on the basis of cause of obstruction: retention cysts, epithelial hyperplasia, mucinous cystadenoma and mucinous cystadenocarcinoma. Appendiceal mucocele can be either benign or malignant. A preoperative diagnosis is crucial in order to choose the correct operative management. The correct surgical management depends on size and location of lesion.

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Laparotomy is the traditionally recommended approach, but minimally invasive surgical approach seems to be as safe as open surgery.

CASE REPORT

A 71-year-old male patient admitted to dialysis unit of our hospital with diagnosis of chronic kidney disease, on routine hemodialysis, complained of lump in right iliac fossa since 4 months with no history of pain abdomen. Abdominal examination revealed a nontender cystic mobile mass around 5 × 6 cm with smooth surface and well-defined margins in the right iliac fossa without any guarding or rigidity. Digital rectal examination was normal. Patient's blood investigations were within normal limits except renal functions.

Ultrasonography (USG) abdomen was suggestive of cystic mass in right iliac fossa followed by abdominal computed tomography (CT) scan which revealed a large well-defined, tubular-shaped hypodense lesion of near fluid attenuation seen in right iliac fossa posterior to cecum. Appendix could not be seen separately. It was extending superiorly along the right pararenal space. The lesion showed saccular dilatation in its mid part with peripheral calcification of its walls. It measured 5.7 cm in diameter and 11.7 cm in length. The radiologist gave differential diagnosis of mucocele appendix, cystic lymphangioma, hydatid cyst, cystic mesothelioma Figure 1 shows CECT abdomen of patient showing mucocele appendix.

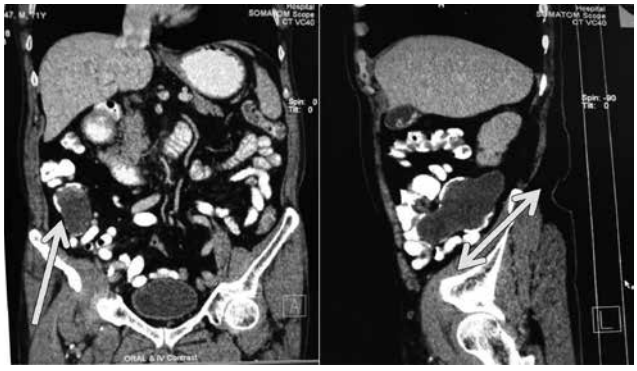

Figure 1. CECT abdomen of patient showing mucocele appendix.

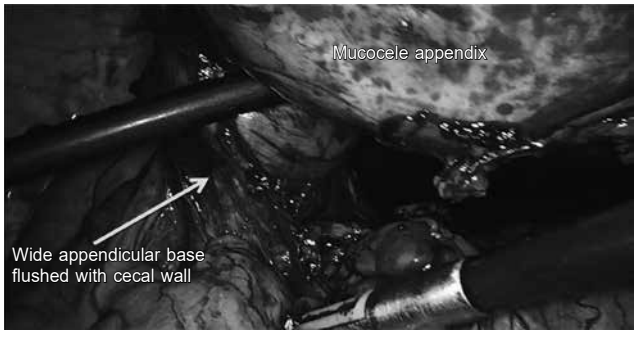

Figure 2. Laparoscopic view of mucocele appendix with wide base flushed with cecal wall.

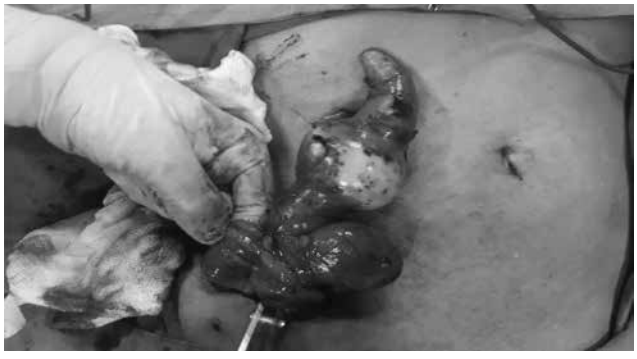

Figure 3. Mucocele appendix safely delivered out after giving skin incision.

Following informed consent, the patient was taken up for laparoscopic appendectomy after a cycle of hemodialysis. There was no evidence of peritoneal tumors, seedling or metastases. A grossly enlarged retrocecal appendix 15 cm long and 5 cm in diameter in the middle was found. Appendix was finger-like in distal part and ball-like in the middle with a wide base around 3 cm merging into the cecum (Fig. 2). Mesoappendix was swollen. The mesoappendix was coagulated and cut using bipolar cautery.

Since the appendix had larger diameter and in order to prevent iatrogenic rupture of mucocele and retrieve the specimen intact, procedure was converted into open. Port incision in right iliac fossa was widened and specimen delivered out as shown in Fig. 3. Appendicular base was held with intestinal clamp and appendix was cut. The mucocele had a lumen separate from cecal lumen (Fig. 4). Cecum was repaired in 2 layers using vicryl because appendix had a wide base of approximately 3 cm.

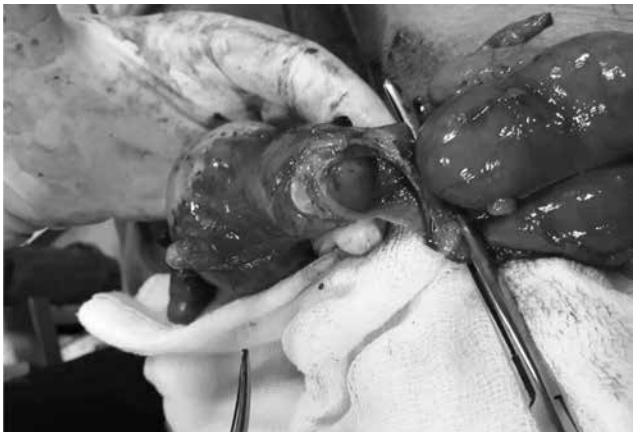

Figure 4. Mucocele with a lumen separate from cecum.

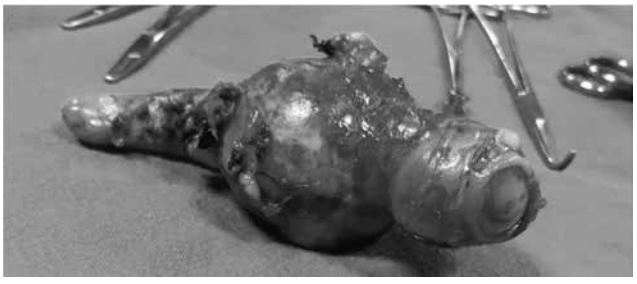

Figure 5. Gross specimen of mucocele appendix.

Postoperatively patient was started on oral liquids next day and the patient was discharged on Day 5 postoperatively in a good condition.

Grossly appendix measured 13 × 6 × 5 cm (Fig. 5), outer surface congested and cut surface showed dilated lumen filled with mucoid material with wall thickness 0.1-0.2 cm. Histopathological examination confirmed the final diagnosis of a benign mucocele appendix arising from the body of the appendix with free margins of resection. The patient remained well on regular follow-up visits over 2 months.

DISCUSSION

Clinical presentation of appendicular mucoceles is usually vague and furthermore, it can be asymptomatic in 25% of patients. Most commonly, patients present with right lower quadrant pain. Palpable masses have been reported in 50% of cases as seen in our patient. USG and CECT abdomen are most helpful in making

preoperative diagnosis. It helps in planning the choice of procedure and avoids complications. Appendicular mucocele can be benign or malignant and the World Health Organization (WHO) classifies them into four histological types: retention cysts, epithelial hyperplasia, mucinous cystadenoma and mucinous cystadenocarcinoma. Mucinous cystadenoma is the most common of the four types. Size is an important factor to consider when dealing with appendiceal mucocele. An appendiceal mucocele that is <2 cm is rarely malignant and those >6 cm are more often associated with cystadenoma and cystadenocarcinoma and a higher rate of perforation. Rupture of either benign or malignant types is associated with pseudomyxoma peritonei, which is associated with a higher morbidity and mortality. Benign appendiceal mucocele has a 91-100% 5-year survival rate, while malignant forms have a 5-year survival rate of 25%. Historically, open surgery was an established procedure but with the advent of minimally invasive surgery, laparoscopic appendectomy has become the gold standard procedure. However, in our case, after total laparoscopic dissection and releasing the mucocele up to the base, we had converted the procedure into open due to its wide base burying into cecum and to retrieve the specimen intact a wide incision was needed. The procedure could have been completed laparoscopically with the help of endostaplers but this would also have required a wide incision to deliver the specimen out. Moreover, it would have added to the cost of procedure with no added advantage. That's why a midway path was adapted by completing the dissection laparoscopically and repairing the cecal defect with standard two-layer technique. Combining both the techniques helped us to cut the procedure cost, deliver the intact specimen out and at the same time avail advantages of minimally invasive surgery. Careful consideration should be given to minimize rupture of the appendiceal mucocele when making a decision on approach of choice. Evidence suggests that appendectomy is curative for benign, grossly intact mucoceles.

CONCLUSION

Appendiceal mucocele is a rare condition. The clinical presentation is often non-specific and the clinician should have appendiceal mucocele in mind in patients presenting with long-term right lower quadrant pain, adnexal masses and acute appendicitis picture. Often, the diagnosis is made incidentally during imaging or surgical procedure. Radiological imaging and careful analysis is critical in planning management. Surgical resection is potentially curative and rupture of the mucocele should be avoided as it may lead to pseudomyxoma peritonei, a condition with high morbidity and mortality. The aim of this publication is to show that hybrid approach with laparoscopic assisted open appendectomy helps in maintaining safety, feasibility as well as cuts the cost of procedure.

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2018

DERMACON INTERNATIONAL 2019 INDIA

Indian Mission - Global Vision

17th - 20th Jan 2019
Clarks Exotica Convention Resort & Spa, Bengaluru.

KEY HIGHLIGHTS

- The 47th Annual conference of IADVL, with an international outreach program and with a theme of "Indian mission with global vision" will bring together.
- 9000 international & national delegates.
- Around 400 national & more than 60 international faculty and experts.
- Around 150 worldwide industry participations from reputed pharmaceutical companies, lasers & dermatological technologies.
- Well-structured plenary, orations, symposia, guest lectures, debates, national quiz, award papers, free communications and posters, apart from other official programs.
- Well planned courses & workshops on dermatosurgery, aesthetic dermatology, lasers and other procedural dermatology.

CONFERENCE & CME REGISTRATION FEES

	SLAB 2 1st May to 31st Aug 2018		SLAB 3 1st Sept to 15th Dec 2018		SLAB 4 / SPOT REG 16th Dec onwards	
Delegate Category	Conference Only	CME + Conference	Conference Only	CME + Conference	Conference Only	CME + Conference
IADVL Members	₹10000	₹12700	₹11500	₹14500	₹15000	₹19000
Post Graduates IADVL members	₹ 7000	₹ 8500	₹ 8000	₹ 9500	₹10000	₹12500
Accompanying Person	₹ 7000	₹ 8500	₹ 8000	₹ 9500	₹10000	₹12500
Workshop Registrations fees						
Workshops	₹ 2000	N/A	₹ 2500	N/A	₹ 3000	N/A
Target Course	₹ 3000	N/A	₹ 3500	N/A	₹ 4000	N/A

INTERNATIONAL EVENTS

- 5 Sister Society has been confirmed (South Africa, Singapore, Iran, SriLanka & SARAD) we are expecting more.
- DERMACON International Quiz Competition.
- Review Article Writing. (Alternative to Essay Competition Announced Earlier)
- DERMACON International Scholarships to Young Dermatologists.
- Global Leadership Session.
- Scholarship Program for International Delegates.

Register early

Dr S. Sacchidanand
Organising Chairperson

Dr R. Raghunatha Reddy
Organising Secretary

Dr Savitha
Treasurer

Dr Venkataram Mysore
International Liaison Chairperson

Dr D.A. Satish
Organising Co-Chair

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Newer and Emerging Topical Therapies in Dermatology

SATISH DA*, RADHIKA VK†, APARNA AD†

Some newer and emerging topical therapies in dermatology in recent times are discussed here.

FENTICONAZOLE

Fenticonazole is an imidazole antifungal agent used to treat fungal infections of the vagina (Vulvovaginal candidiasis). It is active against a range of organisms including dermatophytes, *Malassezia furfur* and *Candida albicans*. It is not recommended for usage in pregnancy and lactation. Side effects include local reactions like burning sensation, itching and rash, which are rare. Fenticonazole nitrate is available for topical use as a 2% cream. Fenticonazole acts by inhibition of the synthesis of aspartate (acid) proteinase, a virulence enzyme of *C. albicans* correlated with the adherence of the yeast to epithelial cells.

HYDROGEN PEROXIDE 40%

It is a proprietary formulation of a stabilized high concentration hydrogen peroxide solution that is the first and only US Food and Drug Administration (FDA) approved topical treatment for raised seborrheic keratoses. It acts by direct oxidation of organic tissues, local lipid peroxidation and generation of reactive oxygen species as well as generation of local concentrations of oxygen that are toxic to seborrheic keratoses cells. It is available as a 40% solution.

TRIFAROTENE 0.005% CREAM

Cellular effects of retinoids are mediated by two types of nuclear receptors: the retinoic acid receptor (RAR) and the retinoid X receptor (RXR), both of which are present in three isoforms (alpha, beta and gamma). Trifarotene is a fourth-generation topical retinoid, a potent and a selective RAR-gamma receptor agonist. This results in better efficacy and a favorable safety profile in acne and ichthyotic disorders. It has completed phase 3 trials in acne vulgaris in November 2017.

ATROPINE SULFATE

It is an anticholinergic agent and antimuscarinic agent (parasympatholytic). It is indicated in primary axillary hyperhidrosis, symptomatic eruptive syringomas and multiple eccrine hidrocystomas. Mechanism of action: Tumor cells differentiate towards dermal duct cells. Cells could get activated during cholinergic stimulation and atropine would antagonize the above action completely. The agent is available as atropine sulfate 1% ointment.

TIMOLOL MALEATE

It is a beta-blocker medication. It has been used in superficial and small infantile capillary hemangiomas and pyogenic granuloma. It causes constriction of the blood vessels, and reduces blood flow, resulting in reduction in size of cells, making the vessels softer. It is available as 0.5% gel.

THYMOL LOTION

Thymol is found in oil of thyme, extracted from *Thymus vulgaris* (plant). Mechanism of action: It alters the hyphal morphology, causes hyphal aggregates which results in lyses of the hyphal wall. It is indicated in Tinea infections and Candidal paronychia.

INDIRUBIN

It is an active ingredient in Indigo naturalis (Chinese medicine). It is a chemical compound (oily extract) produced as a by-product of bacterial metabolism. Lindioil is a refined formulation of Indigo naturalis. Mechanism of action: Indigo naturalis extract regulates proliferation and differentiation of epidermal keratinocytes, restores the epidermal barrier function and inhibits inflammatory reactions. It reduces subungual hyperkeratosis and onycholysis. It acts as an anti-inflammatory and as an antiangiogenic agent. Indications: Psoriasis.

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TOPICAL AGENTS IN THE PIPELINE FOR ACNE

Agents Targeting Sebum Production

- Topical antiandrogens:
  - Cortexolone-17 alpha-propionate (CB-03-01) is a monoester of cortexolone which has anti-androgen actions with no systemic side effects.
  - ASC-J9 cream causes degradation of the androgen receptor. It also causes reduction in the sebum production.
  - NVN-1000 (SB204) is a gel that causes release of nitric oxide with topical application. It decreases cutaneous androgen levels by inhibiting cytochrome P450, reduces 5-alpha reductase activity, thereby reducing sebocyte proliferation. It also exhibits antibacterial effects.
- Melanocortin receptor antagonists: JNJ 10229570, a melanocortin receptor 1 and 5 antagonist, reduces the size of sebaceous glands and the production of sebaceous lipids.
- Insulin-like growth factor 1 inhibitors: Epigallocatechin-3 gallate (EGCG), is a polyphenolic constituent in green tea. It inhibits 5-alpha reductase 1 activity, limiting dihydrotestosterone-dependent sebum production. It also exerts antimicrobial activity against *Propionibacterium acnes*.
- Acetylcholine inhibitors: Botulinum toxin inhibits the presynaptic acetylcholine release, reducing sebum production, pore size and skin oiliness.
- Acetyl coenzyme A carboxylase (ACC) inhibitors: They reduce synthesis of triglycerides, increasing oxidation of fatty acids. DRMO1 7.5% gel is under trial.

Agents that Normalize Abnormal Keratinization within the Pilosebaceous Unit

- Retinoic acid metabolism blocking agents: Talarozole inhibits cytochrome CYP26, increasing levels of retinoic acid, causing normalization of follicular epithelium, reducing comedo formation. 0.35% and 0.7% talarozole gel is formulated that causes less irritation.
- Monoclonal antibodies and anti-interleukin (IL)-1 alpha: RA-18C3, an IL-1 alpha monoclonal antibody is used to treat moderate-to-severe acne. Subcutaneous injections of 100 mg/200 mg of RA-18C3 are given on days 0, 21 and 42 for a total of 3 injections, showing significant improvement.

Agents that Work by Modulating the Inflammatory Response

Phosphodiesterase (PDE) inhibitors, inhibitors of IL-1 beta-mediated inflammatory response - Gevokizumab, Vitamin D analogs, Dapsone gel 5%.

BEXAROTENE GEL

Bexarotene gel 1% is effective in treating mild-to-moderate plaque psoriasis as monotherapy and in combination with narrow band ultraviolet B (NB-UVB). Mechanism of action: It selectively binds to nuclear retinoid X receptor.

EOSIN AND OIL OF CADE

Topical preparation of 2% eosin alone or in combination with oil of Cade is effective in the treatment of flexural/napkin psoriasis in children.

IVERMECTIN 1%

Cream formulation is effective in treating papulopustular rosacea and in periorificial dermatitis in children. In 2014, the US FDA approved this medication for the treatment of rosacea in adults. Ivermectin is efficacious in reducing inflammatory lesion counts and erythema. Mechanism of action: Ivermectin is a topical antiparasitic agent, a macrocyclic lactone with broad-spectrum activity against multiple parasitic organisms. Ivermectin eradicates Demodex mites that reside in the pilosebaceous units of patients with papulopustular rosacea. Anti-inflammatory effects of ivermectin are achieved through reducing neutrophil phagocytosis and chemotaxis, inhibition of inflammatory cytokines and upregulation of anti-inflammatory cytokine.

BRIMONIDINE TARTRATE (0.33% GEL)

It is the first topically effective agent for the treatment of facial erythema of rosacea having a rapid onset, sustained duration of effect for 12 hours, and good tolerability. It is applied once a day. Mechanism of action: It is a highly selective alpha-2 adrenergic receptor agonist and is 1000-fold more selective for the alpha-2 adrenergic receptor than the alpha-1 adrenergic receptor. It is a potent vasoconstrictor of the subcutaneous vessels, acts as an anti-inflammatory agent by reducing edema associated with rosacea. It is metabolized by the liver, and the major route of elimination is urinary excretion.

TAZAROTENE GEL (0.1%)

It has now been recommended in the treatment of moderate-to-severe facial atrophic acne scars.

IJCP SUTRA 516: Kangaroo Mother Care can be given, especially for low birth weight infants, wherein the baby is held in a special way stuck with the chest to provide skin to skin contact with the mother along with exclusive and frequent breastfeeding.

NEWER TOPICAL AGENTS FOR ATOPIC DERMATITIS

Targeting Janus Kinase

Tofacitinib inhibits JAK1 and JAK3, and inhibits TH2 signalling pathways. It also inhibits cytokines such as IL-4, attenuating JAK-STAT signalling in keratinocytes. It has a good safety profile, early onset of effect and local tolerability, with the most common adverse event being self-limited infections, (nasopharyngitis) and application site pain and pruritus. Ruxolitinib, a JAK1/JAK2 inhibitor, is currently under a phase 2 study in adult atopic dermatitis patients.

PDE4 Inhibitors

Crisaborole - It is a boron-based (phenoxybenzoxaborole), nonsteroidal, topical anti-inflammatory, PDE4 inhibitor, identified through the development and screening of various benzoxaborole derivatives. It is a small molecule, the first in its class to be approved by the FDA. Mechanism of action: Inhibition of PDE4 causes increase in the levels of cyclic AMP, thereby controlling inflammation. Once crisaborole reaches systemic circulation after topical application, it is metabolized to inactive metabolites thus limiting systemic exposure to crisaborole and systemic PDE4 inhibition. It is available as a 2% topical ointment. It is used in the treatment of mild-to-moderate atopic dermatitis in children 2 years and older.

Benvitimod

It is a nonsteroidal, anti-inflammatory molecule that was originally derived from the metabolites of nematodes. It causes reduced expression of pro-inflammatory cytokines, inhibition of T-cell viability and infiltration, thus diminishing skin inflammation. Adverse events are folliculitis, contact dermatitis and headache. Two phase 2 trials have been completed and published on the safety and efficacy of topical benvitimod treatment.

BIMATOPROST

It is a synthetic prostamide F2a analog. It exerts its effects by stimulating the prostamide receptor. Eyelash hair follicles are higher in the telogen phase, which supports the effectiveness of bimatoprost for hypotrichosis of the eyelashes. The US FDA approved the use of bimatoprost ophthalmic solution 0.03% in December 2008. The recommended application of bimatoprost 0.03% ophthalmic solution is one drop daily for 16 weeks. Indications: FDA-approved - Eyelash hypotrichosis; Other off label uses - Eyebrow hypotrichosis, androgenetic alopecia, alopecia areata; Others with minimal evidence - Vitiligo.

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■■■■

Medicolegal Corner

KK AGGARWAL*, IRA GUPTA†

REQUEST OF HCFI FOR FORMULATION OF LAW RELATING TO NATIONAL ESSENTIAL DEVICES AND DISPOSABLES IN INDIA HAS BEEN ACCEPTED BY THE CENTRAL GOVERNMENT

Heart Care Foundation of India (HCFI) had filed one RTI Application dated 22.01.2018 with National Pharmaceutical Pricing Authority, Department of Pharmaceuticals and also with Drug Controller General of India, Ministry of Health and Family Welfare asking them to provide following information:

- Is there any law relating to National Essential Medicine in India? If yes, please provide the details of the said law.
- Is there any policy of Ministry of Health relating to National Essential Medicine? If yes, please provide the copy of the said policy.
- Is there any list of National Essential Medicine in India? If yes, please provide the copy of the said list.

In response to the said RTI application dated 22.01.2018, the Ministry of Health and Family Welfare had given its reply dated 09.02.2018 wherein the Ministry of Health and Family Welfare had specifically stated that there is no separate list of National Essential Devices and Disposables and that the Ministry of Health and Family Welfare only issues the National List of Essential Medicines. The relevant portion of the reply dated 09.02.2018 is reproduced hereunder:

"*Reference is invited to your RTI application dated 22.01.2018 forwarded by Shri Arun Kumar Diwan, CPIO, NPPA vide letter No. 23011/07(1)/16-Admn/NPPA-RTI/Pt.-I dated 24.01.2018 (received on 31.01.2018) and it is informed that there is no separate list of National Essential Devices and Disposables. Ministry of Health and Family Welfare issues only the National List of Essential Medicines (NLEM).*"

Thereafter, the Directorate General of Health Services, Office of DCG (I) had also sent a reply dated 20.02.2018 thereby informing that they do not have any information relating to National Essential Devices and Disposables.

Thereafter, HCFI submitted one representation dated 08.06.2018 to Mr. Narendra Modi, Hon'ble Prime Minister of India, Mr. Jagat Prakash Nadda, Hon'ble Minister, Ministry of Health and Family Welfare and also to Mr. Ravi Shankar, Hon'ble Minister, Ministry of Law and Justice thereby **requesting them to recognize and prepare the List of National Essential Devices and Disposables in the same manner as National List of Essential Medicines is being recognized and prepared.**

The request of HCFI of formulation of law relating to National Essential Devices and Disposables in India is duly accepted by Hon'ble Ministers and accordingly, vide letter dated 07.08.2018, the Drug Controller General, Central Drugs Standard Control Organization, DGHS informed HCFI that Ministry of Health and Family Welfare has constituted a committee for preparing detailed guidelines and procedures for revision of National List of Essential Medicines and inclusion of Medical Devices, Medical Disposables and Medical Consumables and other products used for Health and Hygiene of general public in NLEM. The relevant portion of the letter dated 07.08.2018 is reproduced hereunder:

"This office has received a representation vide PMO ID No. PMOPG/D/2018/021845 enclosing your letter dated 08.06.2018 for taking appropriate action on the subject mentioned above.

In this regard, it is pertinent to mention here that Ministry of Health and Family Welfare vide F. No. 11053/923/2017-DRS dated 03.07.2018 has constituted a Standing National Committee on Medicines (SNCM) under the Chairmanship of Secretary, DHR and DG, ICMR.

As per the Term of reference of the SNCM, the committee will prepare detailed guidelines and procedures for revision of National List of Essential Medicines and suggest additions and deletion in the NLEM, Revision of NLEM 2-15, ***Inclusion of Medical Devices, Medical Disposables, Medical Consumables and other product used for Health and Hygiene of general public in NLEM****.*

It is important to mention herein that across the world, the National Essential Devices and Disposables is being recognized by law and are as important as a National List of Essential Medicines. Now, after the constitution of the said Standing National Committee on Medicines,

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in India also there will be National List of Essential Medical Devices, Medical Disposables, Medical Consumables and other product used for Health and Hygiene of general public in NLEM.

The National List of Medical Devices, Medical Disposables, Medical Consumables and other products used for Health and Hygiene will be beneficial for the general public for the following reasons:

- Guide safe and effective treatment of priority disease conditions of a population.
- Promote the rational use of Medical Devices, Medical Disposables, Medical Consumables and other products used for health and hygiene.
- Optimize the available health resources of a country.
- State governments can use this national list as a guide to prepare their list of essential Medical Devices, Medical Disposables, Medical Consumables and other products used for health and hygiene.
- There will be uniformity in prices of Medical Devices, Medical Disposables, Medical Consumables and other products used for health and hygiene included in the national list.

DELHI HIGH COURT: ADVISORY DATED 28.08.2018 OF CENTRAL GOVERNMENT BANNING ENDS IS NOT BINDING ON STATES/UT

In the matter titled as "*Piush* Ahluwalia versus Union of India" the Hon'ble High Court of Delhi vide order dated 14.11.2018 has held that the advisory dated 28.08.2018 issued by the Central Government is not binding and it would be open to the respective states and union territories to take an informed decision in this regard. The Hon'ble Court has further held that the petitioner is at liberty to challenge any action that may be taken by the State Governments/Union Territories in accordance with law.

The said case was filed by the petitioner impugning an advisory dated 28.08.2018 issued by the respondent, whereby the States/Union Territories have been advised to ensure that electronic nicotine delivery systems (ENDS) including e-Cigarettes, Head-Not-Burn Devices, Vape, e-Sheesha, e-Nicotine Flavored Hookah and the like devices that enable nicotine delivery are not sold, manufactured, distributed, traded, imported and advertised in their jurisdiction for the purpose and the manner as may be approved in. The said advisory also indicates that certain states have prohibited manufacture, distribution and import and sale of ENDS.

In the said case, the petitioner had contended that the said advisory is violative of the petitioner's fundamental rights under Article 14, 19 and 21 of the Constitution of India inasmuch as it deprives the petitioner from exercising its discretion to use the aforesaid products. According to the petitioner, the said products are less harmful than cigarettes and are used by smokers to quit the habit of smoking. The petitioner has also referred to the study carried out by Executive Agency of the Department of Health and Social Care, Public Health England, which indicates that e-cigarettes are 95% safer than smoking paper rolled cigarettes (PRCs).

After hearing the arguments from both the parties the court had held that:

> *6. This Court does not consider that any interference with the said advisory is warranted, as the same is an advisory which is required to be considered by the State Governments/Union Territories. The said advisory is not binding and it would be open to the respective states and Union Territories to take an informed decision in this regard. In any event, the petitioner is at liberty to challenge any action that may be taken by the State Governments/Union Territories in accordance with law.*

WHAT ARE THE MCI GUIDELINES FOR CLINICAL RESEARCH?

Regulation 6.8 "Code of conduct for doctors in their relationship with pharmaceutical and allied health sector industry" of the MCI Code of Ethics Regulations 2002 has issued the following guidelines regarding clinical research or trials:

6.8.1 (e) Medical Research: A medical practitioner may carry out, participate in, work in research projects funded by pharmaceutical and allied healthcare industries. A medical practitioner is obliged to know that the fulfillment of the following items (i) to (vii) will be an imperative for undertaking any research assignment/project funded by industry - for being proper and ethical. Thus, in accepting such a position a medical practitioner shall:

(i) Ensure that the particular research proposal(s) has the due permission from the competent concerned authorities.

(ii) Ensure that such a research project(s) has the clearance of National/State/Institutional Ethics Committees/Bodies.

(iii) Ensure that it fulfils all the legal requirements prescribed for medical research.

(iv) Ensure that the source and amount of funding is publicly disclosed at the beginning itself.

(v) Ensure that proper care and facilities are provided to human volunteers, if they are necessary for the research project(s).

(vi) Ensure that undue animal experimentations are not done and when these are necessary they are done in a scientific and a humane way.

(vii) Ensure that while accepting such an assignment a medical practitioner shall have the freedom to publish the results of the research in the greater interest of the society by inserting such a clause in the MoU or any other document/agreement for any such assignment.

IS THE CONSENT GIVEN FOR A DIAGNOSTIC PROCEDURE ALSO VALID AS CONSENT FOR THERAPEUTIC TREATMENT?

Consent given for a diagnostic procedure is not a valid consent for therapeutic treatment as the diagnostic procedure and therapeutic treatment are different and separate consent for both are required. The registered medical practitioner, hospital should always inform the patient and his/her relatives about the diagnostic procedure as well as therapeutic treatment separately and should take informed written consent for both separately.

The **3 Judges Constitution Bench of Hon'ble Supreme Court of India** in the landmark judgment titled as "**Samira Kohli versus Prabha Manchanda, AIR 2008 SC 1385** has held that:

> *"32 We may now summarize principles relating to consent as follows:*
>
> *(iii) Consent given only for a diagnostic procedure, cannot be considered as consent for therapeutic treatment. Consent given for a specific treatment procedure will not be valid for conducting some other treatment procedure. The fact that the unauthorized additional surgery is beneficial to the patient, or that it would save considerable time and expense to the patient, or would relieve the patient from pain and suffering in future, are not grounds of defence in an action in tort for negligence or assault and battery. The only exception to this rule is where the additional procedure though unauthorized, is necessary in order to save the life or preserve the health of the patient and it would be unreasonable to delay such unauthorized procedure until patient regains consciousness and takes a decision."*

WHEN IS IT A CASE OF NEGLIGENCE?

If no inquiry or experts are required, then it is a clear case of negligence. In such cases, medical negligence is established based on the doctrine of *res ipsa loquitur* (the thing speaks for itself).

- If there is any evidence of *prima facie* case, never events or *mens rea* (criminal intent).
- If there is violation of any of the following SCI recommendations (Martin F. D'Souza vs. Mohd. Ishfaq, 3541 of 2002, dated 17.02.2009)
  - Current practices, infrastructure, paramedical and other staff, hygiene and sterility
  - No prescription should ordinarily be given without actual examination
  - The tendency to give prescription over the telephone, except in an acute emergency, should be avoided
  - A doctor should not merely go by the version of the patient regarding his symptoms, but should also make his own analysis including tests and investigations where necessary
  - A doctor should not experiment unless necessary and even then he should ordinarily get a written consent from the patient
  - An expert should be consulted in case of any doubt; Full record of the diagnosis, treatment, etc. should be maintained.
  - Not maintaining complete records of diagnosis, treatment, etc.
- If there is any violation of established treatment guidelines with no consent.
- If informed consent was not taken.
- If a copy of medical records were not given in time despite request by the patient or authorized person.
- If the act in question is a willful act.
- If the patient was neglected at any time or not attended to in an emergency.

CAN AN INSTITUTION RUN BY A PHYSICIAN BE ADVERTISED? SHOULD YOU ADVERTISE YOUR MEDICAL PRACTICE?

As per the provisions of **Clause 6.1.1 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002,** soliciting of patients directly or indirectly by the physician or group of physicians or by institution or organization is unethical.

Further, as per the provisions of Clause 6.1.1 of Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002, the medical practitioner is allowed to make formal announcement in the press about his starting practice, change of type of practice, change in address, etc. The provisions of Clause 6.1.1 are reproduced hereunder:

> *"6.1.1 Soliciting of patients directly or indirectly, by a physician, by a group of physicians or by institutions or organizations is unethical. A physician shall not make use of him/her (or his/her name) as subject of any form or manner of advertising or publicity through any mode either alone or in conjunction with others which is of such a character as to invite attention to him or to his professional position, skill, qualification, achievements, attainments, specialties, appointments, associations, affiliations or honors and/or of such character as would ordinarily result in his self-aggrandizement. A physician shall not give to any person, whether for compensation or otherwise, any approval, recommendation, endorsement, certificate, report or statement with respect of any drug, medicine, nostrum remedy, surgical, or therapeutic article, apparatus or appliance or any commercial product or article with respect of any property, quality or use thereof or any test, demonstration or trial thereof, for use in connection with his name, signature, or photograph in any form or manner of advertising through any mode nor shall he boast of cases, operations, cures or remedies or permit the publication of report thereof through any mode. A medical practitioner is however permitted to make a formal announcement in press regarding the following:*
>
> - *On starting practice.*
> - *On change of type of practice.*
> - *On changing address.*
> - *On temporary absence from duty.*
> - *On resumption of another practice.*
> - *On succeeding to another practice.*
> - *Public declaration of charges."*

Also, as per the provisions of **Clause 6.1.2 of Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002**, printing of self-photograph, or any such material of publicity in the letterhead or on sign board of the consulting room or any such clinical establishment shall be regarded as acts of self-advertisement and unethical conduct on the part of the physician. However, printing of sketches, diagrams, picture of human system shall not be treated as unethical.

Further as per the provisions of **Clause 7.11 of Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002**, the physician is not allowed to contribute to lay press articles and give interviews regarding diseases and treatments which may have the effect of advertising himself or soliciting practices; but is open to write to the lay press under his own name on matters of public health, hygienic living or to deliver public lectures, give talks on the radio/TV/internet chat for the same purpose and send announcement of the same to lay press.

The provisions of **Clause 7.12 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002** allows an institution run by a physician for a particular purpose to be advertised but with some restrictions. The provision of Clause 7.12 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002 is reproduced hereunder:

> *"7.12: An institution run by a physician for a particular purpose such as a maternity home, nursing home, private hospital, rehabilitation centre or any type of training institution, etc. may be advertised in the lay press, but such advertisements should not contain anything more than the name of the institution, type of patients admitted, type of training and other facilities offered and the fees."*

Further, **vide judgment dated 10.01.2014 as passed by the Hon'ble High Court of Delhi** in the matter titled as **"Max Hospital, Pitampura vs. MCI,"** it has been categorically observed by the Hon'ble High Court that MCI has no jurisdiction to pass any order against the hospital under the provisions of 2002 regulations. Thus, as hospitals are not covered under MCI Act and the provisions of Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002 are not applicable on hospitals, so the hospitals can advertise themselves.

In view of the above, it is opined that an institution run by a physician for a particular purpose like maternity home, nursing home, private hospital can be advertised but such advertisement should not contain anything more than the name of the institution, type of patients admitted, type of training and other facilities offered and fees.

The physician or the medical practitioner cannot advertise his medical practice which has the effect of advertising himself or soliciting practices.

ARE LIFE-SAVING MACHINES, DEVICES AND EQUIPMENTS LIKE CPAP MACHINE COVERED UNDER INSURANCE POLICY?

Life-saving machines and devices such as pacemaker, CPAP, BiPAP, orthopedic implants, intracardiac valve

replacements, vascular stents, relevant laboratory diagnostic tests, X-ray and such similar implants and machines are often prescribed by registered medical practitioners to their patients.

Such machines are duly covered under the insurance policy/Mediclaim policy.

If any patient is advised to use CPAP machine for his treatment and such patient has an insurance policy/ Mediclaim policy in his/her name, then the insurance company has to make the payment of the cost of CPAP machine to such patient as the same is covered by the insurance policy. Even if there is no specific clause in insurance policy/mediclaim policy stating that the CPAP machine is covered under the insurance policy, then also the insurance company has to pay the patient for the cost of CPAP machine as the same is life-saving machine and without it, the treatment of the patient is not complete.

All the doctors, registered medical practitioners, hospitals, nursing homes, etc. should educate their patient that the CPAP machine being a life-saving machine is duly covered by the insurance policy/Mediclaim policy obtained by them and they should immediately contact their insurance company for claiming the reimbursement of the cost of the said machine.

In numerous cases, the National Consumer Dispute Redressal Commission and State Consumer Dispute Redressal Commission of Delhi have held that the CPAP machine being a life-saving machine is completely covered by the insurance policy and the claim of the patient for the same has to be paid by the insurance company:

- "New India Assurance Co. Ltd. versus Ghanshyamdas A. Thakur," order and judgment dated 07.02.2014 passed by Hon'ble National Consumer Disputes Redressal Commission.
- Narender Kumar Jain versus United India Insurance Company Limited, Hon'ble State Consumer Dispute Redressal Commission of Delhi.
- "The New India Assurance Co. Ltd. & Anr. versus Mrs. Sonali Sareen & Anr." Delhi State Consumer Disputes Redressal Commission order dated 09.12.2014.

THE PATIENT WAS NOT GETTING CURED. CAN THIS BE TERMED AS MEDICAL NEGLIGENCE?

No doctor can give 100% guarantee about the treatment or surgery. The only assurance which a doctor can give or can be understood to have given by implication is that he is possessed of the requisite skill in that branch of profession which he is practicing and while undertaking the performance of the task entrusted to him he would be exercising his skill with reasonable competence.

The Hon'ble Apex Court in various judgments has duly held that no guarantee is given by any doctor or surgeon that the patient would be cured.

1. In the matter titled as "**P. B. Desai versus State of Maharashtra, AIR 2014 SC 795**, the Hon'ble Apex Court has held that:

> *"39. It is not necessary for us to divulge this theoretical approach to the doctor-patient relationship, as that may be based on model foundation. Fact remains that when a physician agrees to attend a patient, there is an unwritten contract between the two. The patient entrusts himself to the doctor and that doctor agrees to do his best, at all times, for the patient. Such doctor-patient contract is almost always an implied contract, except when written informed consent is obtained. While a doctor cannot be forced to treat any person, he/she has certain responsibilities for those whom he/she accepts as patients. Some of these responsibilities may be recapitulated, in brief:*
>
> *a. to continue to treat, except under certain circumstances when doctor can abandon his patient;*
>
> *b. to take reasonable care of his patient;*
>
> *c. to exhibit reasonable skill: The degree of skill a doctor undertakes is the average degree of skill possessed by his professional brethren of the same standing as himself. The best form of treatment may differ when different choices are available. There is an implied contract between the doctor and patient where the patient is told, in effect, "Medicine is not an exact science. I shall use my experience and best judgment and you take the risk that I may be wrong. I guarantee nothing.*
>
> *d. Not to undertake any procedure beyond his control: This depends on his qualifications, special training and experience. The doctor must always ensure that he is reasonably skilled before undertaking any special procedure/ treating a complicated case.*
>
> *e. Professional secrets: A doctor is under a moral and legal obligation not to divulge the information/knowledge which he comes to learn in confidence from his patient and such a communication is privileged communication."*

2. In the matter **Malay Kumar Ganguly vs. Sukumar Mukherjee & Ors. AIR 2010 SC 1162, the Hon'ble Supreme Court of India** has held that:

   "*INDIVIDUAL LIABILITY OF THE DOCTORS: There cannot be, however, by any doubt or dispute that for establishing medical negligence or deficiency in service, the courts would determine the following:*

   i. *No guarantee is given by any doctor or surgeon that the patient would be cured.*

   ii. *The doctor, however, must undertake a fair, reasonable and competent degree of skill, which may not be the highest skill.*

   iii. *Adoption of one of the modes of treatment, if there are many, and treating the patient with due care and caution would not constitute any negligence.*

   iv. *Failure to act in accordance with the standard, reasonable, competent medical means at the time would not constitute a negligence. However, a medical practitioner must exercise the reasonable degree of care and skill and knowledge which he possesses. Failure to use due skill in diagnosis with the result that wrong treatment is given would be negligence.*

   v. *In a complicated case, the court would be slow in contributing negligence on the part of the doctor, if he is performing his duties to be best of his ability.*

   Bearing in mind the aforementioned principles, the individual liability of the doctors and hospital must be judged."

3. In the landmark judgment of **Jacob Mathew Petitioner vs. State of Punjab & Anr. 2005 (3) CPR 70 (SC) the Hon'ble Supreme Court** has held that:

   "*Para 28: No sensible professional would intentionally commit an act or omission which would result in loss or injury to the patient as the professional reputation of the person is at stake. A single failure may cost him dear in his career. Even in civil jurisdiction, the rule of res ipsa loquitur is not of universal application and has to be applied with extreme care and caution to the cases of professional negligence and in particular that of the doctors. Else it would be counterproductive.* ***Simply because a patient has not favourably responded to a treatment given by a physician or a surgery has failed, the doctor cannot be held liable per se by applying the doctrine of res ipsa loquitur."***

4. In the matter titled as **"Martin F. D'Souza versus Mohd. Ishfaq, 2009(3) SCC 1"** the Hon'ble Supreme Court has held that:

   "Para 124: "It must be remembered that sometimes despite their best efforts the treatment of a doctor fails. For instance, sometimes despite the best effort of a surgeon, the patient dies. That does not mean that the doctor or the surgeon must be held to be guilty of medical negligence, unless there is some strong evidence to suggest that he is."

5. In the matter titled as **"Lok Nayak Hospital versus Prema, RFA No. 56/2006"** the Hon'ble High Court of Delhi vide judgment dated 06.08.2018 has held that:

   "*8. Firstly, it is to be noted that the only allegation of negligence alleged by the respondent/plaintiff against the appellant/defendant is that the tubectomy/ sterilization operation failed.* ***Since medically there is never a 100% chance of success in sterilization operations, the mere fact that the operation was not successful, that by itself cannot be a reason to hold the appellant/defendant and its doctors guilty of negligence.*** *This aspect is no longer res integra and is so held by a Division Bench of this Court in the case of Smt. Madhubala Vs. Govt. of NCT of Delhi, 118 (2005) DLT 515 (DB).*

■■■■

Abdominal Aortic Aneurysm: The Number 5

- Aortic flow should be 50 cm/s slower than flow in the peripheral arteries.
- AAA surgery when the diameter is >5 cm or there is progression of >0.5 cm/year
- Aneurysm size is one of the strongest predictors of the risk of rupture, with risk increasing markedly at aneurysm diameter >5.5 cm.
  - Diameter between 4.0-4.9 cm: Less than 5% risk of rupture
  - Diameter >5 cm: 5% risk.

Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

HEART CARE FOUNDATION OF INDIA
A Not-For-Profit Organisation

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

E-219, Greater Kailash, Part I, New Delhi - 110048 E-mail: heartcarefoundationfund@gmail.com Helpline Number: +91 - 9958771177

"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

Padma Shri, Dr BC Roy National & DST National Science Communication Awardee

Governing Council Members

Sumi Malik
Vivek Kumar
Karna Chopra
Dr Veena Aggarwal
Veena Jaju
Naina Aggarwal
Nilesh Aggarwal
H M Bangur

Advisors

Mukul Rohtagi
Ashok Chakradhar

Executive Council Members

Deep Malik
Geeta Anand
Dr Uday Kakroo
Harish Malik
Aarti Upadhyay
Raj Kumar Daga
Shalin Kataria
Anisha Kataria
Vishnu Sureka
Rishab Soni

This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

http://heartcarefoundationfund.heartcarefoundation.org

Medtalks with Dr KK Aggarwal

"When nations work together, hope prevails and collective solutions can be found", says UN chief. From conflict and economic downturn to disease and climate change, global problems require "more than ever" a strengthening of international cooperation, United Nations Secretary-General António Guterres told world leaders at the Paris Peace Forum recently, commemorating 100 years since the end of the First World War.

The American Heart Association (AHA) looks beyond heart disease and stroke to improve overall health and well-being globally: As heart disease and stroke continue to claim more lives worldwide than all other causes, the AHA is boldly growing beyond borders and its core business to advance health and well-being across the globe. It's all part of the Association's new mission: To be a relentless force for a world of longer, healthier lives. "*We are creating an Emerging Strategies and Ventures group to start stand-alone ventures in areas such as precision medicine, data as an asset, health technology, drug discovery, venture capital investing and brain health and healthy aging*", said Chief Executive Officer Nancy Brown.

Every bite of burger boosts harmful greenhouse gases: Even though meat production is known to be a major contributor to climate change and environmental destruction, worldwide demand for meat continues to rise, said UN environment agency, UNEP, in a statement.

According to the World Economic Forum, the beef and dairy industry is responsible for more greenhouse gas emissions than the world's biggest oil companies, with the combined emissions of the top meat and dairy companies exceeding those of highly industrialized nations such as Germany or the UK. Despite this fact, the global meat industry continues to grow, with the Food and Agriculture Organization (FAO) predicting a 76% increase in global meat consumption by 2050: more meat will be eaten than ever before in our history… (*UN*)

Cardiac arrest survival higher in states with required high school CPR training: Required CPR education in high school may lead to higher bystander CPR and cardiac arrest survival rates, according to preliminary research presented in Chicago at the American Heart Association's Resuscitation Science Symposium 2018. Analysis of data from more than 1,09,668 out-of-hospital cardiac arrests patients revealed that 41.3% of people who suffered cardiac arrest outside of a hospital received bystander CPR before emergency medical services arrived, compared to 36.1% in states without CPR education laws enacted.

A position statement on management of individuals with patellofemoral pain by the National Athletic Trainers' Association recommends a multimodal plan of care, which should include gluteal- and quadriceps-strengthening exercises, patient education and activity modification. Referral for surgical intervention should be considered only if the patient presents with either evident lateral patellar compression or patellar instability and has failed to improve despite exhaustive rehabilitation attempts (*Journal of Athletic Training*. Sept. 2018).

Parents shouldn't worry if their infant doesn't sleep through the night by 6-12 months of age, says a new study reported online Nov. 12, 2018 in the journal *Pediatrics*. As per the authors, a large percentage of developmentally normal, healthy babies don't reach that milestone by 6 months of age, or even a year old. Sleeping through the night was defined as either 6 or 8 hours of sleep without waking up.

Smokers with peripheral artery disease (PAD) would do well to quit smoking, but many doctors may not be giving them enough support to do it, suggests a study titled "*Underutilization of evidence-based smoking cessation support strategies despite high smoking addiction burden in peripheral artery disease specialty care: Insights from the International PORTRAIT Registry*" published in the *Journal of the American Heart Association*. The researchers examined data on 1,272 patients in Australia, the Netherlands and the US with new or worsening PAD symptoms. Overall, one third of patients were current smokers, but fewer than one in five were referred to smoking cessation counseling and just one in 10 were prescribed a medication to help them quit… (*Medscape*)

Proper delegation can help avoid litigation: In the complicated maze of medical referrals and authorizations, a physician's reliance on a competent staff to work with benefit providers to complete any necessary paperwork is eminently reasonable. In the end, though, the patient will look to the physician as the one ultimately responsible for completing the task. **Even if you think paperwork has been completed, it's**

best to check to avoid errors in patient care. Ensure that everyone in the practice understands their duties and responsibilities up front, and review procedures regularly to solidify understanding of all necessary tasks… (*Medscape*)

Adolescent obesity is associated with up to a fourfold increased risk of future pancreatic cancer. Overweight and even higher weight within the "normal" weight range in men may increase pancreatic cancer risk in a graded manner, according to a study published in the journal *Cancer*.

US Department of Health and Human Services (HHS) includes preschoolers for the first-time in the 2nd edition of its guideline on physical activity for Americans, which says that regular physical activity has health benefits for everyone, regardless of age, sex, race, ethnicity or body size. The recommendations published Nov.12, 2018 in *JAMA* are:

- Preschool-aged children (3 through 5 years) should be physically active throughout the day to enhance growth and development.
- Children and adolescents aged 6 through 17 years should do 60 minutes or more of moderate-to-vigorous physical activity daily.
- Adults should do at least 150 minutes to 300 minutes a week of moderate-intensity, or 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. They should also do muscle-strengthening activities on 2 or more days a week.
- Older adults should do multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities.
- Pregnant and postpartum women should do at least 150 minutes of moderate-intensity aerobic activity a week.
- Adults with chronic conditions or disabilities, who are able, should follow the key guidelines for adults and do both aerobic and muscle-strengthening activities.

Of all human diseases, 60% originate in animals; "One Health" is the only way to keep antibiotics working, says WHO: "Human, animal and environment health are all equally responsible for the correct use of antimicrobials and to avert the threat of antimicrobial resistance," said Dr Zsuzsanna Jakab, WHO Regional Director for Europe. "As we strive to ensure that antibiotics are rightly used in the community and in healthcare settings, one sector alone will not solve the problem. A 'One Health' approach brings together professionals in human, animal, food and environment health as one force, and as such is the only way to keep antibiotics working. I call on all European countries to secure the highest commitment to this approach from the whole of society and the whole of government." (*WHO Europe*)

Polypharmacy and legacy prescribing raise risks for drug interactions as well as adverse reactions to individual medications. Such effects include falling, poor nutrition and altered cognition. With more prescriptions to manage daily, patients may face adherence challenges and risk skipping or taking extra doses. "Legacy prescribing" is the prescribing of drugs for a longer period than is typically needed to treat a condition. The primary care setting is a source of legacy prescribing because it is the coordinating center and gatekeeper for managing patients with multiple morbidities, Dee Mangin, MBChB, DPH, FRNZCG, from McMaster University in Ontario and the University of Otago in Christchurch, New Zealand and colleagues write in the *Annals of Family Medicine*… (*Medscape*)

Cancer appears to be overtaking heart disease as the leading cause of death in the US, especially in higher-income populations, according to an observational study of 12 years of county mortality records published in the *Annals of Internal Medicine*.

Antibiotics are used far more in some countries than in others, a survey "WHO Report on Surveillance of Antibiotic Consumption" by the World Health Organization showed recently, suggesting that urgent action was needed to slash unnecessary consumption of the medicines. The survey looked at antibiotic use in 65 countries and found the Netherlands used 9.78 defined daily doses (DDD)/1,000 people, while Britain used twice as much and Turkey almost twice as much again, at 38.18 DDD/1,000 inhabitants. Iran's consumption was similar to Turkey's, while Mongolia's was the highest of all among the countries surveyed, at 64.41 DDD/1,000 people. Collecting the data is vital for tackling antimicrobial resistance, the extremely worrying trend of bacterial infections becoming immune to antibiotics. The lowest score was for Burundi, with just 4.44 DDD/1,000 people, which the WHO said reflected limited data. A low score could also suggest that consumption is too low, leaving the population at risk of infectious diseases… (*Deccan Chronicle*)

All adults should be screened for unhealthy alcohol use, says USPSTF as it recommends screening for unhealthy alcohol use in primary care settings in

adults 18 years or older, including pregnant women, and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce unhealthy alcohol use (B recommendation) in a new updated statement published Nov. 13, 2018 in *JAMA*.

Some definitions on unhealthy alcohol use

- USPSTF: "*Unhealthy alcohol use*" is a spectrum of behaviors, from risky drinking to alcohol use disorder (AUD) (e.g., harmful alcohol use, abuse, or dependence). "*Risky*" *or*" *hazardous*" alcohol use means drinking more than the recommended daily, weekly or per-occasion amounts, resulting in increased risk for health consequences but not meeting criteria for AUD.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA): "*Risky use*" as exceeding the recommended limits of 4 drinks/day (56 g/d based on the US standard of 14 g/drink) or 14 drinks per week (196 g/d) for healthy adult men aged 21-64 years or 3 drinks/day or 7 drinks/week (42 g/d or 98 g/week) for all adult women of any age and men 65 years or older.
- American Society of Addiction Medicine (ASAM): "*Hazardous use*" is alcohol use that increases the risk of future negative health consequences.

A 5-minute neck scan, which analyzes the pulse of blood vessels in the neck, could predict a person's risk of developing dementia a full decade before symptoms emerge, say researchers from University College London. Their findings were presented at the American Heart Association's annual scientific conference.

Malaria control programs in Brazil, Paraguay and Suriname (as below) have received the "Malaria Champions of the Americas" award, given out each year by the Pan American Health Organization (PAHO) and its partners to initiatives that contribute to eliminating the disease in the region (PAHO/WHO).

- Suriname's Malaria program, for introducing a solid, people-centered approach model to health, particularly focused on migrant miners and indigenous communities. The initiative has created local capacities and has led to improvements in diagnosis, treatment and vector control. It has also integrated health services and has sought innovative operational and technological solutions.
- The Machadinho D'Oeste Municipal Malaria Control program, also in Brazil, that implemented a series of strategies that led to greater access to diagnosis and treatment, the use of mosquito nets and a 44% reduction in cases of malaria between 2016 and 2017.
- The Alto Río Solimões malaria program in Brazil, for its efforts to control malaria in indigenous areas. This local program managed to reduce cases of the disease by 70% since 2015 in a hard-to-access area, where 70,000 people live in 13 villages along the banks of the river.
- The National Malaria Control Program in Paraguay, which has provided universal access to malaria diagnosis and treatment. The work of the program has ensured that the country has not registered any autochthonous cases of malaria since 2011. In June 2018, Paraguay became the first country in the Region in 45 years to obtain official WHO certification for having eliminated malaria.

  An estimated 12 million people may be victims of statelessness the impact of which is "immediate and can be dire", the UN refugee agency (UNHCR). Echoing that message, UNHCR Chief Filippo Grandi appealed for "decisive action" from governments to eliminate the problem, noting that it is the right thing to do, "humanly, ethically and politically". Stateless people "still face huge barriers to exercising fundamental human rights", such as education, medical care or legal employment, the High Commissioner said, before calling for States to tackle discrimination in nationality laws, which is regarded as the biggest driver of the problem... (*UN*)

'Make healthy choices' to prevent and manage chronic diabetes, says WHO: The global prevalence of adult diabetes has nearly quadrupled since 1980, the World Health Organization (WHO) said recently on the World Diabetes Day, with the call to "eat healthily, be physically active and avoid excessive weight gain." Diabetes is a major cause of blindness, kidney failure, heart attack, stroke and lower limb amputation," said WHO, noting that about 422 million adults have the disease – a number that has been increasing steadily over the last three decades. WHO Spokesperson Fadela Chaib said that was largely due to changes in lifestyle: "We are eating more heavy foods, full of fat and sugar; we are less physically active; and we have a more sedentary way of living."

A set of guiding principles from an American Medical Association council on assessing the competency of senior/late career physicians failed to gain adoption at the AMA's interim meeting in

National Harbor, Maryland in the US. In a floor vote of 281-222 recently, delegates sent the report back to the Council on Medical Education, which issued the guiding principles. Some hospitals and health systems already require competency testing by older physicians, but there are currently no standards for these tests. In committee discussions, Marlys Witte, MD, a delegate of the Organized Medical Staff section, questioned how one major benefit of aging "wisdom" could be measured… (*Medpage Today*).

Record number of tick-borne diseases reported in US in 2017: New data from the Centers for Disease Control and Prevention (CDC) show tick-borne diseases are again on the rise. In 2017, state and local health departments reported a record number of cases of tick-borne disease to CDC. Cases of Lyme disease, anaplasmosis/ehrlichiosis, spotted fever rickettsiosis (including Rocky Mountain spotted fever), babesiosis, tularemia and Powassan virus disease all increased—from 48,610 cases in 2016 to 59,349 cases in 2017. These 2017 data capture only a fraction of the number of people with tick-borne illnesses. Under-reporting of all tickborne diseases is common, so the number of people actually infected is much higher. While the reason for this increase is unclear, a number of factors can affect tick numbers each year, including temperature, rainfall, humidity, and host populations such as mice and other animals … (CDC)

Steps to protect against tick-borne diseases (CDC)

- Using Environmental Protection Agency (EPA)-registered insect repellents containing DEET, picaridin, IR3535, Oil of Lemon Eucalyptus (OLE), para-menthane-diol (PMD) or 2-undecanone. Always follow product instructions.
- Treating clothing and gear with products containing 0.5% permethrin. Permethrin can be used to treat boots, clothing and camping gear and remain protective through several washings.
- Checking your body and clothing for ticks upon return from potentially tick-infested areas, including your own backyard. Use a hand-held or full-length mirror to view all parts of your body. Place tick-infested clothes in a dryer on high heat for at least 10 minutes to kill ticks on dry clothing after you come indoors.
- Showering soon after being outdoors. Showering within 2 hours of coming indoors has been shown to reduce your risk of getting Lyme disease and may be effective in reducing the risk of other tick-borne diseases. Showering may help wash off unattached ticks and is a good time to do a tick check.

London's low-emission zone ineffective in improving child lung health, suggest a new annual cross-sectional study published November 14, 2018 in *The Lancet*. Within London's LEZ, a smaller lung volume in children was associated with higher annual air pollutant exposures. There was no evidence of a reduction in the proportion of children with small lungs over this period, despite small improvements in air quality in highly polluted urban areas during the implementation of London's LEZ, which are areas with a daily charge for vehicles that do not meet emission requirements were introduced in 2008 and have led to small improvements in nitrogen dioxide and nitrogen oxide levels, found in diesel emissions.

Evidence suggests 'viral association' for acute flaccid myelitis (AFM), says CDC. Ninety-nine percent of children with confirmed AFM had experienced a viral illness with symptoms such as fever and cough about three to 10 days before the onset of paralysis. The CDC also seems to be getting closer to determining a cause of the disease. According to the new report, "Clinical, laboratory, and epidemiologic evidence to date suggest a viral association." (*CNN*)

The American Thoracic Society (ATS) has expressed grave concern and disappointment in the FDA's decision to approve over-the-counter epinephrine for consumer use to treat asthma in a press communication dated Nov. 12, 2018. **FDA's decision contradicts existing and established clinical practice guidelines.** Several expert panels have produced evidence-based recommendations on the treatment of patients with asthma. None of these guidelines recommend the use of inhaled epinephrine to treat asthma. The National Asthma Education and Prevention Program (NAEPP), an expert panel convened by the National Institutes of Health recommends against the use of epinephrine for treating asthma exacerbations, stating:

- Drugs of choice for acute bronchospasm: Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes.
- The less beta 2-selective agents such as epinephrine, isoproterenol, metaproterenol and isoetharine are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.

By approving an over-the-counter epinephrine product to treat asthma, the FDA is endorsing a contraindicated treatment for asthma. The FDA should know that our patients deserve better.

Violent crime in a city has been linked to increased blood pressure (BP) for its residents, including those who live in relatively low-crime areas in a population-based study of more than 53,000 adults in Chicago, Illinois, between May 2014 and August 2016, presented at the recent American Heart Association (AHA) Scientific Sessions 2018 in Chicago. Overall, the areas with lower crime rates had fewer patients with elevated BP than areas with higher crime rates; 22.5% vs. 36.5%, respectively (*Medscape*).

Suicide increasing among workers and varies by occupation in the US, says a new report published in *CDC's Morbidity and Mortality Weekly Report (MMWR)*, which examined lifetime occupations of 22,053 people aged 16-64 years old who died by suicide in the 17 states participating in the National Violent Death Reporting System (NVDRS) in 2012 and 2015.

- Top 3 major occupational groups by suicide rate among males in 2015 were construction and Extraction; Arts, Design, Entertainment, Sports and Media; Installation, Maintenance and Repair.
- Top 3 major occupational groups by suicide rate among females in 2015 were Arts, Design, Entertainment, Sports and Media; Protective Service; Health Care Support.

Farmers on the frontline in battle against drug-resistant microbes: The United Nations FAO has revealed that as some 7,00,000 people are dying each year from antimicrobial resistant infections, an untold number of sick animals are also suffering from diseases that do not respond to treatment. Marking World Antibiotic Awareness Week, FAO stressed that farmers have a vital role to play in stemming the spread of antimicrobial resistance and called on them to boost hygiene practices in day-to-day farm operations. "**When we use antimicrobials excessively on farms, we're contributing to the spread of AMR**, as resistant pathogens move into the environment through animal waste and farm runoff. They can even contaminate our food systems and market chains, moving from the fields and stables to our tables," said Juan Lubroth, FAO's Chief Veterinary Officer.

According to FAO, **one person dies every minute from a drug-resistant infection**, a number that will only increase without global action. By 2050, the growing AMR threat will cost the global economy an estimated $6 trillion dollars every year.

Reliable surveillance helps combat antimicrobial resistance, says CAESAR report (WHO Europe, Nov. 15, 2018): As the international community calls for more and better information to add to the ever-growing body of evidence on the effects of antimicrobial resistance (AMR) on humans, animals, the environment and the economy, policy-makers need access to reliable surveillance data. This data is crucial for monitoring the status of key antimicrobial classes in the European Region, and to track how effective policies have been in addressing this public health challenge. The latest Annual Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) report reveals steady progress towards forming a more complete picture of AMR in Europe. Updates in this reporting period include:

- Eleven countries and one area have an AMR reference laboratory in place.
- Ten countries and one area provide data to the CAESAR network.
- Participation in the external quality assessment (EQA) for laboratories has again expanded with 248 laboratories from 16 countries/areas, and overall results continue to improve.
- Two central Asian countries are preparing to implement a proof-of-principle project, while one additional country concluded a project in October 2018.

"I'm interested in the idea of green space as a drug, as a treatment," said Eugenia South, MD, of the University of Pennsylvania, discussing her study that converted vacant lots in Philadelphia into green space and examined the mental health effects on local residents. The study found that among people exposed to a community-based intervention that converted vacant lots in Philadelphia into green space, self-reported feelings of depression and worthlessness were significantly decreased, and self-reported poor mental health was nonsignificantly reduced for those living near greened vacant land (*JAMA Network Open*. July 20, 2018).

Congo's Ebola outbreak will last at least another 6 months predicts the emergencies chief for the WHO, saying that informal health facilities have become "major drivers" of the current, deadly transmission. Dr Peter Salama said that makeshift "tradi-modern" health centers — offering both traditional and modern treatment — were believed to be linked to more than half of cases in Beni, the largest city affected by the current outbreak that has taken more than 200 lives. Salama, who returned from a trip to Ebola-hit eastern Congo last week, it appeared "very likely" that some cases of Ebola had been misdiagnosed as malaria, because early symptoms are virtually identical. He said that the WHO

IJCP SUTRA 528: Drinking alcohol or taking drugs interferes with judgment. Even those who understand the risks of AIDS and the importance of safer sex may become careless after drinking or using drugs.

is planning on "at least another 6 months before we could declare this outbreak over." (*The Japan Times*)

FDA alerts doctors and patients about risk of serious complications that can occur when implanted pumps are used to deliver pain medications not approved for use with devices that deliver medication into the spinal fluid to treat or manage pain. Complications may include dosing errors, pump failure, opioid withdrawal, infection and other complications like pain, fever, vomiting, muscle spasms, cognitive changes, weakness and cardiac or respiratory distress.

Oral cancer cases rise by 114% in India in 6 years: The number of cancer cases countrywide has gone up in the last 6 years by 15.7%. Data shared by Indian Council of Medical Research's National Institute of Cancer Prevention and Research recently showed that 11.5 lakh cancer cases were reported across the country this year, as against 10 lakh in 2012. ICMR cancer center director Dr Ravi Mehrotra said lip and oral cavity cancers increased by a whopping 114% in the 6-year period. Breast cancer, emerging as a disease linked to urban lifestyle, increased by almost 11%, from 1.4 lakh in 2012 to 1.6 lakh in 2018. However, a sharp decrease in cervical cancer cases has been observed by 21%, from 1.23 lakh in 2012 to 96 in 2018. As per the new data, cancer-related deaths also increased by 12%. While 7 lakh Indians died of cancer-related complications in 2012, the number increased to 7.8 lakh this year… (*ET Healthworld*, Nov. 16, 2018)

Choosing Wisely: Questions parents should ask about their hospitalized child's antibiotics: The American Academy of Pediatrics (AAP), as part of the Choosing Wisely® campaign, wants to protect hospitalized children from the effects of antibiotic resistance by providing a list of recommendations to serve as a starting point of conversation for physicians and patients. **The five items that physicians and patients should question** on the Choosing Wisely List of Antibiotic Stewardship in Hospitalized Children are:

- Before antibiotics are prescribed, testing of the patient's blood, urine and other appropriate cultures should be undertaken to confirm suspected invasive bacterial infection.
- During surgery, the dose and timing of antibiotics to prevent infection are important for optimal effect, and should not be used indiscriminately.
- Ampicillin is the first choice of treatment for children hospitalized with community-acquired pneumonia who are otherwise healthy and immunized. Broader-spectrum antibiotics, such as cephalosporins, have been shown to contribute to antibiotic resistance and are often unnecessary.
- Antibiotics such as vancomycin or carbapenems should be avoided unless a child is known to have a specific risk for pathogens that are resistant to other antibiotics.
- Avoid using prolonged courses of IV antibiotics. For most infections, children respond well to orally administered antibiotics after a brief course of intravenous therapy. Peripherally inserted central catheters, used to facilitate prolonged courses of IV antibiotics, often result in complications.

Multi- and extensively drug-resistant infections, especially Gram-negative infections associated with higher in-hospital mortality rates in India: In an analysis of data from 10 hospitals across India in a retrospective observational study, researchers at the Center for Disease Dynamics, Economics & Policy (CDDEP) report that in-hospital mortality is significantly higher among patients infected with multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens including *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae* and *Acinetobacter baumannii…* (*Clinical Infectious Diseases*, Nov. 8, 2018).

Beijing issues rare public warning on 'serious' swine fever crisis: Chinese authorities have announced strict new measures in an attempt to halt the country's fast-growing African swine fever crisis, which has spread to 18 provinces and led to the culling of more than 2,00,000 pigs. Days after acknowledging the situation was "serious," the Chinese Agricultural Ministry recently reported the first outbreak of the disease in the southwestern province of Sichuan in a farm of 40 pigs.

The directive called for stricter nationwide inspections of all livestock transportation vehicles, and harsher punishments for the illegal transportation and slaughter of pigs: The document comes after the United Nations recently warned that the disease is "here to stay" in China and could quickly turn into an epidemic, with the most virulent strain of swine fever causing a 100% fatality rate for infected pigs …(*CNN*).

Sixty-nine percent of respondents in the 9th Annual Physicians Practice Great American Physician Survey reported that they would consider going part time. And while about two-thirds (64%) of respondents don't want to change workplaces, 29% said the main reason why they would prefer to work somewhere else is to work better hours or achieve greater work-life balance. A growing number of respondents (46%) said they would consider becoming a locum

tenens physician, suggesting the traditional work environment is no longer as appealing to the 91% of respondents who have been practicing at least 11 years. Today, physicians are increasingly open to the idea that they no longer need to be—or perhaps even want to be—tied to a single employer. Portfolio careers, where physicians have the flexibility to pursue multiple areas of focus and manage multiple revenue streams, are gaining traction. This strategy can provide high levels of job satisfaction, some much-desired mental stimulation, and a good income, too, writes Julie Knudson in Physician Practice.

The American Diabetes Association (ADA) reaffirms commitment to insulin access and affordability for all—Transparency on Insulin Pricing Critical: On the second anniversary of the Make Insulin Affordable initiative, the ADA announces that more than 4,00,000 Diabetes Advocates have joined the call for affordable insulin for all who need it—the largest response to an ADA call to action to date. After its examination of the insulin supply chain, ADA and its Insulin Access and Affordability Working Group (Working Group) published recommendations and public policy solutions to address the problem. The ADA reaffirms its commitment to implementing these solutions and achieving affordable insulin for all who need it… (*ADA News Release.* Nov. 16, 2018)

10 Tips for staying healthy during wildfires (American Thoracic Society)

1. Stay indoors with windows and doors closed.
2. Reduce physical activity.
3. Reduce other sources of indoor air pollution such as smoking cigarettes, using a wood-burning stove or frying meat. Do not vacuum anywhere in the house.
4. Use central air conditioner or filters: A home's heater set to the fan mode may be able to filter out some of the particles by "re-circulating" the indoor air through the filter.
5. Use air purifiers with HEPA filters. Note: Do not use filters that produce ozone such as "super oxygenators".
6. When traveling in a vehicle, keep windows closed, run the air conditioner and set air to re-circulate to reduce smoke.
7. An N95 or greater mask can help reduce inhalation of particulates if properly fitted. A surgical or simple dust mask will not protect against particulate exposure. None of these masks protect against hazardous gas inhalation.
8. Consider evacuation to areas with lower air quality index for individuals with lung disease (especially those with asthma, chronic obstructive pulmonary disease (COPD)/emphysema, pulmonary fibrosis).
9. Create a clean room at home. Use an interior room with fewer doors and windows and run an air conditioner and room air cleaner if available.
10. Patients with asthma or COPD should ensure that they continue to take their maintenance ("controller") medications or discuss an appropriate regimen with their physician.

The US FDA has expanded the indications for brentuximab vedotin to include first-line treatment of CD30-expressing peripheral T-cell lymphomas (PTCLs), to be used in combination with chemotherapy.

No association of diabetes and markers of abnormal glucose metabolism with an increased risk for incident knee osteoarthritis (OA). Among older women and men with a high risk of developing knee OA, diabetes status or status fasting glucose or insulin resistance were not associated with odds of incident radiographic knee OA after adjustment for BMI (*Arthritis Care & Research*. Nov. 12, 2018).

Noise pollution is a rising problem in hospitals: In an editorial published Nov. 18, 2018 in the *BMJ*, researchers from King's College London and the University of the Arts London argue that it is a worsening problem, with levels regularly exceeding international recommendations. Dr Andreas Xyrichis, lead author said, "Even in intensive care units, which cater for the most vulnerable patients, noise levels over 100 dB have been measured, the equivalent of loud music through headphones."

Issues to be addressed in noise pollution in hospitals (*BMJ*. Nov. 18, 2018)

- ***Noise is often incorrectly associated with high sound pressure levels (SPLs)***. Dripping taps for example, may register low SPLs yet still be considered noisy. Prioritizing SPL reduction does not ensure improved noise perception. Therefore, a new approach is needed, one that views the hospital soundscape as a positive and malleable component of the environment.
- ***There are a number of potential sources of noise in hospitals***. Alarms, televisions, rattling trolleys, and ringing phones, as well as staff, visitor and patient conversations. However, not all of them are

perceived as noise by patients - for example, some find the sound of the tea trolley pleasing, associating it with receiving a warm drink. Research has also shown that some ICU patients welcome ringing telephones as a sign that they are not alone. So far ways to measure patients' perceptions of noise are limited, and more research investment is needed in this area.

- ***Patients and families need clear information about likely noise levels during admissions, so they are better prepared in advance***, and can consider simple solutions such as headphones with their own choice of audio content. Education for staff is also needed, to encourage a culture that considers noise reduction an integral part of safe high quality healthcare.

Is skipping med school lectures making inferior doctors? A recent study "Classroom attendance patterns and examination performance in preclinical medical students" by a research team at the University of Central Florida College of Medicine, led by assistant professor of pediatrics Christine A. Kauffman, MD, found that lecture attendance during medical school is not as predictive of good grades as is general perceived, given how much we pay for this seemingly invaluable resource. However, this study was undertaken in the second year, which is preclinical and which also means that all lecture-based materials were available online and attending classes in person did not mean that they did not have the class material… (*Medscape*)

Bullying and violence at work increase the risk of new-onset cardiovascular disease, including heart attacks and stroke, according to the largest prospective study involving nearly 80,000 employed men and women from Denmark and Sweden to investigate the link published in the *European Heart Journal*. The population attributable risk (PAR) was 5.0% for workplace bullying and 3.1% for workplace violence, comparable to those for standard risk factors, e.g., diabetes (4%) and risky drinking (3-6%).

Oral immunotherapy for peanut allergy: In the phase 3 PALISADE trial of oral immunotherapy (AR101) in children and adolescents aged 4-17 years, who were highly allergic to peanut, treatment with AR101 resulted in higher doses of peanut protein that could be ingested (tolerated) without dose-limiting symptoms and in lower symptom severity during peanut exposure at the exit food challenge than placebo. Overall, 67% of the participants in the active-drug group could tolerate a single dose of at least 600 mg of peanut protein, the equivalent of approximately two whole peanut kernels, during the exit food challenge… (*New England Journal of Medicine*. Nov. 18, 2018).

The American Academy of Pediatrics (AAP) urges reforms to help teens and young adults overcome healthcare hurdles: In a new policy statement published recently in the journal *Pediatrics*, AAP encourages pediatric training in community health issues such as strategies for prevention and treatment of common diseases in low- and middle-income countries. It also encourages pediatricians to be informed on best practices regarding international medical work for example how best to work with local partners to ensure awareness and respect for global health ethics … (*AAP*. Nov. 19, 2018).

EMA Panel recommends first oral-only treatment for sleeping sickness

The Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA). European Medicines Agency has adopted a positive opinion for fexinidazole, the first oral-only medicine (tablets) for the treatment of human African trypanosomiasis, commonly known as sleeping sickness, due to *Trypanosoma brucei gambiense*.

5 facts about antimicrobial resistance (The Association of the British Pharmaceutical Industry)

1. ***One person a minute:*** In the UK 5,000 people are estimated to die each year (*Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, Dec 2014*) from a bug-resistant to antibiotics, although due to non-recording of antimicrobial resistance on death certificates this is likely to be much higher. Global figures are even harder to ascertain but estimates suggest that 7,00,000 are dying each year. That's one person a minute.
2. ***12 priority pathogens:*** In 2017, the WHO published the first ever list of 12 priority pathogens that are antibiotic resistant. These pathogens are ranked into three categories; critical which includes multidrug-resistant bacteria (most likely to affect those in hospital or care home settings), high and medium priority which are the more common diseases which are increasingly containing drug-resistant bacteria such as gonorrhea and food poisoning from salmonella. These pathogens pose the greatest risk to healthcare right now.
3. ***11 million days of unnecessary antibiotic use:*** Prevention is always critical to tackling a problem. If every child in the world was to be vaccinated against pneumonia, meningitis and middle ear infections (one vaccine), it would prevent an

estimated 11 million days of antibiotic use each year *(Why is vaccination important for addressing antibiotic resistance? Q&A, WHO, Nov. 2016).*

4. ***One in 5 antibiotic prescriptions is unnecessary:*** Research from British Society of Antimicrobial Chemotherapy found that one in 5 antibiotic prescriptions is unnecessary *(J Antimicrob Chemother. 2018;73(Suppl 2):ii36-ii43).*
5. ***70% of people get annoyed if they aren't prescribed antibiotics:*** Evidence from the Wellcome Trust *(Exploring the consumer perspective on antimicrobial resistance, Wellcome Trust, June 2015)* shows that the general public feel irritated or that they haven't been taken seriously by their GP if they're not prescribed antibiotics. Increasing public awareness of antibiotic resistance and when and how to take antibiotics is crucial to supporting appropriate prescribing now and preventing the spread of antimicrobial resistance in the future.

NIH statement on World COPD Day 2018

NIH-supported studies aim to reduce the burden of COPD.

On November 21, World COPD Day 2018, the National Institutes of Health unites with millions of people to renew our long-standing commitment to reducing the burden of COPD, a serious and debilitating lung disease. A leading cause of death, COPD impacts an estimated 251 million people worldwide. While many have been diagnosed with the disease, millions more are believed to have it and not know it. In the United States, 16 million people have COPD, and each year more than 1,50,000 people die because of it.

The numbers tell only part of the story, however. For many who live with the disease, getting through each day is often a struggle. COPD (also known as emphysema or chronic bronchitis) can make it difficult to breathe or perform even the most basic tasks. And because COPD symptoms develop slowly and worsen over time, many who have the disease delay getting diagnosed until they need aggressive treatment or hospitalization. This further compounds the toll on their lives — and on the nation's healthcare system: COPD-related care cost Americans more than $32 billion in 2010, a number expected to increase to $49 billion by 2020.

Through its large research portfolio, the NIH is working hard to make inroads into the fight against this crippling disease.

In 2017, NIH's National Heart, Lung and Blood Institute (NHLBI) developed the COPD National Action Plan in collaboration with federal and nonfederal partners. This comprehensive, unified plan now serves as a guiding document for those affected by COPD and for those invested in doing something about it.

At NIH, intensive COPD research is being conducted and supported at all stages, from the laboratory to clinical trials. Some of it has improved our understanding of COPD and resulted in effective treatment strategies that are used in practice today.

The Nocturnal Oxygen Therapy Trial has given researchers insight into ways long-term oxygen therapy can improve the life expectancy of patients with advanced COPD. The Lung Health Study is helping researchers understand how smoking cessation interventions impact the long-term survival of COPD patients. The National Emphysema Treatment Trial is showing how lung volume reduction surgery might improve the quality-of-life in certain groups with severe COPD.

NIH also supports other studies, many conducted through the NIH COPD Clinical Research Network, that are exploring the effectiveness of various pneumococcal vaccines in COPD patients; the usefulness of azithromycin, an antibiotic, in reducing the severity and occurrence of COPD exacerbations and the role statin drugs might play in preventing or eliminating those exacerbations.

In cooperation with the Centers for Medicare and Medicaid Services, NIH is also supporting the Long-Term Oxygen Treatment Trial, which builds on previous studies that looked at whether supplemental oxygen is beneficial to patients with mild COPD. Other studies are aimed at improving knowledge about the biologic basis of COPD and its biomarkers.

These studies are critical to the research activities of NHLBI-supported scientists, who focus on advancing understanding of the disease process, identifying crucial points in its onset and progression, and sharing the knowledge necessary for early intervention and prevention. The COPDGene Study is currently investigating why some smokers develop COPD while others do not. (Smoking accounts for 75% of COPD cases; secondhand smoke, environmental pollutants and genetic factors also play a role.) Other studies are evaluating how various pharmaceutical medications affect the treatment of COPD. NHLBI also funds research to find out if a proven weight loss and physical activity program can improve COPD symptoms for those with a high BMI. Finally, scientists are continuing their research on the CAPTURE tool, a case-finding mechanism that involves a simple questionnaire and breathing test, that can help healthcare providers identify people at risk for developing COPD before their symptoms get severe.

To further advance the awareness and understanding of COPD nationwide, NHLBI – through its COPD Learn More Breathe Better program – is working with healthcare providers to facilitate discussions with patients in the exam room to make earlier diagnosis more possible. To reach the greatest number of patients, the program collaborates with a large network of partners.

The NIH is thankful for all these collaborators, as well as the many other individuals and entities—from researchers to advocates—who are helping advance the care and management of COPD. By working together to improve awareness and early diagnosis of the disease, we can have a lasting—and positive—impact on the health of the millions who struggle with COPD in the United States and around the world.

Appendix linked to toxic Parkinson's protein: A team led by Dr Viviane Labrie at the Van Andel Research Institute sought to explore whether the gut could be involved in triggering Parkinson's disease. They focused on the appendix. The team analyzed the records of nearly 1.7 million people whose health information was tracked for up to 52 years. They compared the chances of developing Parkinson's disease among those who'd had their appendix removed with those who hadn't.

People who'd had their appendix removed had a 19.3% lower chance of Parkinson's disease. Those who lived in rural areas and had an appendectomy had an even lower chance, 25.4%. People who'd had an appendectomy and developed Parkinson's showed a delayed onset of the disease relative to those who still had their appendix, an average delay of 3.6 years for those who'd had an appendectomy at least 30 years prior.

The team also found a build-up of the toxic form of alpha-synuclein in the appendixes of healthy volunteers suggesting that the appendix may be a reservoir for the disease-forming protein and may be involved in the development of Parkinson's disease.

"We were surprised that pathogenic forms of alpha-synuclein were so pervasive in the appendixes of people both with and without Parkinson's. It appears that these aggregates—although toxic when in the brain—are quite normal when in the appendix. This clearly suggests that their presence alone in the gut cannot be the cause of the disease," Labrie said.

One in four US adults sits for more than 8 hours a day, according to a new study from the US Centers for Disease Control and Prevention (CDC). Four in 10 adults do not exercise to either a vigorous or even moderate degree each week. Add to that, one in every 10 Americans reports both behaviors -- sitting for more than 8 hours a day and being physically inactive, according to the study, published online in *JAMA.*

536 AD revealed as the worst year to be a human by researchers: A team of historians and scientists has identified AD 536 as the beginning of a terrible sequence of events for humankind. A massive volcanic eruption spewed a huge cloud of ash that shrouded the Northern Hemisphere in darkness and caused a drop in temperatures that led to crop failure and starvation, said co-lead study author Professor Christopher Loveluck of the University of Nottingham in the UK. Then the misery was compounded in AD 542 as cold and hungry populations in the eastern Roman Empire were struck by the bubonic plague. The eruption and the 542 plague outbreak caused economic stagnation in Europe, which lasted more than 30 years until 575, when there were early signs of recovery … (*CNN*).

7 fast facts about toilets (UNICEF)

1. Toilets save lives! Without toilets, deadly diseases spread rapidly. Over 750 children under five die every day from diarrhea caused by unsafe water, sanitation and poor hygiene.
2. Globally, 1 in 3 schools do not have adequate toilets, and 23% of schools have no toilets at all.
3. Schools without toilets can cause girls to miss out on their education. Without proper sanitation facilities, many are forced to miss school when they're on their period.
4. Toilets are a great investment. Every dollar spent on sanitation has a return of US $5.50, according to WHO research.
5. But still, 892 million people worldwide practice open defecation, meaning they go outside - on the side of the road, in bushes or rubbish heaps.
6. It's often a matter of where they live: 90% of people who practice open defecation live in rural areas.
7. It's time to make a stink! In order to get everyone in the world using toilets, we need to triple our current efforts. That doesn't just mean more toilets, but creating the desire for people to use them.

European Testing Week 2018 (23-30 Nov, 2018) is a Europe-wide campaign that encourages public and partner organizations, including communities, and public healthcare institutes throughout the WHO European Region to unite for 1 week to scale up voluntary testing. The campaign promotes awareness of the benefits of earlier diagnosis of HIV and viral hepatitis infections

and linkage to treatment and care, while respecting the principle of confidentiality. The primary goal is to make more people aware of their HIV and/or hepatitis status and reduce late diagnosis.

People with migraine with aura were 30% more likely to develop atrial fibrillation (AF) than people who did not have headaches and 40% more likely to develop AF than people with migraine with no aura… (*Neurology*. Online Nov. 14, 2018).

Which oil to choose for cooking? Canola oil and olive oil are very versatile and are great to use in many different recipes, even in baking. These unsaturated oils in place of saturated fats can help reduce the incidence of chronic conditions, such as type 2 diabetes and cardiovascular disease. Plant and seed oils have mono- and polyunsaturated fats, which help to increase the good cholesterol - the high-density lipoprotein (HDL) cholesterol. They also help lower the bad cholesterol - the low-density lipoprotein (LDL) cholesterol. Oils like peanut and sesame have stronger flavor and higher smoke points, so they're great in marinades and stir-fries. The lower smoke point of walnut oil makes it better for dressings.

My view: All oils are high in calories. So, you just want to use them in moderation.

Top News From ESMO 2018: New hope in triple-negative breast cancer with immunotherapy. For the first time, immunotherapy has shown a survival benefit in breast cancer. The result was seen with the anti-programmed cell death ligand 1 (PD-L1) drug atezolizumab used with chemotherapy in triple-negative breast cancer in PD-L1-positive patients. The results from the Impassion130 study were presented by Peter Schmid, MD, PhD, Clinical Director of St. Bartholomew's Breast Cancer center, Barts Health NHS Trust, London UK and were simultaneously published in the *New England Journal of Medicine*.

The trial randomly assigned more than 900 women who had triple-negative disease to receive atezolizumab or placebo + chemotherapy as first-line therapy. Across the board, the addition of atezolizumab was associated with a 20% improvement in progression-free survival (PFS). However, when the researchers assessed a subgroup of patients who were PD-L1+, addition of atezolizumab improved PFS by 38% and increased overall survival by the same percentage, offering patients an additional 10 months of life in comparison with the patients who received chemotherapy alone (*Medscape*).

USPSTF recommends HIV PrEP for all high-risk patients: In a draft recommendation statement published online Nov. 20, 2018 on its website, the USPSTF recommends ("A" recommendation) that clinicians offer pre-exposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high-risk of HIV acquisition.

Glasdegib is the first and only Hedgehog pathway inhibitor to be approved by the US FDA for the treatment of acute myeloid leukemia (AML). The tablets are to be used along with low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are 75 years of age or older or who have other comorbidities that may preclude the use of intensive chemotherapy. The prescribing information for includes a Boxed Warning to advise healthcare professionals and patients about the risk of embryo-fetal death or severe birth defects. The drug should be avoided during pregnancy or while breastfeeding.

Nine causes of altered mental status in the elderly - Delirium: Occurs in 7-10% of geriatric patients in the ED (*Clin Geriatr Med*. 2013;29(1):101-36; *Ann Emerg Med*. 2014;63(5):551-560.e2). It presents as an acute change in consciousness and loss of cognition that waxes and wanes. Patients' conditions can range from sleepy to agitated and combative. Inattention is the hallmark sign/symptom (*Clin Geriatr Med*. 2013;29(1):101-36). Delirium is easier to recognize in patients who become hyperactive; "quiet" delirium may be more difficult to identify.

Delirium is often mistaken for dementia, but the risk of morbidity for delirium is high; therefore, clinicians should make an effort to identify delirium, if present. In addition, inquire about sleep-wake cycle disturbances, hallucinations, confused thinking and symptoms of lethargy or agitation, because these signs/symptoms are not associated with dementia and, if present, should trigger further clinical evaluation (*Clin Geriatr Med*. 2013;29(1):101-36).

Unlike dementia, delirium is sudden in onset, reversible, of waxing and waning nature, disorientation occurs at the onset and the altered mental status presents early.

The American Academy of Pediatrics (AAP) has published new guidelines on diagnosing and managing serious infections in infants born at less than 34 weeks gestation and those born at more than 34 weeks of gestation in two clinical reports published online Nov. 19, 2018 in the journal *Pediatrics*. It includes recommendations on how to identify babies most likely to develop early-onset sepsis, based on their gestational age, circumstances of birth and other factors and addresses the use of multivariate sepsis risk models in clinical care.

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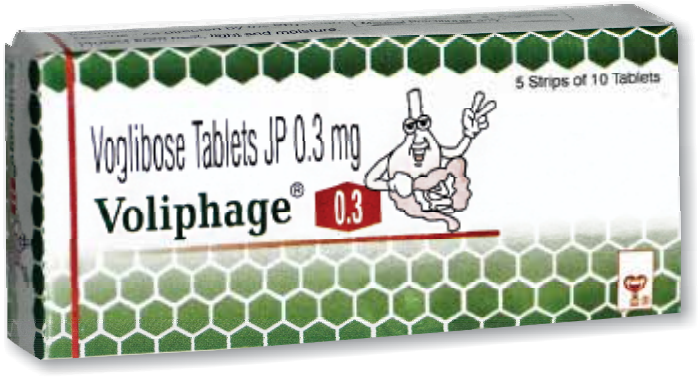

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HEALTH MANAGEMENT FOR NEUROLOGISTS

Dr Pravar Passi, Indore

- Doctors are ignoring their own health. The burnout, depression and suicide rate amongst doctors continues to rise.
- In the last decade or so, the complexity of medicine has increased several-fold. The options are more than ever before. The patients are more demanding, at times unreasonably so. Doctors remain constrained for time and continue to ignore their health.
- Emphasis should be given to positive health.

THERAPEUTICS - GOALS, CURRENT AND EMERGING THERAPY IN MULTIPLE SCLEROSIS

Dr Nishita Singh, New Delhi

- Among clinically isolated syndrome (CIS) patients, conversion rates to clinically definite multiple sclerosis (CDMS) have been found to be 10-65% in those with optic neuritis, 41-61% in those with spinal cord syndrome and 53-60% in those with brainstem syndrome.
- As per the AAN 2018 guidelines, one should prescribe disease-modifying therapy (DMT) to people with a single clinical demyelinating event and two or more brain lesions characteristic of multiple sclerosis (MS) after discussing risks and benefits of therapy with the patient. According to the ECTRIMS EAN guidelines 2018, offer interferon or glatiramer acetate to patients with CIS and an abnormal MRI with lesions suggestive of MS who do not fulfil criteria for MS.
- Therapeutic options in aggressive relapsing-remitting multiple sclerosis (RRMS): Induction therapy with second-line agent; drug treatment options - natalizumab, mitoxantrone, fingolimod, alemtuzumab, ocrelizumab, rituximab, cyclophosphamide and autologous hematopoietic stem cell transplantation (aHSCT). As per the AAN guidelines 2018, there is level B evidence to prescribe alemtuzumab, fingolimod or natalizumab for people with highly active MS.
- Patients most likely to benefit from aHSCT: Relatively young, i.e., <50 years of age; relatively short disease duration, i.e., 5 years or less; have active RRMS and accumulating disability but ambulatory; have ongoing disease activity despite DMT.
- Reasons to stop treatment: Adverse effects, planned pregnancy, logistics, noncompliance.
- According to the AAN guidelines, discontinuation of DMT may be advised in people with secondary progressive multiple sclerosis (SPMS) who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (Expanded Disability Status Scale score 7 or greater) for at least 2 years.

DEVELOPMENT OF NEUROLOGY SERVICES IN THE SULTANATE OF OMAN

Dr Abdullah Al-Asmi, Oman

- The College of Medical and Health Sciences Sultan Qaboos University (SQUH) was established in September 1986.
- Adult/pediatric neurology units at SQUH include general neurology clinic, epilepsy clinic, VNS clinic, movement disorder clinic, botox clinic, memory clinic, vascular neurology clinic, MS clinic, sleep clinic, neurodevelopmental clinic and neurogenetics clinic.
- MOH work force involves Khoula Hospital, Royal Hospital, Salalah Hospital, Nizwa Hospital, Sohar Hospital.
- In Khoula Hospital neurology department, digital neurophysiological equipment, 1.5 T MRI, vascular lab and neuropathology lab are available.
- Neurologists in private are available only in Muscat and approximately 75% of them are Indians.

NEUROLOGICAL SERVICES WITHIN A FREE PUBLIC HEALTHCARE SYSTEM

Dr Harsha Gunasekara, Sri Lanka

- Achievements and challenges of free public healthcare system (PHS):

- Primary preventive care has helped to achieve excellent public health indices.
- In the curative sector, health system has concentrated mostly on tertiary care and to some extent on secondary care.
- What we need is to develop the primary curative care in terms of both quality and quantity.

- Development of Essential Health Service Package (SLESP) with WHO:
  - It aims at universal care at PHC level - to improve and expand the PHC preventive system and develop and re-structure the PHC curative network.
  - Strengthen the referral system for complete and comprehensive care.
  - Develop human resource needs based on workload rather than cadres.
- Future role of the Association of Sri Lankan Neurologists (ASN):
  - Advice health authorities on rational expansion of neurological services on - cadre projections based on population and specialized services; provision of facilities for neurology units and specialized services.
  - Promote research through collaboration, research grants.
  - Establishment of an independent Board of Study to maintain standards of training and to develop subspecialty training.

NEWER THROMBOLYTICS IN STROKE MANAGEMENT

Dr S Meenakshi-Sundaram, Madurai

- Neurologists have only 2 children - Alteplase and tenecteplase. Alteplase vs. tenecteplase fight is preferred over thrombolysis or no thrombolysis fight.
- Alteplase has procoagulant effects and neurotoxicity effects. Another issue with alteplase - Can compromise integrity of the blood-brain barrier; destructive effects on extracellular matrix and endothelial basal lamina; proteolytic activity of alteplase.
- Alternative formulations of recombinant tissue plasminogen activator (rtPA), in the absence of arginine, would provide new insight into rtPA neurotoxicity, and have the potential to offer more efficacious thrombolytic therapy for ischemic stroke.
- Tenecteplase has been shown to be associated with significantly better early major neurological improvement compared to alteplase. Tenecteplase has been associated with better reperfusion, recanalization and NIH Stroke Scale change at 24 hours, with no safety concerns.
- In acute ischemic stroke, tenecteplase 0.25 mg/kg has been found to be superior to alteplase for efficacy outcomes at 24 hours and 90 days.
- Additional thrombectomy procedures are averted with tenecteplase.
- A 2018 study revealed that intravenous tenecteplase 0.2 mg/kg administered within 3 hours of symptom onset was well-tolerated and effective in acute ischemic stroke.
- Tenecteplase bolus allows reducing time between stroke onset and thrombectomy.
- Molecules in the pipeline - Monteplase, pamiteplase, lanoteplase, alfimeprase.

"BLIND SPOTS" IN CLINICAL NEUROLOGY: CHALLENGES AND REMEDIES

Dr Arun B Taly, Bengaluru

- Diagnostic errors are common despite advancement in technology. Most clinicians experience at least one error during their practice, though only a very few admit.
- Errors have not received comparable attention and remain a blind-spot. Missed or misdiagnosis leads to unnecessary or delayed treatment, considerable disability or even death.
- Less often recognized and acknowledged is the impact of medical errors on the "second victim" i.e., the clinician who has to deal with negative emotions such as frustration, guilt, anger, anxiety, loss of confidence, reduced job satisfaction, poor performance, fear of lawsuit, etc.
- Errors are hardly ever intentional. A number of factors contribute to medical errors and can be broadly categorized as "No Fault" errors, "System" errors, "Cognitive" errors and "Medication" errors.
- "Cognitive" errors on the part of clinicians are attributed to knowledge gap, limited experience, adopting short-cuts, diagnostic anchoring, premature closure, faulty hypothesis/cognitive reasoning and over reliance/faulty interpretation of test results, to name but a few.

- Amidst uncertainty and varied probability in clinical neurology, following a "checklist", active knowledge seeking and cognitive flexibility may prevent potential diagnostic errors, ensure patient safety, reduce cost of treatment and improve overall quality of healthcare.

THERAPY OF CONGENITAL MYASTHENIC SYNDROMES

Dr A Nalini, Bengaluru

- Congenital myasthenic syndromes (CMS) are potentially treatable and reversible disorders. They usually begin at birth or early childhood with ocular, bulbar and limb muscles with prominent fatigue. Majority are labeled as congenital myopathies or mitochondrial disorders. Several types can have late adolescent or adult onset.
- The limb-girdle type do not have cranial muscle involvement or have minimal ocular and bulbar symptoms and are frequently mislabeled as limb-girdle muscular dystrophy.
- The fluctuations classically may be diurnal, but may occur over weeks or months, around menstrual cycles and also be seasonal. Tendon reflexes are well preserved and may be exaggerated, except may be hypoactive in the group with CMS and dystroglycanopathies. Creatine kinase level is elevated in CMS-dystroglycanopathy group.
- It is important to do repetitive nerve stimulation (RNS) in all cases of muscle diseases with easy fatigability. Perform sub-tetanic stimulation if routine RNS is negative.
- CHRNE, GMPPB, DPAGT1, GFPT1 respond well to pyridostigmine/neostigmine along with salbutamol. DOK7, MUSK, COLQ respond well to salbutamol; may significantly worsen with acetylcholinesterase inhibitors. Slow channel syndromes respond to fluoxetine and salbutamol. Many of the CMS cases are mislabeled or have a delayed diagnosis and hence should be detected early and treated.

PULSE STEROIDS: NEW DEVELOPMENT IN NEUROMUSCULAR DISORDERS

Dr Birinder Singh Paul, Ludhiana

- Treatment with glucocorticosteroids is an art. A balance must be maintained between the severity of patient's disease and clinical condition.
- Pulse dose of glucocorticosteroids (>250 mg MPS) exhibits, apart from genomic action, an additional nongenomic action. This results in faster, stronger response and fewer side effects compared to classic therapy. Keep in mind concurrent medical issues. Clinical experience is the key factor in using pulse steroids.

MEDIA MANAGEMENT FOR NEUROLOGISTS

Dr Sudhir Shah, Ahmedabad

- Many social media tools are available for Neurologists and healthcare professionals.
- These tools can be used to improve or enhance professional networking and education, organizational promotion, patient care and education, public health programs and research purpose.
- Social media is disruptive, addictive and pervasive.
- There are risks regarding the distribution of poor-quality information, damage to professional image, breaches of patient privacy, violation of personal-professional boundaries and licensing or legal issues.
- There are few ethical and common guidelines available.
- Remember, if it's on social media, it's not private.
- It can affect physical and mental health and can lead to depression, guilt, anxiety, disorientation, insomnia, weight and mood fluctuations.
- So, to prevent career burnout and addiction, one needs to "digital detox".
- Use of social media needs carefully balancing between professional ethics and maintaining personal-professional boundaries.

PATTERN RECOGNITION ON MUSCLE IMAGING IN VARIOUS MYOPATHIES

Dr Rajesh Benny, Mumbai

- MRI is a useful, noninvasive modality to study muscle disease.
- Changes on MRI are due to inflammation, fatty infiltration or SOL in the muscle.
- Some myopathies may have specific imaging characteristics, e.g., collagen VI myopathies.
- Imaging can help choose an involved muscle for biopsy (as the muscle involvement may be focal) or track disease progression (dystrophies)/response to treatment (inflammatory myopathies).

CERVICAL DYSTONIA

Dr Hrishikesh Kumar, Kolkata

- Botulinum toxin injection is the treatment of choice for patients with cervical dystonia.

- Contrary to prevalent belief, it is a simple procedure and only requires some basic knowledge of anatomy and biomechanics of neck muscles.
- There are more than 50 muscles resulting in neck movement and that makes the task of recognizing the dystonic muscles seemingly daunting. But again, there is a silver lining- if we know the anatomy, orientation and function of 6 muscles (sternomastoid, splenius capitis, levator scapulae, trapezius, scalene complex, semispinalis capitis), that suffices for injecting botulinum toxin in majority of patients with cervical dystonia.
- Cervical dystonia can be classified as per the direction of predominant posturing of neck (torticollis, lateral-collis, retrocollis and anterocollis). All of them can be grossly addressed by injecting varying combination of these muscles.
- One may be fooled by compensatory movement of neck and wrong muscles can be selected for the injection. Careful observation and spending some time with the patients will help us determine primary dystonic movement and the muscles involved.
- Concern about safety and side effects can be offset by following some basic principles of injection.

ELECTROPHYSIOLOGY IN CENTRAL AND PERIPHERAL DEMYELINATING DISORDERS

Dr Meena A Kanikannan, Hyderabad

- Myelin plays a key role in transmission and conduction of nerve impulses by insulating the axons.
- Demyelination of the pathological substrate in many inherited and acquired primary central nervous system (CNS) and peripheral nervous system (PNS) disorders leads to slowing the conduction, and if severe, failure of the transmission of nerve impulses leading to motor, sensory and cognitive disturbances.
- Visual evoked potentials (VEP), somatosensory evoked potentials (SSEP) (especially lower limb SSEP) and motor evoked potentials (MEP) are the common evoked responses used in clinical practice and they are useful in detecting silent asymptomatic lesions, especially optic nerve involvement in MS.
- Although MRI is a very sensitive test for showing dissemination in space, it is less sensitive in determining the disability. MMEP is particularly useful in MS in predicting the disability development as well as assessing the severity of the disability. It is very useful for determining the activity of the disease. It is readily available and inexpensive. Hence, evoked potentials do have a role in identifying silent lesions, and when there is a diagnostic dilemma, both clinically as well as on the basis of MRI.
- Nerve conduction studies are an essential neurophysiological test in demyelinating neuropathies.
- It helps distinguish demyelinating from axonal neuropathy and allows accurate diagnosis of treatable and inherited demyelinating neuropathies. Conduction slowing and conduction block (CB) are the hallmark of these neuropathies.
- Several criteria are laid for conduction slowing and CB parameters. Criteria sets for the diagnosis of specific neuropathies require that several variables of demyelination are present in several nerves.
- Inherited demyelinating neuropathies are characterized by uniform slowing in all nerves with absence of CB and TD, whereas acquired neuropathies are marked by asymmetrical multifocal slowing, CB and TD.

HOT TOPICS - EPILEPSY

Dr Manjari Tripathi, New Delhi

- The International League Against Epilepsy (ILAE) announced a new classification of seizures in May 2017. Seizures are now focal (focal- aware, impaired awareness, motor, nonmotor, epileptic spasm, focal to bilateral tonic-clonic convulsive), generalized seizures and unknown onset. Videos of each seizure type are available for viewing on the ILAE website.
- Precision therapies have entered the epilepsy realm based on genetics.
- Evidence concerning the potential anti-seizure efficacy of cannabinoids reached a turning point in the last year, with the completion of three high-quality placebo-controlled adjunctive-therapy trials of a purified CBD product in patients with Dravet syndrome and Lennox-Gastaut syndrome. In these studies, CBD was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome. For the first time, there is now Class I

evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes.

- The highlight is of course our very own trial in *NEJM* at the end of 2017. Children with medication-resistant epilepsy who were randomly assigned to undergo surgery were far likelier to be seizure-free afterward compared to those assigned to continued medical management, according to the first randomized trial of surgery in this pediatric population. About 77% of the patients assigned to surgery were seizure-free, compared to 7% of those assigned to medical management. Significant between-group differences were seen in the change from baseline to 12 months in favor of surgery on the Hague Seizure Severity scale, on the Child Behavior Checklist, on the Pediatric Quality of Life Inventory and on the Vineland Social Maturity Scale (Dwivedi R, et al. Surgery for drug-resistant epilepsy in children. *N Engl J Med*. 2017;377:1639-47).
- Special populations of women with epilepsy (WWE) - Results on major congenital malformations were published showing higher rates across registries in a dose-dependent manner for valproate and least for levetiracetam. This was confirmed by a network meta-analysis too. The effect on infant and childhood IQs also took a hit with valproate which must preferably be avoided in WWE of child-bearing age.

CROSSROADS IN THE PRACTICE OF NEUROLOGY

Dr Sanjeev V Thomas, Thiruvananthapuram

- There have been exciting innovations in neurosciences. However, there are bioethical dilemmas associated with the progress. Dr Thomas quoted HH 14th Dalai Lama, who had stated that humanity is at a critical crossroad. The radical advances that took place in neuroscience and particularly in genetics have led to a new era in human history. The session was based on a talk given by the Dalai Lama at the annual meeting of the Society for Neuroscience in 2005 in Washington, DC. Dr Thomas mentioned an editorial published in *Ann Indian Acad Neurol* in 2008 that highlighted the topic of 'Advocacy'. He had stated the important objectives of advocacy for neurologists in the editorial.
- It was stressed that we should learn the term - "Gene Drive". It could one day transform the world. Emphasis was laid on the National Academies of Science, Engineering and Medicines Principles of Governance of Genome Editing - Promote well-being; due care; responsible science; respect for persons; distributive justice; Trans-National cooperation.
- He mentioned about the United Against Rabies Collaboration: A global catalytic platform to achieve zero human rabies deaths by 2030 (WHO), which focuses on dog immunization; post-exposure prophylaxis; awareness programs; reduce dog bite risk. There are limited number of advanced medical research centers; shortage of research grants; poor coordination between public health and clinical scientists; no institutions like NINDS/NIH Brain Initiative.
- Stroke interventions and stroke prevention were discussed - Statins, antiplatelet drugs, thrombolysis and stroke units, control of high BP, control of diabetes, better lifestyle, awareness.
- What can we do and advise - If you smoke, quit; strive to maintain a healthy weight; stay physically active (at least 30 min of moderate intensity exercise); make vegetables and fruits half of every meal; for the other half, healthy proteins and whole grain carbohydrates; cut back on the amount of salt and sodium you take in; drink water instead of sugary beverages; if you drink alcohol, keep it moderate.
- The Millenium Development Goals (MDG) 2000-2015 were discussed. These include: Extreme poverty eradication; universal primary education; gender equality; reduction in child mortality; improvement in maternal health; combat HIV/malaria; ensure environmental sustainability and global partnership for development.
- There was special mention of victory over Nipah in Kerala in 2018. It was stated that a 28-year-old patient was admitted on May 17 at 2 am and by 9 am, Dr Jayakrishnan had suspected Nipah encephalitis. On May 18, Nipah encephalitis was confirmed. A special mention was also made about Helen Keller who had once said "Alone we can do so little; together we can do so much." It was stressed that helping mankind should be our purpose.

CAN A THERAPEUTIC PLATFORM TO TREAT DMD BE EXTENDED TO OTHER DISEASES?

Dr Steve Wilton, Australia

- Duchenne muscular dystrophy (DMD) is the most common and serious childhood muscle wasting.

- The Eureka moment - Ryszard Kole described suppressing abnormal splicing - AOs targeted to mutant splice site. It was shown in 1999 that molecular intervention at dystrophin pre-mRNA splicing can reduce the severity of a Duchenne mutation to the milder Becker phenotype. Abnormal splicing induced: Exon 23 skipping.
- The US FDA approved the first exon skipping compound in 2016. Eteplirsen is the first drug approved to treat patients with DMD. It is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping.
- Therapeutic alternative splicing - Designing compounds to modify pre-mRNA splicing: Dystrophin and exon skipping; correct abnormal splicing; induce specific isoforms.
- Hypothesis driven translational research - Monitor changes in RNA and protein; if no change in RNA/protein: drug lacks potency or efficient delivery. The DMD future - Gene therapy; next generation PPMOs and delivery; multi-exon skipping; addressing rare DMD mutations.
- Future challenges for precision medicine: Limitations of genomic/exome mutation detection - Comprehensive RNA-based screening; Oligomer production - scale, cost, potency, sustainability; Patient registries, databases and biobanks; Clinical trial challenges - limited patient numbers stratified on mutation, age, disease progression; Quality-of-life issues can be broken down; Stratifying orphan diseases based on mutation type.
- DMD can be the exemplar for so many other diseases.

TÊTE-À-TÊTE WITH PROF (DR) PA MOHAMMED KUNJU

Prof (Dr) PA Mohammed Kunju, Thiruvananthapuram

Can lacosamide monotherapy be used in clinical practice?

The FDA has approved lacosamide as monotherapy in treating partial-onset seizures (POS) in epilepsy patients aged 17 years or older in 2014 and as an oral option for pediatric patients 4 years and older in 2017.

A retrospective, noninterventional study assessed a total of 439 patients (98 first-line and 341 conversion to monotherapy) with focal seizures. Kaplan-Meier estimates of 12-month retention rates were 81.2% and 91.4% for first-line and conversion to monotherapy, respectively. About 66.3% of first-line and 63.0% of conversion to monotherapy patients were seizure free. Lacosamide was effective and well-tolerated as first-line or conversion to monotherapy in a clinical setting in adult and elderly patients with focal seizures.

What is the role of lacosamide in patients with uncontrolled partial-onset seizures?

Patients with uncontrolled seizures experience significant morbidity and mortality and face social stigma and discrimination as well. About 60% of people living with epilepsy have POS and one-third remain uncontrolled, despite trying treatment with a range of antiepileptic drugs (AEDs). Adjunctive therapy with lacosamide significantly reduces seizure frequency in patients with uncontrolled POS.

What is the long-term efficacy of lacosamide in partial-onset seizures?

Lacosamide has demonstrated long-term (5.5 years) efficacy as adjunctive treatment in patients with POS. The median percentage reduction in seizure frequency per 28 days from baseline was 45.9% and the 50% responder rate was 46.6%.

What is known about seizure free days and reduction in seizure frequency with lacosamide?

Lacosamide is able to increase seizure free days in patients. In a clinical trial, it was found that lacosamide 400 mg was able to provide 12% increase in seizure free days while lacosamide 200 mg provided 8% seizure free days compared to 6% with placebo in treatment-resistant seizures.

Can lacosamide be used in patients with renal impairment?

No dose adjustment is necessary in patients with mild-to-moderate renal impairment. A maximum dose of 300 mg/day lacosamide is recommended for patients with severe renal impairment.

At what dose can lacosamide be used in patients with hepatic impairment?

Exercise caution! A maximum dose of 300 mg/day is recommended for patients with mild or moderate hepatic impairment. It is not recommended in severe hepatic impairment.

Can we use lacosamide in pregnancy and pediatric patients?

Safety of lacosamide has not been established in pregnant women.

Lacosamide is approved in the European Union (EU) and the USA for use as monotherapy and adjunctive

therapy for the treatment of focal-onset seizures in adolescents and children aged ≥4 years.

Can we use lacosamide in geriatric patients?

Yes. However, caution should be exercised for dose titration in elderly patients. Blood level may be higher in elderly as, the dose and body weight normalized pharmacokinetic parameters AUC and C_{max} were approximately 20% higher compared to young subjects.

Source: Villanueva V, et al. *Acta Neurol Scand.* 2018; 138(3):186-94.

IDIOPATHIC LATE ONSET CEREBELLAR ATAXIA: A DIAGNOSIS REVISITED

Dr Achal Kumar Srivastava, Meena Lanjiwar; New Delhi

In 1981, the term idiopathic late onset cerebellar ataxia (ILOCA) was first coined by Harding. It is categorized as a group of sporadically occurring degenerative diseases involving cerebellum, its connections and brainstem, of unknown origin, in order to distinguish it from symptomatic ataxias due to identified exogenous and endogenous causes. Estimates of prevalence for ILOCA are limited, but a minimum prevalence of 10.8/1,00,000 has been suggested for UK. ILOCA is a diagnosis of exclusion. One hypothesis is that these disorders may represent monogenic diseases, either as late onset autosomal recessive ataxias or new dominant mutations. Since recessively inherited disorders are more likely to occur sporadically rather than clustered in families, sporadic late onset ataxias might represent late onset variants of Friedreich's ataxia (FRDA) or other recessive ataxias. Also, the occurrence of new dominant mutations in spinocerebellar ataxia (SCA) genes is possible, but appears to be rare. However, the parent who transmitted the disease may have died before clinical symptoms became apparent, making the family history less informative. Additionally autosomal dominant disorders may be apparently sporadic due to false fatherhood. Keogh et al, found that 33% of 'idiopathic' cases harbor compound heterozygous mutations in known ataxia genes, namely SPG7, SYNE1 and ANO10 using whole exome sequencing (WES).

A pilot study done by Nemeth et al, in 50 patients with ataxia who were refractory to diagnosis using next-generation sequencing (NGS) found 58 known human ataxia genes. The overall detection rate was 18% and varied from 8.3% in those with an adult onset progressive disorder to 40% in those with a childhood or adolescent onset progressive disorder. They have found 13 different mutations in eight different genes which are PRKCG, TTBK2, SETX, SPTBN2, SACS, MRE11, KCNC3 and DARS2, of which nine were novel including one causing a newly described recessive ataxia syndrome. Thus, genetic testing using targeted capture followed by NGS was efficient and enabled a molecular diagnosis in many refractory cases. ILOCA includes either pure cerebellar syndrome or additional extracerebellar symptoms such as parkinsonism, bulbar symptoms, vertical gaze paresis, dementia, urinary incontinence, spasticity and other pyramidal tract signs. Noncerebellar symptoms appear in parallel with the worsening of the cerebellar syndrome, thus patients with cerebellar plus syndrome have more pronounced cerebellar symptoms and signs. A retrospective study among 28 patients of ILOCA found that all 13 patients with cerebellar plus syndrome had features of parkinsonism while rest of other symptoms were encountered less frequently. Within 5 years of onset of symptoms, 29-33% ILOCA plus syndrome patients will meet diagnostic criteria for possible or probable multiple system atrophy (MSA) and have a poor prognosis, accumulate greater disability, remain ambulant for a median of 6 years, and survive only 7-9 years. Barbosa et al, in their study of 38 ILOCA patients, also found that 32% patients had a diagnosis of possible or probable MSA. Clinical studies by Schulz et al and Wenning et al showed that many of ILOCA plus patients suffered from MSA. In one large study of over 100 ILOCA patients, less than 30% met the criteria for MSA even after 4 years of onset of symptoms, less than 15% were found to have an identifiable genetic cause and nearly 60% were diagnosed as idiopathic.

Brain imaging, especially MRI is essential in the diagnostic work-up of patients presenting with ILOCA. Besides the most important benefit that is exclusion of an acquired cause, it also provides clues to other causes of sporadic and familial ataxia. In a study of Klockgether et al, brain imaging of patients with pure cerebellar syndrome showed cerebellar atrophy without apparent involvement of brainstem structures while there was atrophy of brainstem along with cerebellum suggestive of olivopontocerebellar atrophy in majority of patients with cerebellar plus syndrome.

Median survival duration from onset of symptoms in pure cerebellar syndrome patients was 20.7 years as compared to 7.7 years in cerebellar plus patients, suggesting faster progression of disease in cerebellar plus syndrome. Patients with pure cerebellar syndrome had a significantly better prognosis as compared to that of patients with additional noncerebellar involvement (annual progression rate: 0.40 vs. 0.80). Prognosis was

even worse in patients who had additional noncerebellar symptoms from the very beginning of disease course as compared to those who developed such symptoms in later course of disease. Early and accurate diagnosis is immensely important not only in guiding treatment but also for patient counseling and support. Availability of WES has further purified the diagnosis of ILOCA.

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IN CONVERSATION WITH DR JS KATHPAL

Dr JS Kathpal, Indore

How should we manage atrial fibrillation patients presenting with acute ischemic stroke while on NOACs?

According to current guidelines and official labeling, thrombolytic therapy with rtPA is approved within 4.5 hours of onset of stroke symptoms but should not be administered in patients on full anticoagulation. Thrombolytic therapy cannot be given within 24 hours after the last intake of a novel oral anticoagulant (NOAC) due to their plasma half-lives, which may even be prolonged in renal insufficiency, the elderly and other situations. The case is different for dabigatran due to the availability of the rapid acting specific reversal agent, idarucizumab.

What are the considerations for NOACs in patients with acute intracranial bleeding?

About two-thirds of all NOAC-related intracranial bleedings (ICBs) are intracerebral and about one-third of all ICBs are subdural bleedings. A recent and large retrospective analysis of the Get With the Guidelines-Stroke program found a more favorable outcome with NOACs compared with vitamin K antagonist (VKA). A neurologist/stroke physician should examine all patients presenting with ICB on an NOAC, and neurosurgical consult should be solicited.

What are the considerations for NOACs in frail (≥75 years) patients?

The incidence of atrial fibrillation (AF) rises steadily with each decade. Stroke prevention in older AF patients is important as stroke risk rises dramatically with age. However, oral anticoagulant (OAC) remains underutilized in older age groups. Older people with AF do better on OAC than not and on NOACs rather than VKA.

Does anticoagulation work in dementia patients?

Dementia is common in older age groups. A stroke is a very significant event for patients with dementia with a greater risk of cognitive and functional decline, loss of independence and institutionalization, compared to nondementia patients. Indeed, AF is itself a risk factor for dementia and there is encouraging evidence that use of OAC may reduce the risk of dementia in AF patients.

What to do if there is (suspected) overdose without bleeding, or a clotting test is indicating a potential risk of bleeding?

In case of a suspected overdose, coagulation tests can help to determine its degree and possible bleeding risk. A normal aPTT excludes high levels of dabigatran; similarly, a normal PT excludes very high levels of rivaroxaban and edoxaban. Given the relatively short plasma half-life of the NOACs, a 'wait-and-see' strategy can be used in most cases without active bleeding. The elimination half-life can be estimated taking into account age and renal function.

What are the considerations for oral anticoagulation in epilepsy patients?

A risk of seizures has been reported in >5% of overall post-stroke patients. Following an unprovoked seizure after stroke, the risk of subsequent unprovoked seizures is about 65% within 10 years. OAC poses a special risk for patients with epilepsy due to the risk of injury during a seizure (with or without falling). Anticoagulation is affected by antiepileptic drugs via various potential interactions. The choice of drug and dose should be as per the clinical judgment of the treating physician.

Source: Steffel J, et al. *Eur Heart J.* 2018;39(16):1330-93.

PREVENTIVE EFFECT OF ROSUVASTATIN IN STROKE

Dr Tapas Kumar Banerjee, Kolkata

Statins are the guideline therapy for primary and secondary stroke prevention. Several large randomized, double-blind trials have shown that statin use in ischemic stroke reduces the risk of incident and recurrent stroke. Statins are known to have lipid-lowering effects. They inhibit HMG-CoA reductase, resulting in a reduction of cholesterol and several other intermediate metabolites. Besides reducing cholesterol, statins also have non-lipid dependent, pleiotropic effects on ischemic stroke. These include improvement in endothelial function

and vasomotor reactivity, antithrombotic effects, anti-inflammatory effects, reduction of oxidative stress and promotion of angiogenesis.

The CARE study revealed significant reduction in incidence of stroke by 31% in patients with myocardial infarction (MI) with pravastatin therapy. Rosuvastatin has also been shown to reduce stroke risk. In the JUPITER trial, rosuvastatin significantly reduced major cardiovascular events and also stroke risk (RRR: 48%; p = 0.002) in apparently healthy individuals but with elevated hsCRP levels. Other statins have also been shown to reduce stroke risk. Several meta-analyses have also shown that pre-stroke statin use is associated with stroke risk reduction. A large meta-analysis of 38 trials revealed that pre-stroke statins use was associated with a stroke RRR of 26%. Yet another meta-analysis including 1,21,000 patients revealed that statins yielded an obvious protection against all-cause mortality and nonhemorrhagic stroke.

Statins thus clearly have a potential preventive effect in stroke. It is noteworthy that statins reduce the risk of stroke in patients with vascular disease or at high risk of vascular disease and their benefit seems to be independent of baseline cholesterol level. Additionally, individuals with normal cholesterol have been found to experience a similar degree of risk reduction as those with high levels of cholesterol.

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BOTULINUM A TOXIN IN POST-STROKE UPPER LIMB SPASTICITY

Dr Nirmal Surya, Mumbai

Botulinum toxin A (BTXA) is a useful tool to reduce the focal spasticity in upper limb following stroke. Advantages of BTXA are that it can be used with other treatments like splinting, casting and active physiotherapy. The effect is local without any systemic side effects and can be repeated after 3 months, if needed. The selection of muscle depends on the spasticity at shoulder, elbow, wrist or fingers. The Modified Ashworth scale is a useful scale to asses the severity of spasticity and to calculate the dose; higher the MAS scale, larger is the dose. The injection can be given under the electromyographic (EMG) guidance or ultrasound use. The treatment aim could be to improve the function, like mobility, transfer or gait improvement or symptomatic, like reduction of pain and spasm, self-care and hygiene, prevention of contracture, etc. The goal of the therapy should be discussed with the patient and caregiver before planning the treatment and should be well documented. Multidisciplinary team care should be ideal for post-stroke care and better outcomes are reported. Post injection treatment could be stretching, electric stimulation or splint and casting, as required by the individual. Finally, outcome will depend on patient selection, appropriate muscle and dosage, post injection treatment and supervised therapy from MDT.

RABIES ENCEPHALITIS - LUCKNOW EXPERIENCE

Dr Neeraj Kumar, Lucknow

Rabies is a preventable neurotropic infection. Rabies infection can occur from many wild and pet animals. Most cases occur in Asia and Africa, especially in children. Timely diagnosis and treatment may be life-saving. Rabies encephalitis is almost 100% fatal. Immunization of animals and pre-exposure prophylaxis in high risk humans is important. Shelter home, immunization, sterilization and monitoring of dogs will be an effective way to eliminate rabies.

DECIPHERING EPILEPTOGENIC AND FUNCTIONAL ZONES USING STEREO EEG

Dr Dinesh Nayak, Chennai

Cortical electrical stimulation is the most reliable form of localizing cerebral functions including language, motor, sensory and visual. Bipolar electrical stimulation is more accurate than monopolar stimulation. Bipolar stimulation is precise focal depolarization block between 2 electrodes. Stereo EEG can simultaneously record activity from superficial and deep cortical structures, in anteroposterior and supro-inferior directions 3-dimensionally. Stereo EEG is a good technique for studying insula, operculum, cingulate, orbital-frontal cortex, depths of the sulcus. Stereo EEG can also be used when bilateral hemispheric coverage is needed.

CURRENT MANAGEMENT STRATEGIES IN MSA

Dr Hrishikesh Kumar, Kolkata

Like other atypical Parkinsonism, multiple system atrophy (MSA) has remained generally unresponsive to treatment. But devising a careful management strategy and modulating it as per the situation often helps in improving the quality-of-life of affected patients. Current treatment strategies target motor impairment, autonomic dysfunction (orthostatic

hypotension, erectile dysfunction, urinary symptoms, etc.), sleep disturbance, sialorrhea, depression and other symptoms. Levodopa remains the mainstay of therapy for motor manifestation despite its modest and non-sustained effect. For orthostatic hypotension, various pharmacological and nonpharmacological measures are being used. Among medications, midodrine has the best evidence as compared to a host of others. Botulinum toxin has limited role in alleviating some of the symptoms like sialorrhea, stridor, overactive bladder, but evidence is not very promising till date. With better understanding of pathogenesis of MSA, novel targets of neuroprotection are being explored and disease-modifying agents are being tried. But as with other neurodegenerative conditions, disease modification still has remained elusive and it seems that there is a long way to go.

THE ROLE OF VITAMIN D IN MULTIPLE SCLEROSIS

Dr Bassem I Yamout, Beirut

There is a strong association between serum vitamin D levels and the risk of MS, supported as a possible causative factor by genome-wide association studies. There is a strong association in patients with MS between serum vitamin D levels and development of relapses or new lesions on MRI. Clinical studies including large randomized controlled trials have shown a consistent effect of vitamin D supplementation on radiological parameters but inconsistent effects on relapse rates and disability progression. Given the strength of indirect evidence, and the low risk of adverse events, it is reasonable to recommend vitamin D replacement at 10,000-50,000 IU weekly, aiming at a serum 25(OH)D level of 75-100 nmol/L to: Persons at high risk of developing MS such as first-degree relatives of MS patients, especially with multiple affected family members; Patients with MS in whom such replacement might prevent disease activity.

PREVENTION OF STROKE

Prof Subhash Kaul, Secunderabad

Risk factors for stroke - *Nonmodifiable*: Age, race, sex, low birth weight, genetic factors; *Modifiable*: High BP, abnormal lipid profile, diabetes, smoking, atrial fibrillation, alcohol, oral contraceptives, diet and physical inactivity. Twin studies data suggest an inheritance of stroke risk. Babies weighing <1.5 kg have a double risk of developing stroke, heart disease or MI before age 50. Men have high age-specific stroke incidence rates. Oral contraceptives/pregnancy put women at risk. Risk doubles for each decade after age 55 years. The good news is that age alone is not a risk factor for stroke. Stroke is a result of interaction of risk factors. Controlling more risk factors reduces the risk. We must know our risk factors. Risk factor assessment in adults should begin at age 20 years. Smoking status, diet, alcohol intake, physical activity and family history should be assessed periodically. High BP increases the risk. Higher the BP, higher the risk. Diabetes doubles the risk of ischemic stroke. All lipid fractions increase the risk and should be treated. High risk patients, even with normal LDL levels, should be treated with statin. Initiate weight management program through caloric restriction and increased caloric expenditure. Body weight in obese should be reduced by 10% in the first year. Should aspirin be used in primary prevention? - As per AHA, you should, if you have >2 risk factors; If you have high-grade asymptomatic vascular disease. Air pollution is now a leading stroke risk factor. Stroke is therefore a result of gene-environment interaction. Strict risk factor control can minimize the risk. Risk factor control is an umbrella for protection.

INVASIVE BIOPSY IN NEUROLOGY: NEUROSURGICAL EXPERTISE

Dr Sumit Thakar, Bengaluru

Invasive biopsy in Neurology must be carefully planned with multidisciplinary input. It is crucial to select an optimal biopsy site to maximize the chance of obtaining representative sample with minimal complications. Patients with focal neurological signs/encephalopathy/focal findings on imaging/cerebrospinal fluid pleocytosis/an abnormal inflammatory screen are more likely to have positive brain biopsies. Brain biopsy can be either open (for superficial or potentially vascular lesions) or more commonly, stereotactic (frame-based or frameless; for well-defined, deep seated or infiltrative lesions or lesions in eloquent cortex). Even though both brain and spine biopsies are not technically demanding, they can be associated with complications, some of which can be irreversible. Given the low overall diagnostic yield, surgical risks and also the added costs, the pros and cons of the procedure should be carefully weighed.

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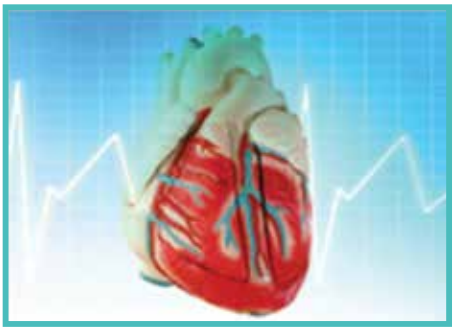

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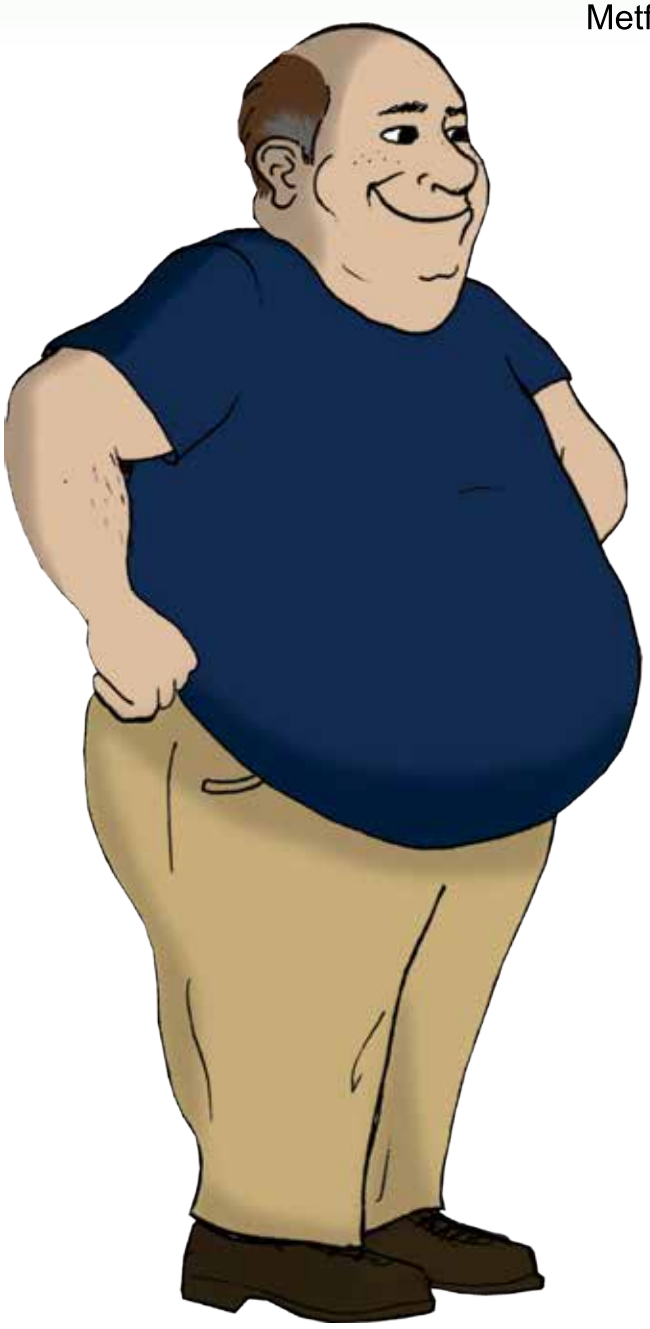

Superior Glycaemic Control In Obese T2DM

2018

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News and Views

FDA Alerts Doctors and Patients About Risk of Complications When Implanted Pumps are Used to Deliver Pain Medications not Approved for Use with the Devices

The US Food and Drug Administration (FDA) has alerted healthcare providers and patients about the serious complications that can occur when using medications not approved for use with implanted pumps that deliver medication into the spinal fluid to treat or manage pain. Complications may include dosing errors, pump failure, opioid withdrawal, infection and other complications like pain, fever, vomiting, muscle spasms, cognitive changes, weakness and cardiac or respiratory distress.

Migraines that Affect Vision may Increase Risk of Atrial Fibrillation

People with migraine with aura were found to be 30% more likely to develop atrial fibrillation than people who did not have headaches and 40% more likely to develop atrial fibrillation than people with migraine with no aura, according to a study published in the November 14, 2018, online issue of the journal *Neurology*. Also, the stroke rate in the migraine with aura group was 4 out of 1,000 people annually compared to 2 out of 1,000 people annually in those with migraine without aura, and 3 of 1,000 people annually in those with no headache.

Treatment Withdrawal in Patients Who have Recovered from Dilated Cardiomyopathy Leads to Relapse

Results of the TRED-HF study show that many patients deemed to have recovered from dilated cardiomyopathy will relapse following treatment withdrawal. In this pilot study, treatment was withdrawn successfully in only 50% of patients, while 40% had a relapse of their dilated cardiomyopathy within 6 months. The results are published online November 11, 2018 in *The Lancet*.

Prednisone Prevents Paradoxical Tuberculosis-associated IRIS

Prednisone treatment during the first 4 weeks after the initiation of ART for HIV infection resulted in a lower incidence of tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) than placebo, without evidence of an increased risk of severe infections or cancers in a study reported November 15, 2018 in the *New England Journal of Medicine*.

LT4 Monotherapy that Normalizes Serum TSH for Overt, Primary Hypothyroidism does not Normalize Total and LDL Cholesterol

A systematic review and meta-analysis of 99 studies published online August 15, 2018 in the *Journal of Clinical Endocrinology & Metabolism* concluded that in studies of levothyroxine (LT4) monotherapy at doses that normalized serum thyroid-stimulating hormone (TSH) for overt, primary hypothyroidism, not all systemic biological markers of thyroid hormone signaling were normalized, including the serum low-density lipoprotein (LDL) and total cholesterol levels.

Five-minute Hands-only CPR Kiosk Training as Effective as a 30-minute Class for Learning CPR Skills

People who learn hands-only CPR using a 5-minute, kiosk-based program performed CPR as well as those who attended a 30-minute, facilitator-led training session, according to a new research by the American Heart Association, which examined three methods of teaching hands-only CPR published November 12, 2018 *in Annals of Emergency Medicine*. People who watched the 1-minute training video scored lower than the classroom group in total score, but there were no significant differences in total score between classroom and kiosk participants.

Combining Two Imaging Modalities Helps View the Retina in Great Detail

Using two imaging modalities together - adaptive optics and angiography - can facilitate detailed visualization of live neurons, epithelial cells and blood vessels deep in the eye's light-sensing retina and may transform the detection and treatment of diseases such as age-related macular degeneration (ARMD), say investigators at the National Eye Institute (NEI).

Study Shows Better Prognosis with Metabolic Surgery vis-à-vis Medical Therapy in Type 2 Diabetes

In a systematic review and meta-analysis of 19 trials, people who underwent metabolic surgery saw 66% reduced odds for all-cause mortality, including

macrovascular complications when compared with medical therapy for patients with type 2 diabetes. These findings were presented at Obesity Week, a joint meeting of the Obesity Society and the American Society for Metabolic and Bariatric Surgery (ASMBS) in Nashville in Tennessee, USA.

Preventing Mother-to-child Transmission of Chagas Disease: From Control to Elimination

The World Health Organization (WHO) is shifting its focus towards active screening of girls and women of childbearing age to detect the presence of *Trypanosoma cruzi*, the causative parasite of Chagas disease. Recent evidence demonstrates that diagnosing and treating women of this age group before pregnancy can effectively prevent congenital transmission.

"Identifying pregnant women already infected with the parasite, as well as newborns and siblings, has been a major challenge in both endemic and non-endemic countries" said Dr Pedro Albajar Viñas, Medical Officer, WHO Department of Control of Neglected Tropical Diseases. *"With the progressive control of transmission by vectors and through blood transfusion, updating, reinforcing and expanding standardized screening measures for congenital transmission make absolute sense."*

Up to now, control and prevention strategies for Chagas disease largely relied on the early detection and treatment of infected newborns and siblings of pregnant women. But a recent shift in approaches to prevent transmission globally - including in non-endemic countries - is through active, systematic screening of girls and women at risk of infection and provides excellent opportunities for prevention of posterior transmission throughout pregnancy and birth… (*WHO*, Nov. 16, 2018)

A New Drug to Treat Travelers' Diarrhea

The US FDA has approved rifamycin, an antibacterial drug indicated for the treatment of adult patients with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*, not complicated by fever or blood in the stool.

Inhaling Deodorant Spray to Get "High" can be Fatal

The *BMJ* has reported a case of a 19-year-old man under treatment for ketamine and cannabis abuse, who relapsed. In a bid to get high, he put a towel over his head and inhaled the spray from a deodorant. He quickly became hyperactive, before going into cardiac arrest and collapsing. Basic life support and six rounds of defibrillation failed to revive him and he was admitted to intensive care where he was put into an induced medical coma. His condition did not improve and realising that further treatment would be pointless, doctors withdrew it and he died shortly afterwards.

As per the authors, the main toxic substance in deodorant spray inhalation is butane (hydrocarbon), which is lipophilic and therefore easily crosses the air-blood and blood-brain barrier. Butane dissolves into tissues with a high fat content such as the nervous system, fat tissue, liver and kidneys.

Different Types of Physical Activity Offer Varying Protection Against Heart Disease

New research, presented at the ACC Latin America Conference 2018 in Lima, Peru, found that while all physical activity is beneficial, static activities—such as strength training—were more strongly associated with reducing heart disease risks than dynamic activities like walking and cycling. Patients who did both types of physical activity had better outcomes than patients who simply increased the level of one type of activity.

Long-term Exposure to Road Traffic Noise may Increase Obesity Risk

Long-term exposure to road traffic noise is associated with increased risk of obesity, as per a study published in *Environment International* online November 16, 2018. A 10 dB increase in mean noise level was associated with a 17% increase in obesity.

Vagus Nerve Stimulation + Upper Limb Rehabilitation Improves Arm Function Post-stroke

Vagus nerve stimulation paired with rehabilitation was acceptably safe and feasible in patients with upper limb motor deficit after chronic ischemic stroke in a blinded randomized pilot study published in the journal *Stroke*.

Study Recommends Surveillance for Liver Cancer in Older Patients with Hepatitis B

Surveillance for hepatocellular carcinoma (HCC) should continue in patients older than 50 years, even after they have undergone 5 years of therapy for chronic hepatitis B, according to an analysis of the PAGE-B cohort presented November. 12, 2018 at The Liver Meeting 2018: American Association for the Study of Liver Diseases (AASLD) in San Francisco.

Increasing Tumor Stage is a Risk Factor for Local Regrowth of Rectal Cancer After Watch and Wait Management

A study evaluating factors affecting local regrowth after watch and wait for patients with rectal cancer and a clinical complete response following chemoradiotherapy in rectal cancer found some evidence that increasing clinical T (cT) stage increases the risk of local regrowth of the cancer.

Modulation of Gut Microbiome may Alleviate Immunotherapy-associated Colitis

Researchers have reported the first case series of immune checkpoint inhibitors-associated colitis successfully treated with fecal microbiota transplantation, with reconstitution of the gut microbiome and a relative increase in the proportion of regulatory T-cells within the colonic mucosa in the journal *Nature Medicine*, online November 12, 2018.

The First Treatment Specifically for Patients with Refractory Primary Hemophagocytic Lymphohistiocytosis

The US FDA has approved emapalumab-lzsg for the treatment of pediatric (newborn and above) and adult patients with primary hemophagocytic lymphohistiocytosis (HLH) who have refractory, recurrent or progressive disease or intolerance to conventional HLH therapy.

Persistent Inflammation Increases Chances of Adverse Outcomes in Post-PCI Patients

Patients who have persistently high levels of inflammation following percutaneous coronary intervention (PCI) for coronary artery disease (CAD) are significantly more likely to die from any cause or to have a heart attack within a year, according to a study of 7,026 patients published in the *European Heart Journal*, online November 19, 2018. Residual inflammatory risk (RIR) refers to the risk of further heart and blood vessel problems caused by vascular inflammation in patients with known CAD. High sensitivity C-reactive protein (hsCRP) is used as a biological marker to examine the level of risk.

ACOG New Guidelines on Dysmenorrhea and Endometriosis in Adolescents

The American College of Obstetricians and Gynecologists (ACOG) has published a new committee opinion on dysmenorrhea and endometriosis in adolescents, online November 20, 2018. Some key recommendations include:

- Most adolescents experience primary dysmenorrhea, defined as painful menstruation in the absence of another pelvic disease.
- Recommended treatment is conservative surgical therapy for diagnosis and treatment combined with ongoing suppressive medical therapies to prevent endometrial proliferation.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be the mainstay of pain relief for adolescents with endometriosis.
- Evaluate for secondary endometriosis, if dysmenorrhea does not improve or worsens while using recommended treatments, or who present with other symptoms immediately indicating secondary dysmenorrhea (e.g., a family history of endometriosis, abnormal or irregular bleeding or severe pain immediately following their first period).
- In adolescents, endometriotic lesions differ from those in older women; they are typically clear or red and can be difficult to identify for gynecologists unfamiliar with endometriosis in adolescents.

Eyes of CJD Patients Show Evidence of Prions

Researchers from the National Institutes of Health (NIH) have found evidence of prion seeding in the eyes of deceased patients of sporadic Creutzfeldt-Jakob disease (CJD). The retina consistently showed the highest seed levels; prion seeds were also present in the optic nerve, extraocular muscle, choroid, lens, vitreous and sclera. These results show that sCJD patients accumulate prion seeds throughout the eye, indicating the potential diagnostic utility as well as a possible biohazard.

USPSTF Recommends HIV PrEP for High-risk Patients

In a draft recommendation statement published online November 20, 2018 on its website, the US Preventive Services Task Force (USPSTF) recommends ("*A*" *recommendation*) that clinicians offer pre-exposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high risk of HIV acquisition.

Obesity Increases Risk of Type 2 Diabetes and Heart Disease

In a systematic review and meta-analysis of nearly 1 million participants, obesity was associated with an increased risk of developing type 2 diabetes and CAD but not with stroke. The study was published online

November 16, 2018 in *JAMA Network Open*. For each unit increase in body mass index (BMI), the risk of type 2 diabetes increased by 67%, while the risk of CAD increased by 20%.

Omalizumab is Effective as Rescue Therapy for Status Asthmaticus

A case report published November 20, 2018 in *Annals of Internal Medicine* describes the successful use of omalizumab as rescue therapy for refractory status asthmaticus in a 41-year-old man with a history of asthma with pollen allergy, who developed severe dyspnea while working at an outside construction site.

Complementary Treatments may Help Relieve Headache Patients

Acupuncture, massage, yoga, biofeedback, meditation and other complementary practices can have a positive effect on migraine and tension headaches, as reported at the American Headache Society's Scottsdale Headache Symposium in Scottsdale, Arizona.

Older Obese Never-smokers should also be Routinely Screened for COPD

In a study published in the *Journal of Obesity*, chronic obstructive pulmonary disease (COPD) is much more common among never smoking older women who are morbidly obese (BMI of 40 or higher) than among their female peers in the normal weight range (13.4% vs. 3.5%, respectively). Morbidly obese older men who have never smoked also had a much higher prevalence of COPD than never-smoking men who were normal weight (7.6% vs. 2.5%).

Increased Alcohol Consumption in Colder Climates, Says Study

According to new research from the University of Pittsburgh Division of Gastroenterology published online in *Hepatology*, as temperature and sunlight hours dropped, alcohol consumption increased. People living in colder regions with less sunlight drink more alcohol than their warm-weather counterparts. Climate factors also were tied to binge drinking and the prevalence of alcoholic liver disease.

Cabinet Approves the Allied and Healthcare Professions Bill, 2018 for Regulation and Standardization of Education and Services by Allied and Healthcare Professionals

The Union Cabinet chaired by Hon'ble Prime Minister Shri Narendra Modi has approved the Allied and Healthcare Professions Bill, 2018 for regulation and standardization of education and services by allied and healthcare professionals. The Bill provides for setting up of an Allied and Healthcare Council of India and corresponding State Allied and Healthcare Councils which will play the role of a standard-setter and facilitator for professions of Allied and Healthcare.

Details:

- Establishment of a Central and corresponding State Allied and Healthcare Councils; 15 major professional categories including 53 professions in Allied and Healthcare streams.
- The Bill provides for Structure, Constitution, Composition and Functions of the Central Council and State Councils, e.g., Framing policies and standards, Regulation of professional conduct, Creation and maintenance of live registers, Provisions for common entry and exit examinations, etc.
- The Central Council will comprise 47 members, of which 14 members shall be ex-officio representing diverse and related roles and functions and remaining 33 shall be non-ex-officio members who mainly represent the 15 professional categories.
- The State Councils are also envisioned to mirror the Central Council, comprising 7 ex-officio and 21 non-ex officio members and Chairperson to be elected from amongst the non-ex officio members.
- Professional Advisory Bodies under Central and State Councils will examine issues independently and provide recommendations relating to specific recognized categories.
- The Bill will also have an overriding effect on any other existing law for any of the covered professions.
- The State Council will undertake recognition of allied and healthcare institutions.
- Offences and Penalties clause has been included in the Bill to check malpractices.
- The Bill also empowers the Central and State Governments to make rules.
- Central Govt. also has the power to issue directions to the Council, to make regulations and to add or amend the schedule.

Targets:

- An Interim Council will be constituted within 6 months of passing of the Act holding charge for a period of 2 years until the establishment of the Central Council.

- The Council at the Center and the States are to be established as body corporate with a provision to receive funds from various sources.
- Councils will also be supported by Central and State Governments respectively through Grant-in-aid as needed. However, if the State Government expresses inability, the Central Government may release some grant for initial years to the State Council.

Major Impact, including employment generation potential:

- Bring all existing allied and healthcare professionals on board during the first few of years from the date of establishment of the Council.
- Opportunity to create qualified, highly skilled and competent jobs in healthcare by enabling professionalism of the allied and healthcare workforce.
- High quality, multi-disciplinary care in line with the vision of Ayushman Bharat, moving away from a 'doctor led' model to a 'care accessible and team based' model.
- Opportunity to cater to the global demand (shortage) of healthcare workforce which is projected to be about 15 million by the year 2030, as per the WHO Global Workforce, 2030 report.

Expenditure involved:

Total cost implication is expected to be Rupees 95 crores for the first four years. About four-fifths of the total budget (i.e., Rupees 75 crores) is being earmarked for the States while the remaining fund will support the Central Council operations for 4 years and also establish the Central and State Registers.

Number of beneficiaries:

It is estimated that the Allied and Healthcare Professions Bill, 2018 will directly benefit around 8-9 Lakh existing Allied and Healthcare related professionals in the country and several other graduating professionals joining workforce annually and contributing to the health system. However, since this Bill is directed to strengthen the healthcare delivery system at large, it may be said that the entire population of the country and the health sector as a whole will be benefited by this Bill.

Background:

- In the current state of healthcare system, there exist many allied and healthcare professionals, who remain unidentified, unregulated and underutilized. Our system is highly focused on efforts towards strengthening limited categories of professionals such as doctors, nurses and frontline workers (like Accredited Social Health Activist or ASHAs, Auxiliary Nurse Midwife or ANMs). However, numerous others have been identified over the years, whose potential can be utilized to improve and increase the access to quality driven services in the rural and hard to reach areas.
- Allied and Healthcare Professionals (A&HPs) constitute an important element of the health human resource network, and the skilled and efficient A&HPs can reduce the cost of care and dramatically improve the accessibility to quality driven healthcare services.
- Globally, A&HPs typically attend undergraduate degree program of a minimum of 3-4 years to begin with and may attain up to PhD level qualification in their respective streams. However, most of Indian institutions offering such courses lack standardization.
- Majority of the countries worldwide, have a statutory licensing or regulatory body that is authorised to license and certify the qualifications and competence of such professionals, particularly those involved in direct patient care (such as physiotherapist, nutritionist, etc.) or those whose occupation impact patient care directly (such as lab technologists, dosimetrists, etc.).
- Though such professionals have existed in the Indian healthcare system for many decades, a considerable gap in the allied and healthcare space is because of a lack of a comprehensive regulatory framework and absence of standards for education and training of A&HPs.
- The Bill thus seeks to establish a robust regulatory framework which will play the role of a standard-setter and regulator for Allied and Healthcare professions.

(*Press Information Bureau. Nov. 22, 2018*)

Skin Autofluorescence can Predict Type 2 Diabetes and Heart Disease

New research published online November 21, 2018 in the journal *Diabetologia* has shown that noninvasive skin autofluorescence measurement predicts incident type 2 diabetes, cardiovascular disease (CVD) and mortality in the general population independent of several traditional risk factors such as obesity, metabolic syndrome, glucose and A1c. A 1-unit higher

skin autofluorescence was associated with a 3-fold increase in risk of type 2 diabetes or CVD, and a 5 times increased risk of death.

Leafy Greens and Orange Juice Reduce Risk of Memory Loss in Men

Eating a diet rich in leafy greens, dark orange and red vegetables, berries and orange juice lowers the risk of memory loss over time in men, suggests a study published online November 21, 2018 in *Neurology*. The men who consumed the most vegetables were 34% less likely to develop poor thinking skills than the men who consumed the least amount of vegetables. The men who drank orange juice every day were 47% less likely to develop poor thinking skills than the men who drank less than one serving per month.

No Benefit with Probiotic in Children with Acute Gastroenteritis

Two randomized double-blind controlled trials published online in the *New England Journal of Medicine* showed that the probiotic *Lactobacillus rhamnosus* proved no more effective than placebo for treating young children with acute infectious gastroenteritis.

NSAIDs may be Administered to Postpartum Patients with Hypertensive Disorders of Pregnancy

Administration of NSAIDs to postpartum patients with hypertensive disorders of pregnancy is not associated with a change in blood pressure or requirement for antihypertensive medication, suggests a retrospective cohort study published in the December 2018 issue of *Obstetrics & Gynecology*.

Slower Walking Speed Associated with Greater Risk of Dementia

In a study published in the *Journal of the American Geriatrics Society*, participants with faster baseline walking speeds were at lower risk of developing dementia. Those with a greater decline in walking speed from Wave 1 to 2 were at greater risk of developing dementia. Participants with better baseline cognition were at lower risk of developing dementia.

National Blood Transfusion Council Advisory for Blood Banks and Potential Blood Donors to Prevent Zika Virus Infection in the Country by Blood Transfusion

All blood banks in the country should ensure following precautions:

- Blood banks strictly adhere to donor selection criteria and do proper donor screening. Blood banks must ask for travel history to ensure that individuals returning from outbreak zone are not accepted for blood donation till 120 days of return. These donors must be symptom-free during this period prior to blood donation.
- Blood banks should not accept blood from donors till 2 weeks following complete recovery from acute viral infection and cessation of any therapy/ medications.
- Potential blood donors who have returned from outbreak zone should:
  - Not donate blood for 120 days from date of return.
  - Blood donors should report to blood bank if they develop sign and symptoms of Zika infection within 2 weeks of blood donation.
- The National Blood Transfusion Council (NBTC) has not approved any blood donor screening tests for Zika virus.
- No human plasma should be imported from Zika outbreak regions/countries.

WHO and EU Commit to Work Together to Accelerate Progress on Health

Dr Tedros Adhanom Ghebreyesus, Director-General of WHO has completed a series of meetings with President Juncker and senior European Commission officials. He also signed a joint statement with the European Parliament. Dr Tedros commended the fruitful cooperation between the Commission and WHO, particularly in the fields of antimicrobial resistance, strengthening health systems and preparedness for outbreaks of communicable diseases in developing countries. President Juncker confirmed the support of the European Commission to the Global Action Plan on Health and Well Being to accelerate progress to achieve Sustainable Development Goals, including goal number 3, related to healthy lives and well-being at all ages.

President Juncker and Dr Tedros also spoke about the importance of focusing on air pollution and agreed to jointly organize a Global Vaccination Summit, building on initiatives to increase vaccination and improve vaccination confidence in the EU, with the aim of avoiding unnecessary deaths from preventable diseases… (WHO, Nov. 21, 2018)

Study Shows Clinical Benefit of Treating Low-risk Stage-1 Hypertension

Korean National Health Insurance Database Analysis published in the December 2018 issue of the journal *Hypertension* has shown that the blood pressure (BP) associated with the lowest risk of all-cause mortality was 120 to <130 mmHg (systolic BP) and 70 to <80 mmHg (diastolic BP). There was an increased risk of myocardial infarction in patients with mean systolic BP <120 mmHg and diastolic BP <80 mmHg. BP <140/90 mmHg was associated with a significant reduction in the risk of mortality, stroke and end-stage renal disease, with the lowest mortality risk at BP ranges of 120 to <130 and 70 to <80 mmHg.

B_{12} Deficiency is Common in Patients on Metformin

Vitamin B_{12} should be monitored in patients with diabetes on metformin to avoid peripheral neuropathy, suggests a study presented November 21, 2018 at the Society for Endocrinology BES 2018 conference in Glasgow. The study found that 64% of patients had not been tested for vitamin B_{12} deficiency. Almost 10% of patients were found to have vitamin B_{12} deficiency, although only just over 6% were being treated.

Deceased-donor Acute Kidney Injury is not Associated with Kidney Allograft Failure

Use of kidneys from deceased donors with acute kidney injury (AKI) appears safe in multiyear follow-up and could make many more organs available for transplant, according to a multicenter study published November 20, 2018 in *Kidney International*.

Both Divide-and-Conquer and Stop-and-Chop Techniques Efficient in the Learning Curve for Cataract Surgeons

A study comparing two popular nuclear disassembly techniques for cataract surgeons in training concluded that both divide-and-conquer and stop-and-chop techniques are efficient in the learning curve. Stop and chop dissipates less energy in harder nuclei. Once surgeons reach sufficient experience with both techniques, they should switch to a stop-and-chop technique, allowing lower levels of ultrasound energy. The study is published in the journal *International Ophthalmology*, November 21, 2018.

A Multimodal Program may Reduce Job Stress Among ICU Nurses

In a randomized clinical trial including 198 intensive care unit (ICU) nurses in France, the prevalence of job strain (assessed by a questionnaire that included psychological demand and decision latitude evaluation) was significantly reduced at 6 months among nurses in the 5-day intervention group (13%) that included education, role-play and debriefing compared with those in the control group (67%).

Ezetimibe Reduced First Cardiac Events in Older Adults

Results of the Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-risk, Elderly (75 years old or over) Patients with Elevated LDL-Cholesterol (EWTOPIA75) presented at the American Heart Association Scientific Sessions 2018 in Chicago show that ezetimibe reduced the rate of a first cardiac event—a composite of sudden cardiac death, myocardial infarction, coronary revascularization, and stroke—more than diet alone in 75- to 104-year-old Japanese patients with elevated LDL cholesterol and a second risk factor.

Study Shows Hydrocephalus as a New Complication of Congenital Zika Syndrome

Hydrocephalus may be a complication of congenital Zika syndrome, and the presenting signs and symptoms are challenging to recognize, says a study published online November 19, 2018 in *JAMA Neurology*. The researchers recommend that monitoring for hydrocephalus, including assessing the potential harbinger of cerebellar or brainstem hypoplasia, should be part of the standard care of these patients.

Over Half of Former ICU Patients Report Symptoms of Psychological Disorders

A study from the UK published in journal *Critical Care* shows that patients who have survived critical illnesses requiring care in an ICU frequently report symptoms of anxiety, Post-traumatic stress disorder (PTSD) and/or depression. Those reporting symptoms of depression after critical illness were at a greater risk of death.

Night Shifts and Unhealthy Lifestyle Together Increase the Risk of Developing Diabetes

Working night shifts and having an unhealthy lifestyle appear to have an additive effect on the likelihood of developing type 2 diabetes, and women with both have a greater risk than simply adding the impact of either factor alone. The study published online on November 21 in *BMJ* indicates that every 5 years of rotating night shift work increased the risk of type 2 diabetes by around 30%.

IJCP SUTRA 551: You can mix turmeric with milk and drink it at night before sleeping. It helps get rid of cough and cold, boosts immunity, reduces inflammation and keeps you warm.

Voclosporin is Effective in Patients with Lupus Nephritis

The addition of low-dose voclosporin to mycophenolate mofetil and corticosteroids for induction therapy of active lupus nephritis (LN) results in a superior renal response compared to mycophenolate mofetil and corticosteroids alone, as per results of the AURA-LV trial published November 9, 2018 in the journal *Kidney International*. However, higher rates of adverse events including death were observed.

Gujarat Tops in Implementing Ayushman Bharat

Two months after the launch of Ayushman Bharat-Pradhan Mantri Jan Arogya Yojana (AB-PMJAY), Gujarat has emerged as the top performer of the Centre's ambitious health financing scheme. As of November 23, the state accounted for around 26% of the total number of hospital admissions cleared under the scheme so far.

AB-PMJAY, which was launched on September 23, promises health coverage of Rs. 5 lakh per family to over 10 crore poor families. Over 3.4 lakh beneficiaries have been treated under the scheme since its launch until November 24, according to the National Health Agency. Claims of Rs. 400 crore have been raised under this scheme so far, of which Rs. 350 crore has already been given out by the center and states, said a senior government official, requesting anonymity. Earlier this month, the finance ministry was asked for an additional Rs. 2,000 crore to keep the scheme running for the rest of this financial year, ET has learnt.

While Gujarat clocked in around 76,000 hospital admissions since September 23, Tamil Nadu ranked second at 54,273 and Chattisgarh third at 53,180, according to data from the health ministry. Karnataka and Maharashtra, which came on board for the scheme close to its launch, also rank among the top five performers at 40,216 and 27,237, respectively, ET has learned … (*ET Bureau, November 26, 2018*).

Early HIV Diagnosis Means Successful Treatment

Late diagnosis of HIV remains a challenge across the WHO European Region. Every second newly diagnosed person has already reached an advanced stage of the infection. In the European Union/European Economic Area, the latest data from 2017 show that almost 90% of AIDS diagnoses happened within just 90 days of the HIV diagnosis. This indicates that the majority of these AIDS cases could have been avoided with early diagnosis.

Yet being tested for HIV has never been easier. Across Europe, peer counselors, who are not necessarily medical professionals but have received special training, give advice, support and are able to deliver results in a matter of minutes at community-based testing facilities. In the event of a positive test result, confirmation at a healthcare facility will be needed. If confirmed, doctors follow-up and are then able to provide treatment using antiretroviral drugs. These drugs prevent the HIV infection from developing into AIDS and make it possible for people to live long, healthy lives with HIV. In the majority of cases, treatment leads to an undetectable level of the virus in the blood, meaning there is no need to fear transmitting the virus to sexual partners ... (*WHO Europe*).

Use of Tanning Bed Increases Risk of Second Melanoma

According to a retrospective study reported in the *Journal of the American Academy of Dermatology*, 56% of patients exposed to artificial ultraviolet radiation (arUVR) were diagnosed with a second primary melanoma within 1 year of their first diagnosis compared with 18% of patients who had not been exposed to arUVR.

Lipoprotein Levels may Inform Timing of Aortic Valve Replacement

The higher the plasma levels of certain lipoproteins and their components, the faster the progression of calcific aortic valve stenosis among people with mild-to-moderate jets - with no threshold found for this relationship. Valve stenosis was more likely to progress rapidly (Vpeak going up by at least 0.20 m/s per year) with increasing baseline levels of: Lipoprotein(a), oxidized phospholipids on apolipoprotein B (OxPL-apoB) and oxidized phospholipids on apolipoprotein(a). These findings are published online in *JAMA Cardiology*.

Nonsurgical Approaches as Effective as Surgery in Patients with Gleason 9-10 Prostate Cancer

For prostate cancer patients with aggressive, Gleason 9-10 disease, treatment with aggressive radiotherapy (MaxRT) plus hormone therapy was at least as effective as an aggressive surgical approach (MaxRP) in a retrospective study reported in *JAMA Oncology*. The mortality outcomes were similar between the two groups of patients.

Risk of Falls with Trazadone Similar to that with Atypical Antipsychotics

Trazadone, which is often used as an alternative drug is also associated with similar risk of falls and major fractures as antipsychotics in seniors with dementia, according to new research in *CMAJ (Canadian Medical Association Journal)* reported online published November 26, 2018. Patients who were given trazadone had a rate of falls and major fractures, including hip fractures, similar to that of the group receiving atypical antipsychotics. But, trazadone was associated with a lower risk of death in these patients.

Obese Children, Unlike Obese Adults, do not have More Pain After Surgery

While obese adults often report more pain after surgery, the same does not appear to be true for obese children, according to the largest study of its kind presented at the Anesthesiology 2018 annual meeting in San Francisco. The findings suggest the current protocol for managing pain in children after surgery—in which dosing is based on the patient's actual body weight and not BMI or whether the child is considered obese—should continue.

FDA Approves an Oncology Drug that Targets a Key Genetic Driver of Cancer, Rather Than a Specific Type of Tumor

The US FDA has granted accelerated approval to larotrectinib, a treatment for adult and pediatric patients whose cancers have a specific genetic feature (biomarker). This is the second time the agency has approved a cancer treatment based on a common biomarker across different types of tumors rather than the location in the body where the tumor originated. The approval marks a new paradigm in the development of cancer drugs that are "tissue agnostic."

A Second Human Case of Rat Hepatitis Discovered, Making it also the Second Recorded Globally

A 70-year-old woman from the Wong Tai Sin district of Hong Kong was diagnosed with the disease this month, according to Hong Kong's Department of Health. She does not recall having direct contact with rodents or their excreta (feces and bodily fluids) and didn't notice any rodents in her residence, the Department of Health said in a statement. The woman was admitted to a public hospital on May 4, 2017, for headache, anorexia, malaise, abdominal pain and palpitations, which she had developed since May 1, 2017. She soon recovered and was discharged 4 days later, on May 8. The woman had underlying illnesses, according to the Department of Health.

In September, the first case was reported, involving a 56-year old man. Before this, it was not known that the disease could be passed from rats to humans… (CNN)

One in 40 US Children has an ASD Diagnosis According to Parents

Researchers from the Health Resources and Services Administration's (HRSA) Maternal and Child Health Bureau, the Centers for Disease Control and Prevention, Harvard, Drexel, and George Washington Universities estimated that parents of 1 in 40 US children reported their child had autism spectrum disorder (ASD). The study is published online November 26, 2018 in the journal *Pediatrics*.

Lung Disease in Middle Age may be a Risk Factor for Dementia Later in Life

Middle-aged adults with lung disease may be at greater risk of developing dementia or cognitive impairment later in life, according to new research published online November 26, 2018 in the *American Journal of Respiratory and Critical Care Medicine*. Compared to those without lung disease, the odds of dementia or mild cognitive impairment were 58% higher among those with restrictive lung disease and 33% higher among those with obstructive lung disease. Low results on forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were also associated with dementia.

Cerebellar TMS may Improve Post-stroke Motor Functions in Post-stroke Hemiparesis

Transcranial magnetic stimulation of the cerebellum led to improved post-stroke motor functions in a small phase IIa randomized, double-blind sham-controlled trial in Italy as reported in *JAMA Neurology*. After 3 weeks of repetitive, intermittent theta-burst magnetic stimulation to the cerebellum (CRB-iTBS) and physical therapy, hemiparetic patients following ischemic stroke improved their ability to walk and keep their balance more than patients who received sham stimulation and physical therapy.

■■■■

Temple Enhances Soul to Soul Connectivity

KK AGGARWAL

A Temple, Gurudwara or a Masjid can also be understood by studying the concept of computer internet-based virtual e-communication. The physical body can be compared to that of computer hardware and the subtle body with three application softwares of a computer namely, Mind (Microsoft Word), Intellect (Excel) and Ego (Power Point).

These three application softwares are controlled by *Chitta* or the life force, which is a combination of *Prana*, *Tejas* and *Ojas* (or Operational Software in computer language). Without *chitta* or operational software, the body cannot function. A dead person (dead computer) will be devoid of *chitta* (operational software).

The application and operation softwares in turn are controlled by the soul, which is nothing but energized information or soul. This energized information in the body in Vedic language is called *Shiva Shakti*, where *Shiva* represents information and *Shakti* represents the energy or the power of the software.

This energized information or the soul can be equated to a very high speed internet connection www.god.com-drkkaggarwal for me. For another person, for example, Mr BS Sokhi, the soul communication will be www.god.com-bssokhi.

Both these souls will be communicated to a virtual internet called GOD or SPIRIT. The same can be represented as www.GOD.com and in this virtual consciousness or GOD, these pages will be similar to Facebook pages for individual members. For example, there will be a page called www.GOD.com-drkkaggarwal and another page called www.GOD.com-bssokhi.

Whatever you do is converted into a virtual memory and a copy of that is saved in both www.god.com and www.GOD.com. This way the phrase that GOD is watching each and every action can be explained.

Increasing one's connectivity with GOD is like increasing the bandwidth of a computer internet. The same can be done in the body by controlling the mind, intellect and ego and by learning the process of Meditation, Pranayama and living a parasympathetic lifestyle.

Mobile towers or satellites are used to enhance connectivity for computers.

The natural towers in the body are called *Chakras* or the automatic ganglion. They behave like internal towers and intensify our communication with the soul and the spirit. In the outside world, this work is done by a Temple, Gurudwara or a Masjid.

According to the Vedic philosophy, we should practice focusing on our *Chakras* or ganglions regularly to increase our internal communication.

With collective consciousness of people (more than 1% of the population) focusing on a particular area or a stone, it acquires the powers of a communication tower or satellite.

A stone that becomes a focus of the collective consciousness of the people becomes a GOD ideal and the process is called *Pratishthan*.

A Mandir, Gurudwara or a Masjid, where the collective consciousness of the people gets focused, becomes a source of increase connectivity between the body and the soul. A person sitting in such an environment therefore, finds himself more near God, Allah or Wahe Guru.

The story of Hiranyakashyap where God comes out of the pillar on the request of the Prahlad and kills Hiranyakashyap basically proves that even the impossible is possible if you focus your concentration on the object of concentration and give preference to object of concentration over other thoughts.

This explains how in the past the collective consciousness of the people could bring rains or light candles or diyas. This also forms the basis of collective prayer.

The collective thoughts of the people get posted to the virtual Mandir, Gurudwara and Masjid and when a critical mass of 1% is reached, everyone will start working towards what is taught.

(*Disclaimer: The views expressed in this write up are my own*).

Group Editor-in-Chief, IJCP Group

INSPIRATIONAL STORY

Positive Thinking

Jerry was the kind of guy you love to hate. He was always in a good mood and always had something positive to say. When someone would ask him how he was doing, he would reply, "If I were any better, I would be twins!"

He was a unique manager because he had several waiters who had followed him around from restaurant to restaurant. The reason the waiters followed Jerry was because of his attitude. He was a natural motivator. If an employee was having a bad day, Jerry was there telling the employee how to look on the positive side of the situation.

Seeing this style really made me curious, so one day I went up to Jerry and asked him, "I don't get it! You can't be a positive person all of the time. How do you do it?" Jerry replied, "Each morning I wake up and say to myself, Jerry, you have two choices today. You can choose to be in a good mood or you can choose to be in a bad mood." I choose to be in a good mood. Each time something bad happens, I can choose to be a victim or I can choose to learn from it. I choose to learn from it. Every time someone comes to me complaining, I can choose to accept their complaining or I can point out the positive side of life. I choose the positive side of life. "Yeah, right, it's not that easy," I protested.

"Yes it is," Jerry said. "Life is all about choices. When you cut away all the junk, every situation is a choice. You choose how you react to situations. You choose how people will affect your mood. You choose to be in a good mood or bad mood. The bottom line: It's your choice how you live life."

I reflected on what Jerry said. Soon thereafter, I left the restaurant industry to start my own business. We lost touch, but often thought about him when I made a choice about life instead of reacting to it. Several years later, I heard that Jerry did something you are never supposed to do in a restaurant business: he left the back door open one morning and was held up at gunpoint by three armed robbers. While trying to open the safe, his hand, shaking from nervousness, slipped off the combination. The robbers panicked and shot him. Luckily, Jerry was found relatively quickly and rushed to the local trauma center. After 18 hours of surgery and weeks of intensive care, Jerry was released from the hospital with fragments of the bullets still in his body. I saw Jerry about six months after the accident. When I asked him how he was, he replied, "If I were any better, I'd be twins. Wanna see my scars?"

I declined to see his wounds, but did ask him what had gone through his mind as the robbery took place. "The first thing that went through my mind was that I should have locked the back door," Jerry replied. "Then, as I lay on the floor, I remembered that I had two choices: I could choose to live, or I could choose to die. I chose to live."

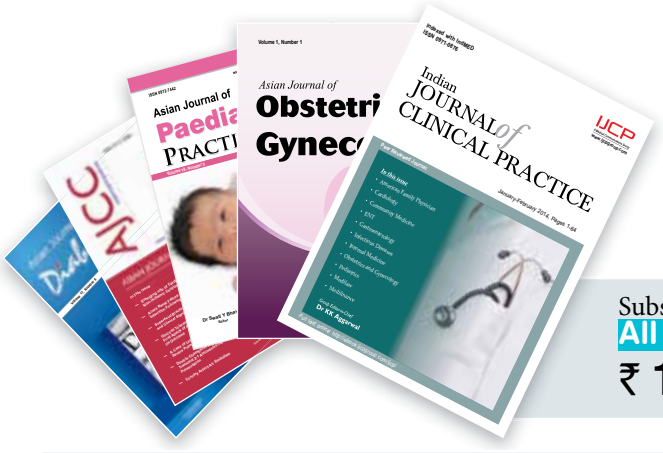
"Weren't you scared? Did you lose consciousness?" I asked. Jerry continued, "The paramedics were great. They kept telling me I was going to be fine. But when they wheeled me into the emergency room and I saw the expressions on the faces of the doctors and nurses, I got really scared. In their eyes, I read, 'He's a dead man.' I knew I needed to take action."

"What did you do?" I asked.

"Well, there was a big, burly nurse shouting questions at me," said Jerry. "She asked if I was allergic to anything". 'Yes,' I replied. The doctors and nurses stopped working as they waited for my reply… I took a deep breath and yelled, 'Bullets!' Over their laughter, I told them, "I am choosing to live. Operate on me as if I am alive, not dead."

Jerry lived thanks to the skill of his doctors, but also because of his amazing attitude. I learned from him that every day we have the choice to live fully. Attitude, after all, is everything.

■■■■



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Lighter Side of Medicine

HUMOR

A WALKING ECONOMY

This guy is walking with his friend, who happens to be a psychologist. He says to this friend, "I'm a walking economy."

The friend asks, "How so?"

"My hairline is in recession, my stomach is a victim of inflation, and both of these together are putting me into a deep depression!"

UPSET IS UNHEALTHY

The mother of a problem child was advised by a psychiatrist, "You are far too upset and worried about your son. I suggest you take tranquilizers regularly."

On her next visit the psychiatrist asked, "Have the tranquilizers calmed you down?"

"Yes", the boy's mother answered.

"And how is your son now?" the psychiatrist asked.

"Who cares?" the mother replied.

I KNOW, DOC

A man swallowed a mouse while sleeping on the couch one day. His wife quickly called the doctor and said, "Doctor, please come quickly. My husband just swallowed a mouse and he's gagging and thrashing about."

"I'll be right over," the doctor said. "In the meantime, keep waving a piece of cheese over his mouth to try to attract the mouse up and out of there."

When the doctor arrived, he saw the wife waving a piece of fish over her husband's mouth. "Uhh, I told you to use cheese, not fish, to lure the mouse."

"I know, doc," she replied, "but first I've got to get the darn cat out of him."

SCIENCE LESSON

Miss Jones had been giving her second-grade students a lesson on science. She had explained about magnets and showed how they would pick up nails and other bits of iron. Now it was question time, and she asked, "My name begins with the letter 'M' and I pick up things. What am I?"

A little boy on the front row proudly said, "You're a mother!"

NEW TEETH

Our local minister had all of his remaining teeth pulled and new dentures made a few weeks ago.

The first Sunday, his sermon lasted 10 minutes. The second Sunday, he preached only 20 minutes. But, on the third Sunday, he preached for an hour and a half.

I asked him about this. He then told me "well, John, that first Sunday, my gums were so sore it hurt to talk. The second Sunday, my dentures were still hurting a lot. Now the third Sunday, I accidentally grabbed my wife's dentures AND I COULDN'T STOP TALKING!"

Dr. Good and Dr. Bad

SITUATION: An obese male with type 2 diabetes was advised behavioral therapy, dietary changes and increase in physical activity to lose weight. He was told to consult a trained interventionist for achieving better outcomes.

LESSON: According to the ADA, diet, physical activity and behavioral therapy designed to achieve over 5% weight loss must be prescribed to overweight and obese individuals with type 2 diabetes who are ready to achieve weight loss.

Diabetes Care. 2017;40(Suppl 1):S57-S63.

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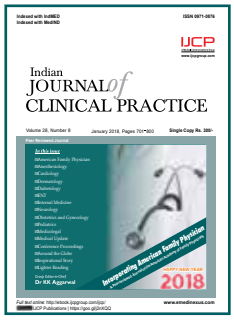

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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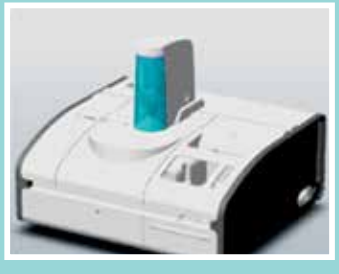

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