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The Evidence in Medicine

Harish Kumar

We live in an era where “Evidence Based Medicine” is the new mantra. “Anecdotal Medicine” as the practice of medicine based on experience or observations is referred to, has become an unfashionable term and is frowned upon as quaint and unscientific. Today everything in medicine is acceptable only if it is evidence-based. This has resulted in a situation where data presented in a statistically skillful manner may make huge changes in the way we practice. For example if there is evidence that giving Aspirin to people with diabetes results in reduced risk of heart disease, it actually means that a small percentage of people who receive this treatment will benefit, but since we have no mechanism of assessing which patient with diabetes will benefit, we end up in a situation where we recommend that all people with diabetes should be on Aspirin. Due to this trend, many patients end up getting a long list of medications each of which has evidence of benefit in a certain percentage of users, but may or may not be beneficial for the specific patient under consideration.

One day a man was walking down a street, when a friend called out to him and told him that he had seen his father lying dead in the next street. The man immediately went to the nearby bookshop and scanned all the newspapers and found no mention of his father’s death in any of them. He concluded that since there was no mention in print of his friend’s observation that his father was dead, his friend must be wrong. This same analogue applies to medicine as well. We all believe that any thing that is printed in journals or textbooks is true and also that anything which is not in the books is false. But anyone with common sense and experience of life knows that what one sees and hears is as true as what one reads and learns.

The other aspect of evidence-based medicine is that many of the drug-trials are pharman-sponsored and by their very nature, are biased. Since doctors are now very focused on “evidence”, the pharma companies have become very adept at providing us with evidence that will wilt under close scientific scrutiny.

The plus side of evidence-based medicine is that doctors are now better read and the way we practice can be justified on scientific grounds. The practice of medicine has become more scientific and organized. Protocol driven management has made things more systematic and introduced a degree of uniformity in practice, which didn’t exist before. But what we need is hard, cold facts to be combined with the warmth of our experience and a proper understanding of how best to apply the evidence to the individual patient in front of us for the betterment of his health.

The Fine Print

Swami Paramatmananda Puri

Although sadly forgotten by us most of the time, the frailty of the human body is clearly seen almost every day by those who work in the medical profession. Amma tries to remind us that, *“These bodies of ours are not eternal. They can perish at any moment. Try to remember that we are born as human beings to experience our true nature as consciousness, the hidden source and support of our mind.”*

Although the modern world tells us that there is no particular goal in life except material happiness, the wise sages of ancient India, after much reflection, conceived of human life as a place to make gradual efforts towards the goal of directly experiencing consciousness as one’s true self. Even though many physicians perform surgery, none so far have either found or seen that principle of consciousness in the physical body. This doesn’t mean that it doesn’t exist, but only that it must be looked for where it truly is and with the proper instrument. Amma says that it must be sought within the mind, by the mind. Humans are uniquely endowed with the capacity to directly experience consciousness as it is, thereby resulting in the highest satisfaction and peace.

If, in addition to our “normal” life, we are fortunate enough to feel an urge to pursue a path leading to this experience, we need a “plan of action” or a “flow chart.” Fortunately, Amma has given us some practical guidelines, which can and should be followed at the different stages of our life. She says,

“Parents should start explaining spiritual ideas to children at an early age. They should learn to respect their elders by rising when elders enter the room, sitting down only after they take their seat, answering them politely, obeying their instructions, and refraining from making fun of them or answering them loudly or in a contrary way. They should learn prayers, listen to spiritual stories, do yogasanas, meditation and japa, and engage in seva, apart from their secular studies. Even if they acquire bad habits when they grow up, these good impressions which are dormant in their subconscious mind will bring them back to the right path in due course.”

After growing up, most of us will desire to have a spouse and children, wealth and position, comforts and possessions. The spiritual practices that we learned as children should be continued. Destructive passions such as anger and jealousy are to be gradually reduced, but not so gradually that nothing at all is done about them! This is the stage of life where there are plenty of opportu-

nities for self-improvement. As they say, there are no problems, only opportunities.

If one sincerely follows the instructions in this “user manual,” eventually one will feel a strong sense of detachment from worldly affairs and an urgency to prepare to meet one’s Maker. As Amma says,

“Once the children are grown up and are able to take care of themselves, husband and wife should lead a purely spiritual life, working for their spiritual improvement by engaging in meditation, japa and selfless service. If we spend the remainder of our lives in sadhana, the accumulated spiritual power will help both us and the world. Therefore, cultivate the habit of withdrawing the mind from countless worldly subjects and turn it totally towards God.”

For many of us, the idea of eventually spending all our time in spiritual pursuits might seem very difficult if not impossible to do, and this might be so. In fact, very few indeed would be willing to sign on the dotted line! However, there is a saving grace, some “small print” at the bottom of this contract. It reads,

“There are many ways to reach Me, and all are equally acceptable in My eyes. Try your best and leave the rest to Me.”

Some of history’s greatest souls were just ordinary people like most of us. By living at home but, constantly making efforts to improve themselves, they experienced the same high state of consciousness that a sincere sannyasi does. Listen to this story.

There once was a hermit who lived high up on a mountain-side in a tiny cave. His food was roots and berries, a bit of bread given by a shepherd, or some milk brought by a woman who wanted his prayers. His only work was praying and thinking about God. For forty years he lived so, praying for the people, comforting them in their troubles, and most of all, worshipping in his heart. There was just one thing he cared about - to make his mind so pure and perfect that it could behold God.

One day, he had a great longing to know how far along he had got with his work, how it looked to the Lord. So he prayed that he might be shown someone whose spirituality was neither more or less than his own. As he looked up from his prayer, a white-robed angel stood before him. The hermit bowed before the messenger with great awe and happiness; for he knew that his wish was answered. “Go to the nearest town,” the angel said,

“where there is a small farm where two women live. In them you will find two souls like your own.”

When the hermit came to the door of the little farm, the two women who lived there were overjoyed to see him, for everyone loved and honoured the hermit. They put a chair for him on the porch and brought food and drink. But the hermit was too eager to wait. He longed greatly to know what the souls of the two women were like, and from their looks he could see only that they were gentle and honest. One was old, and the other of middle age.

Presently he asked them about their lives. They told him the little there was to tell. They had worked hard always, in the fields with their husbands, or in the house; they had many children; they had seen hard times, sickness and sorrow, but they had never despaired.

“But what of your good deeds,” the hermit asked, “what have you done for God?”

“Very little,” they said, sadly, for they were too poor to give much. To be sure, twice every year, during harvest time, they gave some rice to their poorer neighbors.

“That is very good,” the hermit said. “And is there any other good deed you have done?”

“Nothing,” said the older woman, “unless, unless — it might be called a good deed.” She looked at the younger woman, who smiled back at her.

“What?” said the hermit.

Still the woman hesitated; but at last she said, timidly, “It is not much to tell, only this, that it is twenty years since my sister-in-law and I came to live together in this house; we have brought up our families here. And in all the twenty years there has never been an angry word between us, or a look that was less than kind.”

The hermit bent his head before the two women and gave thanks in his heart. “If my soul is as these,” he said, “I am blessed indeed.”

A great light suddenly came into the hermit’s mind, and he saw how many ways there are of spiritual practice and serving God. Some go to churches, temples, or mosques, and some live in ashrams or caves, praying and meditating. Some poor souls who had been very wicked, turn from their evilness with great sorrow, and serve Him with remorse. Some live faithfully and gently in humble homes, working, bringing up children, staying kind and cheerful. And some bear pain patiently, for His sake. Endless, endless ways there are that only the Lord sees.

Obesity in Children and Adolescents

M. Raj, M. Paul

INTRODUCTION

The global disease profile is changing at an astonishingly fast rate especially in low and middle-income countries. The looming epidemics of obesity, cardiovascular disease (CVD) and diabetes form the center stage of this transformation. Worldwide, obesity in children and adults has become a massive epidemic¹. Obesity is an independent risk factor for CVD. Obesity is associated with an increased risk of morbidity and mortality as well as reduced life expectancy. Health service use and medical costs associated with obesity and related diseases have risen dramatically in recent times².

For children and adolescents, overweight and obesity are defined using age and sex specific normograms for Body Mass Index (BMI). Children whose body mass index that exceeds the age-gender-specific 95th percentile are defined obese. Those whose BMI is between the 85th and 95th percentiles are overweight and are at increased risk for obesity related co-morbidities³. This article focuses on epidemiology, etiopathogenesis, comorbidities, prevention and treatment of obesity in children and adolescents.

EPIDEMIOLOGY

The prevalence of obesity in children is increasing worldwide. In 2003, the International Obesity Task Force reported that worldwide 1 out of 10 child, aged 5-17 years, is overweight or obese¹. Of the countries suffering from childhood obesity, England tops the list. In England, between 1974 and 2003, among children aged 5-10 years

the prevalence of obesity increased from 1.8% to 6.0% in boys and from 1.3% to 6.6% in girls⁴. A similar tendency was reported in Australia, where between 1985 and 1995 the prevalence of obesity among children aged 7-15 years increased 4.6-fold among girls and 3.4-fold among boys⁵. Asian countries are not immune to this phenomenon. For example, in China, the prevalence of overweight and obesity among children aged 7-9 years increased from 1-2% in 1985 to 17% among girls and 25% among boys in 2000⁶. In addition, obesity prevalence varies across socioeconomic strata. In developed countries, children of low socioeconomic status are more affected than their affluent counterparts^{4,7}. The opposite is observed in developing countries: children of the upper socioeconomic strata are more likely than poor children to be obese^{8,9}. Limited data is available from India regarding current trends in childhood obesity. An unpublished study conducted in 24,000 school children in South India showed that the proportion of overweight children increased from 4.94% of the total students in 2003 to 6.57% in 2005¹⁰. Differences in overweight and overweight trends also occur by social class and by ethnic groups, emphasizing the importance of non-genetic variables^{7,11,12}.

ETIOPATHOGENESIS OF CHILDHOOD OBESITY

Etiopathogenesis of childhood obesity is multifactorial. Interactions between genetic, neuroendocrine, metabolic, psychological, environmental and sociocultural factors are clearly evident in childhood obesity.

GENE MUTATIONS AND OBESITY

Naturally occurring single and polygenic gene mutations producing obesity are known in rodents like mice and rats. The prototypic obese mice with single gene defects are the obese (*ob/ob*, *Lep^{ob}*) and diabetes (*db/db*, *Lepr^{db}*) autosomal recessive mutations. These mutations produce phenotypes of severe hyperphagia, obesity, type 2 diabetes, defective thermogenesis, and infertility. The mutant gene responsible for the phenotype in *Lep^{ob}* mice encodes a protein termed leptin, which is deficient in these animals³. Leptin deficiency has been documented in subsets of human obesity. Severe early-onset human obesity caused by a mutant leptin receptor has also been identified. In the fatty (*fat/fat*) mouse, the recessively inherited mutation causes hyperinsulinemia without hyperglycemia and postpubertal obesity that is less severe than that seen in *ob/ob* or *db/db* mice. The yellow mutation of agouti mice is a dominant trait that causes yellow coat color, obesity, and diabetes³. The polygenic mouse models of obesity closely resemble the human obesity phenotypes than single gene models and have mutations that influence obesity, plasma cholesterol levels, body fat distribution, and propensity toward development of obesity on a high-fat diet.

Genetic conditions known to be associated with predilection for obesity include Prader-Willi syndrome, Bardet-Biedl syndrome, and Cohen syndrome. It has been observed that obesity has a familial tendency. For young children, if one parent is obese, the odds ratio is approximately 3 for

obesity in adulthood, but if both parents are obese, the odds ratio increases to more than 10. Before 3 years of age, parental obesity is a stronger predictor of obesity in adulthood than the child's weight status¹³.

NEUROENDOCRINOLOGY OF ENERGY METABOLISM

Food intake and energy expenditure is controlled by complex neuroendocrine interactions. The hormone leptin is an important component of this complex system. Leptin is made almost exclusively in adipose tissue and acts centrally in the hypothalamus. Low plasma concentrations of leptin and insulin (e.g., during fasting and weight loss) increase food intake and decrease energy expenditure by stimulating neuropeptide Y (NPY) synthesis, and perhaps by inhibiting sympathetic activity and other catabolic pathways³. High leptin and insulin concentrations (e.g., during feeding and weight gain) decrease food intake and increase energy expenditure through release of melanocortin and corticotropin-releasing hormone (CRH), among others. The major peptides that stimulate feeding are orexins A and B, which are secreted by the hypothalamus, and ghrelin, which is secreted by the stomach³.

VITAL PERIODS IN DEVELOPMENT OF OBESITY

There are vital periods of development for excessive weight gain. Intrauterine influences play a major role in the genesis of obesity by influencing proportions of fat and lean body mass, central nervous system appetite control, and pancreatic structure and function. Epidemiological studies have demonstrated a direct affirmative relationship between birth weight and BMI attained in later life¹⁴. In addition, lower birth weight for gestational age has been associated with later risk for more central deposition of fat, which also confers increased cardiovascular risk. Rapid weight gain during infancy is also associated with obesity later in childhood¹⁵.

The combination of lower birth weight and higher attained BMI is most robustly associated with later CVD risk¹⁶.

Extent and period of breastfeeding have been found to be inversely associated with risk of obesity in later childhood¹⁷⁻²⁰. The normal tendency during early puberty for insulin resistance may be a natural cofactor for unwarranted weight gain as well as various comorbidities of obesity²¹. Early menarche is clearly associated with extent of obesity, with a twofold increase in rate of early menarche associated with BMI greater than the 85th percentile²². The risk of obesity persisting into adulthood is higher among obese adolescents than among younger children¹³. Observations suggest that up to 80% of overweight adolescents will become obese adults²³.

ENVIRONMENTAL RISK FACTORS FOR OBESITY

Environmental risk factors for overweight and obesity, including family and parental issues, are numerous and complicated. Poor cognitive stimulation in the home and low socioeconomic status predicts development of obesity²⁴. Parental food choices influence child food preferences²⁵, and degree of parental adiposity is a marker for children's fat preferences²⁶. Children and adolescents of lower socioeconomic status have been reported to be less likely to eat fruits and vegetables and to have a higher intake of total and saturated fat²⁷⁻²⁹. Early rebound of the BMI is associated with an augmented risk of higher BMI in adulthood. A recent study links early rebound of BMI to glucose intolerance and diabetes in adults³⁰.

SOCIETAL CHANGES AND OBESITY

Widespread and intense societal changes during the last several decades have contributed to childhood obesity. Leisure activity is ever more sedentary and there has

Table 1: Adverse Outcomes in Childhood Obesity

Metabolic	Type 2 diabetes mellitus, impaired glucose tolerance
	Metabolic syndrome, hyper insulinism
Cardiovascular	Dyslipidemia, atherosclerosis
	Hypertension, left ventricular hypertrophy
Psychological	Depression, poor quality of life
Orthopedic	Slipped capital femoral epiphysis
	Blount's disease, osteoarthritis
Neurological	Pseudotumor cerebri
Hepatic	Nonalcoholic steatohepatitis, gall bladder disease
Pulmonary	Obstructive sleep apnea, asthma (exacerbation)
Renal	Proteinuria, FSGS
Malignancy	Of ovary, breast, colon

been a decrease in frequency and duration of physical activities of daily living for children³¹. The results of a randomized trial to decrease television viewing for school-aged children has provided the strongest evidence to support the role of limiting television in prevention of obesity³².

COMORBIDITIES RELATED TO OBESITY

Obesity is associated with a number of comorbidities in adolescents and children. Table 1 presents common comorbid conditions related to obesity in adolescents and children.

METABOLIC SYNDROME

Metabolic syndrome is a cluster of traits that include acanthosis nigricans, hyperinsulinemia, obesity, hypertension, and hyperlipidemia³³. Metabolic syndrome is becoming common among children and adolescents and its prevalence increases directly with the degree of obesity. Each component of the syndrome worsens with increasing obesity – an association that is independent of age, sex, and pubertal status³⁴. The prevalence of the metabolic syndrome in adolescents is 4%, but it increases to 30% to 50% in overweight children^{34,35}. The initiating event of the syndrome appears to be obesity leading to excess insulin production, which later leads to insulin resistance. Insulin resistance leads to increased hepatic synthesis of very-low-density lipoprotein, resistance of the action of insulin on lipoprotein lipase in peripheral tissues, enhanced cholesterol synthesis, increased high-density lipoprotein degradation, increased sympathetic activity, proliferation of vascular smooth muscle cells, and increased formation and decreased reduction of plaque. The metabolic syndrome significantly influences cardiovascular disease risk in young individuals. Berenson et al³⁶ demonstrated a striking increase in the extent of coronary atherosclerotic lesions with obesity and an increasing number of metabolic syndrome risk factors in young individuals. The significant adverse effect of worsening obesity on each component of the metabolic syndrome, underscores the deleterious effect of increasing BMI in this age group.

TYPE 2 DIABETES MELLITUS

The development of type 2 diabetes in obese adolescents has been well-documented³⁷. Predictions imply that obesity driven type 2 diabetes might become the most common form of newly diagnosed diabetes in adolescent youth within 10 years³⁸. There is strong evidence suggesting a global spread of type 2 diabetes in childhood³⁹. Evidence is emerging of an increase in type 2 diabetes among urban Indian children as well⁴⁰. Type 2 diabetes mellitus had been primarily a disease of adulthood; however, type 2 diabetes now occurs in adolescents typically with a BMI > 30 kg/m²²³. Various studies dem-

onstrate increased risk of nephropathy^{41,42} and retinopathy⁴³ compared to young people with type 1 diabetes, whilst recent data indicate early signs of cardiovascular disease in youth with type 2 diabetes⁴⁴. The rapid increase in the incidence of type 2 diabetes points towards emergence of an epidemic of advanced cardiovascular disease due to the synergistic effects of other components of the metabolic syndrome, as well as chronic low-grade inflammation, as obese adolescents become obese young adults.

CARDIOVASCULAR ABNORMALITIES

It is well recognized that obesity substantially contributes to morbidity and mortality from cardiovascular disease across ages. Obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, as well as through yet unrecognized mechanisms. Landmark studies like Bogalusa and Muscatine have demonstrated that obesity during childhood and adolescence is a determinant of a number of cardiovascular risk factors^{36,45,46}. One study conducted on children and adolescents have shown that lean body mass, fat mass, and systolic blood pressure were independently associated with left ventricular mass, which is a strong independent predictor of coronary heart disease, stroke, and sudden death in adults⁴⁷. Obstructive sleep apnea, a cardiovascular risk factor is also associated with obesity in children and adults⁴⁸. As a whole, obesity predisposes or is associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death through its impact on the cardiovascular system.

PSYCHOSOCIAL ABNORMALITIES

Psychosocial abnormalities are closely associated with obesity in children and adolescents. In a study by Pine, et al⁴⁹ adults who had been diagnosed with clinically defined major depression during their youth had a greater BMI than adults who did not suffer from depression during their youth. In another study, Goodman et al⁵⁰ demonstrated that depression scores were highest in the children with the greatest increase in BMI. Observations point to the fact that obese children have smaller friend circles with the relationships being peripheral and isolated. Obesity related psychological issues have been shown to be associated with an increase in both suicidal ideation and number of suicide attempts in youth⁵¹.

MEDICAL EVALUATION OF COMORBIDITIES

All children and adolescents who are overweight require a detailed medical examination for identifying potential Comorbidities. A standard protocol is presented in Table 2.

Table 2: Medical Evaluation of a Child or an Adolescent Who Is Overweight

Evaluation of growth: Normal growth (especially height) makes metabolic or genetic form of overweight less likely
Family history of premature coronary heart disease, dyslipidemia, diabetes
Diet history, history of smoking
History of sleep-disordered breathing
Assessment of physical activity and sedentary behaviour
Psychiatric assessment
History of irregular menstrual periods, acne, and hirsutism in adolescent girls (evidence of polycystic ovarian syndrome).
Skin disorders like intertrigo, monilial dermatitis, acne and acanthosis nigricans.
Blood pressure measurement (multiple readings with attention to proper cuff size)
Physical assessment for orthopedic abnormalities
Urine analysis, fasting lipid profile, Serum uric acid, C-Reactive Protein,
Fasting glucose, fasting insulin, HbA1c level
Liver function tests, thyroid function tests
Renal function tests (if hypertension is present)
Abdominal USG (for fatty liver, ovarian cysts)

PREVENTION OF OBESITY

The ideal preventive strategy for obesity is to prevent children with a normal, desirable BMI from becoming overweight or obese. Preventive strategies should start as early as newborn period. Both initiation and duration of breast-feeding may reduce the risk of later overweight⁵². A reasonable goal for preschool interventions would be to aim toward weight gain of 1.0 kg/2 cm of growth. This rate of gain from preschool age (3 to 4 years) onward predicted desirable weight at 8 to 9 years of age, whereas a gain of 1.8 kg/2 cm predicted obesity at elementary school age⁵³. The important role of healthful behaviors has increasingly been documented. Behavior modifications should focus on increasing consumption of fruits, vegetables and fiber-containing grain products, avoidance of high calorie/high fat food items, increasing daily physical activity, and limiting sedentary time.

Interventions that include classroom and physical education sessions, changes in school meals, vending machines, and cafeterias, and after-school programs, can increase physical activity and improve dietary patterns in children and adolescents^{54,55}. One recent study has emphasized reducing television, videotape/DVD, and video game use³². There are also successful examples of physical education interventions designed with higher-intensity or more motivating activities, specifically endurance training⁵⁶ and popular dance⁵⁷. Exposure to various media is critical. A substantial proportion of the advertising on children's television promotes food, and there is a direct

relationship between television viewing and obesity⁵⁸. Reducing television viewing has reduced weight gain and the prevalence of obesity in experimental trials^{32,59}. It has been hypothesized that television promotes obesity through the consumption of food while watching television, the consumption of foods advertised on television, or reduced physical activity^{58,60,61}.

TREATMENT OF OBESITY

In treating children with overweight and obesity, the immediate goal is to bring down the rate of weight gain, followed by a period of weight maintenance and finally weight reduction to improve BMI. Children 2 to 4 years old who are overweight or obese will achieve reductions in BMI percentile by achieving a rate of weight gain < 1 kg/2 cm of height gain. Older Children who are obese without comorbidities may achieve BMI percentile reductions to below overweight cut-offs with BMI maintenance. Children who are obese with comorbidities require an aggressive approach to bring in weight loss in concurrence with other treatment strategies. A gradual weight loss is preferred because it is achievable and more easily sustained giving long-term benefits. Older adolescents who have completed linear growth and have a BMI > 30 kg/m² require more aggressive weight loss similar to that for adults⁶². The principles for the treatment of obesity can be summarized as follows:

1. Establish individual treatment goals and approaches on a case-to-case basis.
2. Ensure family involvement through out the treatment period.

Table 3: Treatment Strategies for Sub groups

BMI Status	Classification	Treatment Goal
< 85th percentile	Normal weight for height	Maintain BMI percentile to prevent future obesity
85th–95th percentile	Overweight	Maintain BMI to reduce BMI to < 85th percentile when age increases; if BMI > 25kg/m ² , weight maintenance
> 95 th percentile	Obese	Weight maintenance (younger children) or gradual weight loss (adolescents) to reduce BMI percentile
> 30 kg/m ²	Adult obesity range	Gradual weight loss (1–2 kg/mo) to achieve healthier BMI
> 95th percentile and comorbidity present*	Obesity with comorbidity	Gradual weight loss (1–2 kg/mo) to achieve healthier BMI; treatment of comorbidities

*See Table 2.

3. Provide regular assessment and ensure follow up compliance.
4. Provide attention to behavioral, psychological, and social factors in the treatment plan.
5. Provide situations that can be implemented within the subject's environment.

DIETARY MANAGEMENT

Dietary management should aim to provide appropriate calorie intake and optimum nutrition. Due emphasis should be given to developing and sustaining healthy eating patterns. A standard protocol is to recommend a fat intake of 30% to 40% kcal in children 1 to 3 years old, with a reduction to 25% to 35% in children 4 to 18 years old; a carbohydrate intake of 45% to 65% kcal in all children and adults; and protein intakes of 5% to 20% kcal in children 1 to 3 years old with gradual increase to 10% to 30% kcal in children 4 to 18 years old⁶³. Care should be taken to provide adequate nutrition by offering a variety of foods that are low in saturated fat (< 10% kcal), total fat (H²30% kcal), and cholesterol (< 300 mg/d); promoting age-appropriate serving sizes including > 5 servings of fruit and vegetables, > 3 servings of milk or dairy products, and > 6 servings of whole-grain and grain products per day as well as consuming adequate amounts of dietary fiber (age in years + 5 g/d)²³. Limiting the intake of salt (< 6 g/d) and sugar is also important⁶⁴.

Every child who is either overweight or obese will have unique caloric requirements making individualizing the dietary intervention important. Due emphasis should be given to reduction of eat outs, planning for healthy snacks, balanced diet, adequate intake of fruits and vegetables, fiber content of diet and avoidance of high calorie/ high fat foods.

PHYSICAL ACTIVITY

Moderate intensity regular physical activity is essential for the prevention of overweight and obesity as well as for treatment of the same. The current recommendation for the amount of physical activity is 30 to 60 minutes of regular exercise²³ for a minimum of 5 days per week. Longer periods (more than 30 minutes) of moderate intensity exercises like brisk walking burn more fat as calories and are excellent for reducing body fat⁶⁵. Children should be prescribed physical activity that is interesting, practical and has a social element. Involving other members of the family in the exercise program and supervising the activity on a regular basis will improve compliance.

RESTRICTION OF SEDENTARY ACTIVITY

Any physical activity intervention will be successful only if sedentary habits are restricted or avoided. Children and adolescents typically indulge in sedentary activity like watching TV, sitting in front of computers and video games. Every hour of sedentary activity (measured as sitting index) increases the chance of obesity and is also contributory to failure of many weight reduction attempts in adolescents and children. A complementary approach to a successful weight loss intervention is to restrict the sedentary activity to less than two hours per day⁶⁶.

PHARMACOLOGICAL TREATMENT

Data supporting the use of pharmacological therapy for pediatric overweight are limited and inconclusive⁶⁷. Sibutramine, a serotonin non-adrenaline reuptake inhibitor enhances satiety and has been shown to be effective in treating obesity. This drug may be associated with side effects including increases in heart rate and blood pressure⁶⁸. Orlistat, which is a pancreatic lipase inhibitor, acts by increasing fecal fat loss. It is approved for use in adolescence but is associated with gastrointestinal side

effects and requires fat-soluble vitamin supplementation and monitoring^{69,70}. For rare genetic and metabolic disorders, pharmacological treatment may be useful. For example, recombinant leptin is useful in hereditary leptin deficiency. Octreotide may be useful in hypothalamic obesity⁷¹. Metformin has been used in insulin-resistant children and adolescents who are overweight, but long-term follow up data is lacking⁷².

SURGICAL TREATMENT

Many cases of severe adolescent obesity with or without co morbidities warrant aggressive approaches including surgical treatment. The bariatric procedures include gastric bypass, gastric binding and vertical banded gastroplasty. Indications for surgery used include a BMI > 40 kg/m² and severe associated comorbidities, such as obstructive sleep apnea, type 2 diabetes mellitus, and pseudotumor cerebri. More severe elevation of BMI (> 50kg/m²) may be an indication for surgical treatment in the presence of less severe comorbidities²³. An experienced team approach including comprehensive medical and psychological evaluation is critical⁷³. Surgical therapy should only be advised for full-grown adolescents with the severest obesity-related morbidity.

SUMMARY

Obesity in adolescents and children has risen to significant levels globally including developing countries with serious public health consequences. In addition to cardiovascular, emotional and social issues, it poses serious threat to the basic health care delivery system of developing and under developed countries. Unless this massive epidemic is contained in the near future, the implications of this global phenomenon on future generations will be disastrous. The reversibility of this disease by proper interventions, should be seen as an opportunity and all efforts to avert this catastrophe duly attempted for the sake of generations to come.

REFERENCES

1. IOTF. Childhood obesity - the new crisis in public health. London: International Obesity Task Force; 2003.
2. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Circulation* 2006 Feb 14;113(6):898-918.
3. Donohoue PA. Obesity. In: Behrman RE, Kleigman RM, Jenson HB (eds). *Nelson textbook of Pediatrics*, 17th ed. Philadelphia: WB Saunders. 2004;173-7.
4. Stamatakis E, Primates P, Chinn S, et al. Overweight and obesity trends from 1974 to 2003 in English children: what is the role of socioeconomic factors? *Arch Dis Child* 2005;90:999-1004.
5. Magarey AM, Daniels LA, Boulton TJ. Prevalence of overweight and obesity in Australian children and adolescents: reassessment of 1985 and 1995 data against new standard international definitions. *Med J Aust* 2001;174:561-4.
6. Wang L, Kong L, Wu F, et al. Preventing chronic diseases in China. *Lancet* 2005;366:1821-4.
7. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986-1998. *JAMA* 2001;286:2845-8.
8. Salmon J, Timperio A, Cleland V, et al. Trends in children's physical activity and weight status in high and low socio-economic status areas of Melbourne, Victoria, 1985-2001. *Aust N Z J Public Health* 2005;29:337-42.
9. Chhatwal J, Verma M, Riar SK. Obesity among pre-adolescent and adolescents of a developing country [India]. *Asia Pac J Clin Nutr* 2004;13:231-5.
10. Raj M, Sundaram KR, Paul M, et al. Obesity in Indian Children-time trends and relationship with hypertension. *Journal in press*, 2007.
11. Saxena S, Ambler G, Cole TJ, et al. Ethnic group differences in overweight and obese children and young people in England: cross sectional survey. *Arch Dis Child* 2004;89:30-6.
12. Gordon-Larsen P, Adair LS, Popkin BM. The relationship of ethnicity, socioeconomic factors, and overweight in US adolescents. *Obes Res* 2003;11:121-9.
13. Whitaker RC, Wright JA, Pepe MS, et al. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med* 1997;337:869-73.
14. Parsons TJ, Power C, Logan S, et al. Childhood predictors of adult obesity: a systematic review. *Int J Obes Relat Metab Disord* 1999;23:S1-S107.
15. Stettler N, Zemel BS, Kumanyika S, et al. Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics* 2002;109:194-9.
16. Dietz WH. Overweight in childhood and adolescence. *N Engl J Med* 2004;350:855-7.
17. Agras SW, Kraemer HC, Berkowitz RI, et al. Influence of early feeding style on adiposity at 6 years of age. *J Pediatr* 1990;116:805-9.
18. von Kries R, Koletzko B, Sauerwald T, et al. Breast feeding and obesity: cross sectional study. *BMJ* 1999;319:147-50.
19. Gilman MW, Rifas-Shiman SL, Camargo CA Jr, et al. Risk of overweight among adolescents who were breastfed as infants. *JAMA* 2001;285:2461-7.
20. Hediger ML, Overpeck MD, Kuczumski RJ, et al. Association between infant breastfeeding and overweight in young children. *JAMA* 2001;285:2453-60.

21. Travers SH, Jeffers BW, Bloch CA, et al. Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. *J Clin Endocrinol Metab* 1995;80:172-8.
22. Adair LS, Gordon-Larsen P. Maturational timing and overweight prevalence in US adolescent girls. *Am J Public Health* 2001;91:642-4.
23. Daniels SR, Arnett DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. *Circulation* 2005 Apr 19;111(15):1999-2012.
24. Strauss RS, Knight J. Influence of the home environment on the development of obesity in children. *Pediatrics* 1999;103(6).
25. Ray JW, Klesges RC. Influences on the eating behavior of children. *Ann N Y Acad Sci* 1993;699:57-69.
26. Fisher JO, Birch LL. Fat preferences and fat consumption of 3- to 5-year-old children are related to parental adiposity. *J Am Diet Assoc* 1995;95:759-64.
27. Neumark-Sztainer D, Story M, Resnick MD, et al. Correlates of inadequate fruit and vegetable consumption among adolescents. *Prev Med* 1996;25:497-505.
28. Krebs-Smith SM, Cook A, Subar AF, et al. Fruit and vegetable intakes of children and adolescents in the United States. *Arch Pediatr Adolesc Med* 1996;150:81-6.
29. Kennedy E, Powell R. Changing eating patterns of American children: a view from 1996. *J Am Coll Nutr* 1997;16:524-9.
30. Bhargava SK, Sachdev AS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N Engl J Med* 2004;350:865-75.
31. Berkey CS, Rockett HR, Field AE, et al. Activity dietary intake, and weight changes in a longitudinal study of preadolescent and adolescent boys and girls *Pediatrics* 2000; 105(4).
32. Robinson T. Reducing children's television viewing to prevent obesity: a randomized controlled trial. *JAMA* 1999;282:1561-7.
33. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173-94.
34. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004 Jun 3;350(23):2362-74.
35. Cook S, Weitzman M, Auinger P, et al. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med*. 2003;157:821-7.
36. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650-6.
37. Pinhas-Hamiel O, Dolan LM, Daniels SR, et al. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr*. 1996;128:608-15.
38. Type 2 diabetes in children and adolescents. American Diabetes Association. *Pediatrics* 2000;105(3 Pt 1):671-80.
39. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr* 2005;146(5):693-700.
40. Ramachandran A, Snehalatha C, Satyavani K, et al. Type 2 diabetes in Asian-Indian urban children. *Diabetes Care* 2003;26(4):1022-5.
41. Svensson M, Sundkvist G, Arnqvist HJ, et al. Signs of nephropathy may occur early in young adults with diabetes despite modern diabetes management. *Diabetes Care* 2003;26(10):2903-9.
42. Yokoyama H, Okudaira M, Otani T, et al. Higher incidence of diabetic nephropathy in type 2 than in type 1 diabetes in early onset diabetes in Japan. *Kidney Int* 2000;58(1):302-11.
43. Yoshida Y, Hagura R, Hara Y, et al. Risk factors for the development of diabetic retinopathy in Japanese type 2 diabetic patients. *Diabetes Res Clin Pract* 2001;51(3):195-203.
44. Gungor N, Thompson T, Sutton-Tyrrell K, et al. Early signs of cardiovascular disease in youth with obesity and type 2 diabetes. *Diabetes Care* 2005;28(5):1219-21.
45. Lauer RM, Lee J, Clarke WR. Factors affecting the relationship between childhood and adult cholesterol levels: the Muscatine Study. *Pediatrics* 1988;82:309-18.
46. Lauer RM, Clarke WR. Childhood risk factors for high adult blood pressure: the Muscatine Study. *Pediatrics* 1989;84:633-41.
47. Daniels SR, Kimball TR, Morrison JA, et al. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. *Circulation* 1995;92:3249-54.
48. Amin RS, Kimball TR, Bean JA, et al. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;165:1395-9.
49. Pine DS, Goldstein RB, Wolk S, et al. The association between childhood depression and adulthood body mass index. *Pediatrics* 2001;107:1049-56.
50. Goodman E, Whitaker RC. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics* 2002;110:497-504.
51. Eisenberg ME, Neumark-Sztainer D, Story M. Associations of weight-based teasing and emotional well-being among adolescents. *Arch Pediatr Adolesc Med* 2003;157:733-8.
52. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, et al. Risk of overweight among adolescents who were breastfed as infants. *JAMA*. 2001;285:2461-7.
53. Williams CL, Strobino BA, Bollella M, et al. Cardiovascular risk reduction in preschool children. *J Am Coll Nutr*. 2004;23:117-23.
54. Resnicow K, Robinson TN. School-based cardiovascular disease prevention studies: review and synthesis. *Ann Epidemiol*. 1997;7: S14-S31.

55. Campbell K, Waters E, O'Meara S, et al. Interventions for preventing obesity in childhood. A systematic review. *Obes Rev*. 2001; 2:149-57.
 56. Dwyer T, Coonan WE, Leitch DR, et al. An investigation of the effects of daily physical activity on the health of primary school students in South Australia. *Int J Epidemiol*. 1983;12:308-13.
 57. Flores R. Dance for health: improving fitness in African American and Hispanic adolescents. *Public Health Rep*. 1995;110:189-93.
 58. Gortmaker SL, Must A, Sobol AM, et al. Television viewing as a cause of increasing obesity among children in the United States, 1986–1990. *Arch Pediatr Adolesc Med*. 1996;150:356-62.
 59. Gortmaker SL, Peterson K, Wiecha J, et al. Reducing obesity via a school-based interdisciplinary intervention among youth: Planet Health. *Arch Pediatr Adolesc Med*. 1999;153:409-18.
 60. Robinson TN. Television viewing and childhood obesity. *Pediatr Clin North Am*. 2001;48:1017-25.
 61. Matheson DM, Killen JD, Wang Y, et al. Children's food consumption during television viewing. *Am J Clin Nutr*. 2004;79:1088-94.
 62. Barlow SE, Dietz WH. Obesity evaluation and treatment: expert committee recommendations. *Pediatrics*. 1998;102:29.
 63. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington, DC: National Academies Press; 2002.
 64. Williams CL, Hayman LL, Daniels SR, et al. Cardiovascular health in childhood: *Circulation*. 2002;106:143-60.
 65. Poirier P, Despres JP. Exercise in weight management of obesity. *Cardiol Clin*. 2001 Aug;19(3):459-70.
 66. Epstein LH, Paluch RA, Gordy CC, et al. Decreasing sedentary behaviors in treating pediatric obesity. *Arch Pediatr Adolesc Med*. 2000;154:220-6.
 67. Yanovski JA. Intensive therapies for pediatric obesity. *Pediatr Clin North Am* 2001;48:1041–53.
 68. Berkowitz RI, Wadden TA, Tershakovec AM, et al. Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. *JAMA* 2003;289:1805-12.
 69. McDuffie JR, Calis KA, Uwaifo GI, et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res*. 2002;10:642-50.
 70. McDuffie JR, Calis KA, Booth SL, et al. Effects of orlistat on fat-soluble vitamins in obese adolescents. *Pharmacotherapy* 2002;22:814-22.
 71. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2003;88:2586-92.
 72. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics* 2001;107:55.
 73. Inge TH, Krebs NF, Garcia VF, et al. Bariatric surgery for severely overweight adolescents: concerns and recommendations. *Pediatrics* 2004;114:217-23.
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Hypercoagulable States

R. Rajat, D.S. Shaishav, K.P. Gireeshkumar

Hypercoagulable states can be defined as a group of inherited or acquired conditions that are associated with a predisposition to venous thrombosis.

The concept of a “state of hypercoagulability” dates back to 1854, when German pathologist Rudolph Virchow postulated that thrombosis results from three interrelated factors: (1) “decreased blood flow” (venous stasis); (2) “inflammation of or near the blood vessels” (vascular endothelial injury); and (3) “intrinsic alterations in the nature of the blood itself.” These “blood changes” alluded to in “Virchow’s triad” have become what are contemporarily known as “hypercoagulable states,” or “thrombophilias.”

Patients with hypercoagulable states are at greater risk for developing a thrombotic event than those without such disorders, not all persons with a well-defined hypercoagulable state will develop an overt thrombosis and not all persons with thrombosis have an identifiable hypercoagulable state.

This chapter will focus on the most common hypercoagulable states and their association with Venous Thromboembolism (VTE).

THE ANTICOAGULANT SYSTEM

The function of the natural anticoagulant system is to confine a normal hemostatic plug to the site of vessel wall injury and to prevent the beneficial thrombus from propagating to form

a pathologic thrombus, which occludes the lumen of the vessel or embolizes to occlude distant vessels. The recognized anticoagulant components of this system include Antithrombin III, Protein C, and Protein S. The anticoagulant system is activated in parallel with the procoagulant system. Protein C is a circulating vitamin K-dependent zymogen, which is activated to APC (Activated Protein C), the active enzyme, by the thrombin- thrombomodulin complex. APC functions as a natural anticoagulant by inactivating (via proteolysis) procoagulant factors Va and VIIIa in the presence of Protein S. Antithrombin III is a Serine Protease inhibitor (SERPIN) and acts as a pseudosubstrate to irreversibly inhibit thrombin by covalently binding the

Table 1: Classification of Hypercoagulable Conditions

Primary (inherited)	Secondary (acquired)
Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden (resulting in APC* resistance) Prothrombin 20210 mutation Hyperhomocystinemia Elevated factor VIII levels Dysfibrinogenemia Factor XII deficiency Disorders of plasmin generation	Pregnancy Immobility Trauma Postoperative state Use of oral contraceptives, estrogen, tamoxifen Antiphospholipid antibody syndrome Hyperhomocystinemia Other disease states: <ol style="list-style-type: none"> 1. Malignancy 2. Nephrotic syndrome 3. Myeloproliferative disorders 4. Congestive heart failure 5. Heparin-induced thrombocytopenia with thrombosis Paroxysmal nocturnal hemoglobinuria 6. Behçet’s disease

*APC, activated protein C.

thrombin enzymatic active site. The rate of thrombin inhibition by Antithrombin III is increased markedly by glycosaminoglycans (e.g. heparin).

Familial reductions in plasma Antithrombin III, Protein C, or Protein S activity due to either reduced plasma protein levels (i.e. altered protein expression), or normal levels of a dysfunctional protein (i.e. altered protein structure), are strongly associated with deep vein thrombosis and pulmonary embolism (venous thromboembolism), and validate the important role of these proteins in the natural anticoagulant system.

Our understanding of these mechanisms continues to evolve as new genetic abnormalities are defined and new anticoagulant pathways are discovered.

ANTITHROMBIN, PROTEIN C, AND PROTEIN S

Deficiencies of Antithrombin, Protein C, and Protein S are inherited in an autosomal dominant pattern. All three generally present with a first episode of thrombosis between the ages of 10 and 50 years.

Adults with heterozygous Protein C or Protein S deficiency may experience skin necrosis shortly after starting warfarin therapy without concomitant heparin therapy. Both Protein C and Protein S are vitamin K-dependent cofactors whose levels may drop precipitously after initiation of warfarin, leading to transient hypercoagulation. Several acquired conditions, including liver disease and disseminated intravascular coagulation, can lead to decreased activity of Protein C and Protein S. A decreased

Protein S level has also been specifically noted to occur with pregnancy, oral contraceptive use, and the nephrotic syndrome.

Acquired Antithrombin deficiency is seen with liver disease, oral contraceptive use, the nephrotic syndrome, pregnancy, and disseminated intravascular coagulation.

FACTOR V LEIDEN

APC resistance is most commonly due to a point mutation in the gene encoding factor V. Factor V Leiden is the single most common inherited thrombophilic defect. Heterozygosity for factor V Leiden mutation imparts a sevenfold increased lifetime risk of venous thromboembolism, whereas homozygous expression confers an 80-fold increased risk.

Although Antithrombin, Protein S, and Protein C deficiencies usually present with thrombosis relatively early in life, the risk of thrombosis due to factor V Leiden increases with age. Coinheritance of other thrombophilic mutations, such as Protein C deficiency, Prothrombin 20210, or Hyperhomocystinemia, further increases thrombotic risk.

PROTHROMBIN 20210

Prothrombin 20210 is an autosomal dominant inherited defect. Prothrombin 20210 confers a weaker thrombotic risk (about threefold) than factor V Leiden^{1,2}. Coinheritance of both Factor V Leiden and Prothrombin 20210 compounds the risk of venous thromboembolism, pregnancy-associated venous thromboembolism, and recurrent venous thromboembolism.

Table 2: Unusual Venous Thrombotic Presentations of Certain Hypercoagulable States

VTE Presentation	Hypercoagulable Condition
Cerebral vein thrombosis	Prothrombin G20210A, Antiphospholipid antibodies, Antithrombin deficiency, Essential Thrombocythemia, Paroxysmal Nocturnal Hemoglobinuria
Cerebral vein thrombosis in women using oral contraceptive pills	Prothrombin G20210A
Inferior vena cava, renal vein, mesenteric vein, portal and hepatic vein thrombosis	Antiphospholipid antibodies, Cancer, Antithrombin deficiency, Myeloproliferative syndromes, Paroxysmal Nocturnal Hemoglobinuria
Migratory superficial thrombophlebitis (Trousseau's syndrome)	Cancer (particularly adenocarcinoma of the gastrointestinal tract)
Recurrent superficial thrombophlebitis	Factor V Leiden, Polycythemia Vera, Deficiencies of natural anticoagulants
Warfarin skin necrosis	Protein C and Protein S deficiencies
Neonatal purpura fulminans	Homozygous Protein C and Protein S deficiencies
Unexplained fetal loss (three or more first-trimester miscarriages or one second- or third-trimester unexplained death of a morphologically normal fetus)	Antiphospholipid antibodies

HYPERHOMOCYSTEINEMIA

Elevated levels of homocysteine, an intermediary in methionine metabolism, have been associated with both arterial and venous thrombosis. Hyperhomocystinemia, defined as fasting plasma levels greater than 15 micromole/L, is relatively common in the general population and can result from inherited enzyme deficiencies or acquired disorders³. Dietary deficiencies of folate and vitamins B₆ and B₁₂, chronic renal failure, pernicious anemia, and hypothyroidism have all been associated with elevated homocysteine levels.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APLAS)

The antiphospholipid antibody syndrome is caused by a heterogeneous group of antibodies to various proteins complexed with negatively charged phospholipids. It can be a primary or secondary condition.

Causes: APLAS is an autoimmune disorder of unknown cause. The search for possible triggers has uncovered a wide array of associated autoimmune or rheumatic diseases, infections, and drugs that are associated with the Lupus anticoagulant (LA) or Anticardiolipin (aCL) antibodies.

1. Common autoimmune or rheumatic diseases and percent with aPL antibodies
 - a. SLE, Sjögren syndrome, Rheumatoid arthritis
 - b. Autoimmune thrombocytopenic purpura
 - d. Autoimmune hemolytic anemia - No figure available
 - d. Psoriatic arthritis, Systemic sclerosis
 - e. Mixed connective-tissue disease, Behçet syndrome
 - f. Polymyalgia rheumatica or giant cell arteritis
2. Infections
3. Syphilis, Hepatitis C, HIV/HTLV infection
4. Malaria, Bacterial septicemia
5. Drugs
 - a. Cardiac - Procainamide, quinidine, propranolol, hydralazine
 - b. Neuroleptic or psychiatric - Phenytoin, chlorpromazine
 - c. Other - Interferon alfa, quinine, amoxicillin
6. Genetic predisposition

CANCER AND THROMBOSIS

The link between malignancy and thrombosis, first described by Trousseau, has been recognized since the 1800s. Although often associated with adenocarcinoma,

thrombosis has been described with many types of cancer and likely occurs through multiple mechanisms.

Factor VIII

Recently, elevated levels of factor VIII has been implicated as an independent risk factor for venous thromboembolism.

SIGNS AND SYMPTOMS OF HYPERCOAGULABLE STATES

The most common clinical manifestation of an underlying hypercoagulable state is lower-extremity deep venous thrombosis with or without pulmonary embolism. Because the clinical signs and symptoms associated with deep venous thrombosis and pulmonary embolism are insensitive and nonspecific, objective diagnostic confirmation by the use of an imaging method, such as contrast venography and duplex ultrasound, is mandatory.

SCREENING LABORATORY EVALUATION

Circumstances that require a Laboratory Workup for Thrombophilia

1. Venous thrombosis before 40-50 years of age.
2. Unprovoked thrombosis at any age.
3. Recurrent thrombosis at any age.
4. Unusual sites such as cerebral, mesenteric, portal, or hepatic veins.
5. Positive family history for thrombosis.
6. Thrombosis during pregnancy, recurrent pregnancy loss (≥ 3 consecutive first-trimester pregnancy losses without an intercurrent term pregnancy).
7. Unexplained abnormal laboratory test such as prolonged PTT.

WHEN SHOULD TESTS BE PERFORMED?

Ideally, testing should be performed in the outpatient setting at least 4 to 6 weeks after any acute thrombotic event. This is because acute illness states, including VTEs, can cause elevations of a number of acute-phase reactants, including factor VIII, C4b-binding protein, fibrinogen, and IgM anticardiolipin antibodies, all of which may interfere with testing and often lead to false-positive diagnoses. Heparins (unfractionated and low-molecular-weight) can interfere with Antithrombin activity and with lupus anticoagulant assays, and warfarin predictably lowers Protein C and S activity levels⁴. Low activity levels of natural anticoagulants also occur as a result of liver disease, because Protein C, Protein S, and Antithrombin are all synthesized in the liver^{5,6}. Antithrombin activity level may be reduced in nephrotic syndrome and active colitis, and protein S activity may also be reduced in the setting of HIV infection⁴.

Table 3: Recommended Laboratory Evaluation for Patients Suspected of-

Having an Underlying	Hypercoagulable State
1. Activated protein C resistance	1. Factor V Leiden PCR
2. Prothrombin G20210A mutation testing by PCR	2. Antigenic assays for Antithrombin, Protein C, and/or Protein S
3. Antithrombin, protein C, and protein S activity (functional) levels	3. Confirmatory tests for lupus anticoagulants include at least one of the following: platelet neutralization procedure, hexagonal phase phospholipids, Textarin/Ecarin test, platelet vesicles.
4. Factor VIII activity level	
5. Screening tests for lupus anticoagulants (sensitive aPTT, aPTT mixing studies, dilute Russell viper venom time)	
6. Anticardiolipin antibody testing by ELISA	
7. Fasting total plasma homocysteine level	
PCR = polymerase chain reaction; aPTT = activated partial thromboplastin time; ELISA = enzyme-linked immunosorbent assay.	

Recommendations for Lab Test (As per Guidelines for Investigation and Management British Journal of Haematology 2001)

1. APTT, PT and Thrombin clotting time should be used as initial screening

APTT may identify some patients with APLA, but is not sufficient to exclude them.

PT is useful in interpretation of low protein C and protein S results.

2. For protein C – chromatogenic assays while for protein S immunoreactive assays are preferred.
3. For Prothrombin G 20210A – PCR based assay is required as there is no screening test.
4. Labs must establish their own reference standard ranges for assays and tests and should undergo rigorous quality assessment.

Comprehensive assays for APL Abs C both lupus anticoagulant and anticardiolipin Abs should be done

Diagnosis of APLAS is confirmed by the occurrence of one or more clinical manifestations in the presence of positive antibody studies on two occasions more than 3 months apart⁸. Antiphospholipid antibodies can be demonstrated by a lupus anticoagulant assay, such as the dilute Russell's viper venom time test, or by an enzyme-linked immunosorbent assay for anticardiolipin antibodies.

5. The hallmark result from laboratory tests that defines APLAS is the presence of aPL antibodies or abnormalities in phospholipid-dependent tests of coagulation. The following laboratory tests should be performed in a patient suspected of having APS:
 - a. aCL antibodies - Of the 3 known isotypes of aCL (i.e. immunoglobulin G [IgG], immunoglobulin M [IgM], immunoglobulin A [IgA]), IgG correlates most strongly with thrombotic events.

- b. Anti-beta-2 glycoprotein I antibodies
- c. Activated partial thromboplastin time (aPTT)
- d. LA tests such as dilute Russell viper venom time (DRVVT)
- e. Serologic test result for syphilis (false positive)
- f. CBC count (thrombocytopenia, Coombs-positive hemolytic anemia)

TREATMENT

There are no specific therapies to reverse most hypercoagulable states. FFP has traditionally been the source of factors to treat coagulation factor deficiencies. ATIII deficiency may be quickly corrected with infusions of ATIII concentrates. Long-term therapy for congenital deficiency is generally not indicated, as an asymptomatic period may last decades. Once thrombosis has occurred, warfarin therapy is generally undertaken. Hyperhomocysteinemia is treatable, and plasma homocysteine levels can be lowered in many individuals by folic acid or other B-complex vitamin supplementation. It is not known whether normalization of plasma homocysteine levels reverses the hypercoagulability completely. The presence of a hypercoagulable state should not affect acute VTE treatment [i.e. initial anticoagulation with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin followed by oral anticoagulation with warfarin (except during pregnancy)] and monitored with the international normalized ratio (INR). A target international normalized ratio (INR) of 2.5 (therapeutic range 2.0-3.0) is aimed for most patients, except those with a lupus anticoagulant. Because these antibodies can prolong the activated partial thromboplastin time, monitoring of unfractionated heparin therapy in this scenario should be performed by heparin assay (protamine titration or anti-factor Xa activity assay). If such assays are not immediately available, the use of weight-based, subcutaneous low-molecular-weight heparin should be considered instead of unfractionated heparin, because the former compounds

do not require monitoring. Moreover, 26.8% to 53% of all patients with a lupus anticoagulant have an abnormal, prolonged baseline prothrombin time, and in many of these patients the international normalized ratio is not an adequate tool for monitoring warfarin therapy. In this situation, monitoring by chromogenic factor X activity assay is recommended⁷. Initiation of oral anticoagulation for primary VTE prophylaxis in asymptomatic carriers of any hypercoagulable state has not been advised, mainly because the annual absolute risk of idiopathic VTE is either low or not high enough to be favorably balanced against the annual risk of oral anticoagulation-related major and fatal hemorrhage⁸. However, because most VTEs (50% to 70%) in patients with a predisposition to hypercoagulability occur following a situational risk factor, such as major or orthopedic surgery, aggressive VTE prophylaxis should be prescribed to asymptomatic carriers of hypercoagulable states during high-risk situations⁸.

MANAGEMENT OF ACUTE THROMBOEMBOLIC EVENTS

1. Initial management of DVT / pulmonary embolism in patients with heritable thrombophilias – is same, with target INR 2.5, as in venous thrombosis in any other patient. 2. After 1st venous thromboembolism, anticoagulant therapy is generally administered for 6 months. A shorter period of treatment may be acceptable when thrombosis is confined to distal veins (calf veins). It is recommended that when there is persistent thrombotic risk factors e.g. cancer or already identified high-risk thrombotic defects, usual period of anticoagulation can be extended, on an individual patient basis.

MANAGEMENT OF RECURRENT VENOUS THROMBOSIS.

Recurrent event occurring while the patient is not on anticoagulant, introduce coumarine at a target INR of 2.5, after initial treatment with heparin; when recurrent event has occurred while on anticoagulants, increase the target of INR to 3.5 (range 3 to 4) (Grade C recommendation). Patients who have had two or more apparently spontaneous venous thrombotic events require consideration for indefinite anticoagulant prophylaxis.

MANAGEMENT OF APLA SYNDROME

A) Thrombosis:

Acute management of arterial or venous thrombosis in-patient with antiphospholipid syndrome is no different from the treatment of other patients with similar complications. Thus the patient should receive heparin (1000 units/h). Prophylactic oral anticoagulant is advised following venous thrombosis for a prolonged period of time since patients with antiphospholipid syndrome are prone to recurrent thrombosis. In patients with stroke or other arterial thrombotic event, aspirin (80-100 mg/day),

aspirin plus clopidogrel, or oral anticoagulation has been used by various groups. In cases in which thrombosis continues despite adequate anticoagulation high doses of corticosteroids, initially, and cyclophosphamide have been used in addition to anticoagulation.

B) Recurrent Pregnancy Losses:

Management of women during pregnancy is controversial. Subcutaneous heparin (5000-15000 units) twice daily prophylaxis is recommended for patients with antiphospholipid syndrome. Some centers have reported successful pregnancy outcome with prednisone (20-60 mg/day) and aspirin (80-100 mg/day). Another alternative management is immunoglobulin therapy (0.5 mg/kg/day) for 3-5 day each month.

SUMMARY

Venous thromboembolism is a common disease that causes significant morbidity and mortality. In recent years, the ability to diagnose inherited genetic defects and common acquired conditions predisposing to thrombosis has greatly increased. Venous thromboembolism is now understood to be a complex interaction of genetic and acquired factors leading to thrombosis. Integrating the various factors to individually assess thrombotic risk still poses a challenging clinical problem that will likely become easier as more data accumulate. As the ability to accurately assess risk increases, the data can then be translated into more refined treatment regimens. Until then, only general guidelines regarding evaluation and management are available.

REFERENCES

1. Van Cott EM, Laposata M. Laboratory evaluation of hypercoagulable states. *Hematol Oncol Clin North Am* 1998;12(6):1141-66.
2. Nachman RL, Silverstein R. Hypercoagulable states. *Ann Intern Med* 1993;119(8):819-27.
3. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Engl J Med* 1998;338(15):1042-50.
4. Van CM, Laposata M. Laboratory evaluation of hypercoagulable states. *Hematol Oncol Clin North America* 1998;12:1141-66.
5. Van BHH, Lane DA. Antithrombin and inherited deficiency states. *Semin Hematol* 1997;34:188-204.
6. Aiach M, Borgel D, Gaussem P, et al. Protein C and S deficiencies. *Semin Hematol* 1997;34:205-16.
7. Kearon C, Crowther M, Hirsh J. Management of patients with hereditary hypercoagulable disorders. *Annu Rev Med* 2000;51:169-85.
8. Moll S, Ortel TL. Monitoring warfarin therapy in patients with lupus anticoagulants. *Ann Intern Med.* 1997;127:177-85.
9. *British Journal of Hematology*, 2001;114:512-28. Guidelines for investigation and management of Heritable Thrombophilia.

Statistics in Evidence Based Medicine

K.R. Sundaram

In the fast evolving clinical research and decision-making process, a new paradigm has emerged in the recent past—"Evidence Based Medicine." This is based on intuition, systematic as well as unsystematic clinical experience and pathophysiologic rationale as grounds for clinical decision making and stresses the examination of evidence from clinical research—mainly by literature search and gathering all available information (evidence) and applying formal scientific and statistical methods in evaluating the clinical literature. Easier access to the computer and Internet facilities have made literature search much easier and faster. This is a method which helps the clinicians to make decisions about the care of individual patients using the current best evidence consciously, and in a judicious manner.

While reviewing the evidences in clinical trials and epidemiological investigations, several important questions need to be asked before taking a decision—similarity of the groups to be compared at the start of the study, allocation of patients to different groups, whether random or not, validity of the diagnostic tests, drop out rate, the results on the treatment effect, its precision, its clinical importance and applicability etc. In the diagnostic test validity analysis, the concepts of pre-test probability and likelihood ratios are extensively used. One of the important statistical methods commonly used in EBM is the risk analysis. The concept of "Number Needed to Treat" (NNT), which is computed from the risk analysis, has gained a lot of popularity now because

of its simple and fashionable translation, which has attracted the clinicians. Perhaps the term itself was coined mainly for the sake of clinicians. When clinicians and policy makers are presented with research results in different formats like NNT, ARR (Attributable Risk Ratio) and RRT (Relative Risk Ratio), it was found that they make more conservative decisions when presented with NNTs than when they are presented with ARR or RRR. NNT gives the number of patients who need to be treated to achieve one additional favourable outcome (say, cure) or to avoid one additional bad outcome (say, death). Several Meta-analysis methods are extensively used in EBM to integrate the results of all available studies, published or reported otherwise in order to increase the statistical power of the results and thus to help the clinicians to reach a valid decision in patient care. In this article, the important statistical tools related to NNT, applied in EBM are discussed, explaining them with examples.

STATISTICAL PARAMETERS IN NNT

The basic parameter in defining NNT is 'Risk'. Risk of an event due to a factor can be expressed in two ways—Proportion or Odds

$$(1) \text{ Proportion} = a \div (a + b)$$

Example:

a: Number of smokers who have lung cancer

b: Number of smokers who didn't have lung cancer

(a + b): Total number of smokers with or without lung cancer

$a / (a + b)$ = Percentage of smokers with lung cancer

(2) Odds = $a \div b$ = Ratio of event to non-event

Example: Ratio of lung cancer cases to without lung cancer cases in smokers.

Similarly, Benefit of an event due to a factor can be expressed in two ways

$$(1) \text{ Proportion} = a \div (a + b)$$

Example:

a: Number of patients who responded to the drug positively

b: Number of patients who didn't respond to the drug positively

(a + b): Total number of patients who received the drug

$a / (a + b)$ = Percentage of patients who responded to the drug positively.

$$(2) \text{ Odds} = a \div b$$

Example:

Ratio of responded to the non-responded in those patients who received the drug.

Combining these two measures (proportion and odds), Absolute Risk Reduction (ARR) / Absolute Benefit Increase (ABI) and Relative Risk (RR) / Relative Benefit (RB) can be defined as follows: -

If R_1 is the risk of the disease in the exposed group and R_2 , in the unexposed group, ($R_1 - R_2$) is called **Absolute Risk Reduction (ARR)**, assuming that risk of disease in the exposed group is higher than that in the unexposed group.

Or, if B_1 is the benefit of positive response in the treated group and B_2 , in the untreated group, ($B_1 - B_2$) is called **Absolute Benefit Increase** assuming that benefit of positive response in the treated group is higher than that in the untreated group.

Relative Risk Reduction (RRR) can be defined as

$$ARR / R_1$$

and **Relative Benefit Increase (RBI)** can be defined as

$$ABI / B_1$$

NNT can be defined based on ARR (ABI)

NNT = 100 ÷ ARR (ABI) in case of percentages and
= **1 / ARR (ABI)** in case of proportions.

95 % confidence interval of NNT: $1/ARR_L$ & $1/ARR_U$
or $1 / ABI_L$ & $1 / ABI_U$

$$\chi^2 = \frac{[|ad-bc| - n/2]^2 \times n}{(a+b)(c+d)(a+c)(b+d)} = 9.95 > 10.83 (p < 0.001)$$

Mortality is significantly associated with treatment (surgery done or not done) at 0.1 % level of significance. Mortality in those patients on whom surgery was not done (30%) is significantly higher than on whom surgery was done (5%)— $p < 0.001$

$$r_1 = \text{Risk of mortality in Group A}$$

$$= a / (a + b) = 30/100 = 0.30$$

$$r_2 = \text{Risk of mortality in Group B}$$

$$= c / (c + d) = 5/100 = 0.05$$

$$RR = r_1 / r_2, \text{ For the data, } RR = 0.30 / 0.05 = 6$$

i.e. for every death on whom surgery was done, there will be 6 deaths on whom surgery was not done.

$$ARR = 0.30 - 0.05 = 0.25 = 25 \%$$

$$95\% \text{ confidence Interval of ARR: } ARR \pm 1.96 \sqrt{\{r_1(100-r_1)/n_1\} + \{r_2(100-r_2)/n_2\}}$$

For the data, 95 % CI of ARR:

$$0.25 \pm 1.96 \sqrt{\{(0.30 * 0.70) / 100\} + \{(0.05 * 0.95) / 100\}}$$

$$= 0.25 \pm (1.96 \sqrt{0.0507}) = 0.25 \pm 0.0994$$

i.e. 95 % confidence interval of ARR are :

0.1506 and 0.3494 i.e., 15 % and 35 % .

$$RRR = (ARR * 100) / r_1 = (0.25 * 100) / 0.30 = 83.3\%$$

Reduction in Risk of mortality on whom surgery was done as compared to those on whom surgery was not done is 83.3 %.

RRR is also called as: "Attributable Risk" or "Etiologic fraction"

$NNT = 100 / ARR = 100 / 25 = 4$ i.e., Number of patients to be treated with surgery to avoid one additional death is 4

95 % Confidence Limits of NTT are given by

$$1 / ARR_L \text{ and } 1 / ARR_U$$

i.e. $1 / 0.1506$ and $1 / 0.3494$ i.e., 2.9 & 6.6

Example 2

$$b_1 = 20 / 50 = 0.4 \quad b_2 = 35 / 50 = 0.7 \quad (b = \text{Benefit})$$

$$ABI = b_2 - b_1 = 0.7 - 0.4 = 0.3 \quad RBI = 0.3 / 0.7 = 0.4286$$

$$NNT = 1 / ABI = 1 / 0.3 = 3.33$$

3.33 patients are required to be treated with the new drug to get one additional improved patient.

i.e. 10 patients are required to be treated with the new drug for getting 3 improved patients

95 % CL of ABI:—

$$0.3 \pm 1.96 \times \sqrt{[(0.24 + 0.21) / 50]}$$

$$0.3 \pm 1.96 \times 0.095$$

$$= 0.1138 \text{ and } 0.4862$$

95 % CL of NNT: —

$$1 / 0.1138 \text{ and } 1 / 0.4862$$

i.e., 2.06 and 8.78 or 2 & 9

Example 3

$$b_1 = 30 / 50 = 0.6 \quad b_2 = 10 / 50 = 0.2 \quad RB = 0.6 - 0.2 = 3$$

For every smoker without health education, who stopped smoking, there were 3 smokers with health education, who stopped smoking.

$$ABI = 0.6 - 0.2 = 40 \% \quad RBI = (0.6 - 0.2) / 0.6 = 66.7 \%$$

$$NNT = 100 / ABI = 100 / 40 = 2.5$$

i.e. Five smokers need to be given health education to produce two additional stoppers.

95 % CI of ABI are:

$$0.4 \pm 1.96 \sqrt{(0.6 \times 0.4) / 50 + (0.2 \times 0.8) / 50}$$

i.e. 0.4 ± 0.175 i.e. 22.5 % and 57.5 %

$$95 \% \text{ CI of NNT: } \begin{matrix} 100 & 100 \\ 57.5, & 22.5 \end{matrix}$$

i.e.: 1.74 and 4.44

Example-1: The following table gives the results of a 5 years' cohort study on mortality in coronary heart patients with respect to their treatment (surgery done or not done):-

Surgery	OUTCOME		
	Dead	Living	Total
Not done (A)	30 (a)	70 (b)	100
Done (B)	5 (c)	95 (d)	100
Total	35	165	200

Example –2: Results of a clinical trial comparing the effect of the standard drug and a new drug in improving the condition of the disease are given below:—

DRUG - OUTCOME			
	Improved	Not improved	Total
A (Standard)	20	30	50
B (New)	35	15	50
Total	55	45	100

While interpreting NNT due consideration should be given to the other factors such as age, severity, duration and other epidemiological factors. Also, when different NNTs are to be compared with respect to different treatments, proper care should be taken to see whether the groups are comparable otherwise. NNT should be calculated when there is a comparator (placebo, no treatment or any other treatment), which is followed, in any standard experimental study. NNT gives more information than the Relative risk because it takes into consideration the baseline frequency of the outcome (with respect to the comparative group). It is a summary measure which can be easily understood and interpreted even by a non-mathematical / statistical person. Comparison of NNT values for different treatments may help the clinicians in decision-making process. NNTs are very widely and increasingly used in many clinical trials and epidemiological experimental studies.

Example-3: The following data gives the results of a study where continuous planned health education was given to 50 smokers for three months for stopping the smoking habit and another 50 smokers were not given any health education.

SMOKING			
Health education	Stopped	Not-stopped	Total
Yes	30	20	50
No	10	40	50
Total	40	60	100

REFERENCES

1. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *British Medical Journal* 1995;310:452-4.
2. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998; 317:1309-12.
3. Sackett DL, Deeks JJ, Altman DG. Down with odds ratios! *Evidence Based Medicine*, 1996,1:164.
4. Davies HT. Interpreting measures of treatment effect. *Hosp Med* 1998;59(6) 479-501.
5. Moriarty PM. Relative risk reduction versus number needed to treat as measures of lipid lowering trial results. *Am J Cardiol* 1998;82(4)505-7.
6. Rembold CM. Number needed to screen-development of a statistic for disease screening. *BMJ* 1998;317(7154)307-12.
7. Vickers AJ, Tijssen JG, Kleijnen J, et al. Number needed to treat and placebo controlled trials. *Lancet* 1998;351(9099)310.
8. Thomas R, Padma P, Braganza A, et al. *Indian J Ophthalmol* 1996,44(2)113-5.
9. Rajkumar SV, Sampathkumar P, Gustafson AB. Number needed to treat is a simple measure of treatment efficacy for clinicians. *J Gen Intern Med* 1996;11(6)357-9.
10. Wiffen PJ, Moore RA. Demonstrating effectiveness – the concept of numbers needed to treat. *J Clin Pharm Ther* 1996;21(1)23-7.

Nanosciences Research at the Health Sciences Campus of Amrita Vishwa Vidyapeetham

S. V. Nair

The word "Nanotechnology" was coined in 1974 by Norio Taniguchi, professor at the Tokyo Science University, with regard to ion sputter machining with nanometer precision (nanometer = 10^{-9} meters), although the understanding and application of nanotechnology is much older. The Romans manufactured gold nanoparticle reinforced glass¹ and, even long before this, metal nanoparticles have been used for medicinal purposes in ayurvedic sciences in India. Such metallic nanoparticles used in India have been of Na, K, Ca, Mg, V, Mn, Fe, Cu, and Zn, and their role in medicine continue to be a matter of current controversy and research². Furthermore, ancient ayurvedic sciences have proposed "nano" or "subtle" constituents such as "doshas"³ in the human body, such that disease states are caused when the concentration of these nanoscale substances exceed some critical value.

In this context, modern nanotechnology is in its infancy, with its serious evolution beginning only in the 1990s in the West, spurred by the earlier advent in the 80s of the scanning tunneling and scanning probe microscopy. Yet, in the short span of the last 15 years, there has been an explosion of studies in this area bringing modern and ancient sci-

ence together in ways that were not thought possible. While India has had an ancient history in the nanosciences, much of this has languished over the past several centuries and modern nanotechnology was taken up actively only after about 2000. One of the early strong initiatives taken up by the Government of India was to establish the Nanoscience and Nanotechnology Initiative (NS & NT) in October 2001. By 2007, seven Centres of Excellence in Nanotechnology were established under this initiative and the Centre at Amrita Vishwa Vidyapeetham in Cochin is one of those seven, the newest one, and the only one in the biomedical area.

AMRITA CENTRE FOR NANOSCIENCES

The Amrita Centre for Nanosciences (ACNS) was established in May 2006 and inaugurated in February 2007 by Professor C.N.R. Rao, India's visionary in nanosciences research. The Centre was funded to explore the role of nanomaterials in tissue engineering and stem cell research for the purpose of developing novel new implants that mimic natural tissues so as to preclude issues of biological incompatibility and rejection. Subsequently, two new research programs were initiated: one, on surface nanostructuring of conventional materials to provide value added improvements to synthetic implants and two, on use of quantum dots for tar-

geting oral cancer cells for early diagnosis of a highly prevalent cancer in India. A 10,000-sq. ft space was dedicated to ACNS and the following laboratories were established:

1. The nano-imaging lab containing the scanning electron and scanning probe microscopes.
2. The nanochemistry lab for wet chemical processing of nano particles.
3. A mechanical testing laboratory for characterization of the mechanical properties of nano materials.
4. A chemical characterization laboratory for elemental characterization using FTIR, a Gel Permeation Chromatograph for determining the molecular weights of polymer molecules, a nanoparticle sizer for laser-based determination of the charge and size of nanoparticles and a Differential Scanning Calorimeter for the thermal characterization of polymeric materials.
5. A polymer processing lab for synthesis of polymeric nanomaterials of novel new polymer systems.
6. A nanofiber lab utilizing electrospinning for nanofiber processing.
7. A polymer processing lab for the generation of polymeric nano composites by melt blending.

There are other areas of research also that the Centre has plans to de-

velop in the near future. This includes the toxicological effects of nanomaterials, use of naturally occurring materials in nanomedicine and the development of nanostructured materials for solar energy applications.

ACNS will also have a strong academic focus with a college of nanosciences devoted to the training of the next generation of Indian nanotechnologists, nanobiotechnologists and nanomedical scientists. A beginning to this is the start of a two-year Master of Technology program in Nanomedical Sciences that is starting in August 2007 with 30 students admitted each year. The focus of this Master of Technology program is to provide a fundamental understanding of nanomaterials sciences that have applications in the medical sciences as well as a thorough training in the medical sciences relevant to current potential applications.

TISSUE ENGINEERING

The coinage "tissue engineering" immediately and correctly implies a combination of the disciplines of biology and technology. Modern tissue engineering took its birth in the late 1980s in Boston, USA, through the pioneering efforts of Dr. Joseph Vacanti of Boston Children's Hospital and Dr. Robert Langer of Massachusetts Institute of Technology⁴. The basic concept involves the development of a scaffold into which are introduced appropriate cells that eventually multiply into the tissue-specific cells and regenerate the target tissue. The dream is that this approach can eventually regenerate an entire organ although that reality is still fairly distant. Much of the current research in the world is focused on how to expand the cells *in vitro* in the scaffold so that one can generate sufficiently large volumes starting with limited cells and how to prevent cell death during subsequent implantation. Since mature cells can only be expanded to a very limited extent much research is focused on the use of stem cells, and even here, tissue-specific adult stem cells may be the choice of the future⁴.

One role of nanotechnology in tissue engineering is the ability of nanomaterials to more efficiently expand cells. This has been observed in our labs at the ACNS where our preliminary observations show more efficient attachment and proliferation of cells on nanostructured surfaces⁵. A second role that nanomaterials can play is in controlling the chemical and mechanical properties of scaffolds. Nanoparticle reinforcements can effectively influence the strength as well as the biodegradability of the scaffold. This property becomes important when implantation is done before complete tissue regeneration. In this case, the scaffold must temporarily fulfill the mechanical functions of the tissue. Further, in many cases of tissue engineering, the scaffold is designed to be biodegradable and ideally the degradability is matched so that degradation is complete when the tissue has fully regenerated. There is work that shows that nanoparticles

tend to enhance material degradability⁶ and can therefore be used to tune the degradability of scaffolds.

Currently at ACNS we are developing novel methods to process scaffolds out of many candidate biodegradable materials, including naturally occurring materials, such as chitosan. One useful technique, developed in the 90s in the US is electrospinning⁷, which is capable of readily generating nanofibrous materials, which have a strong resemblance in structure to the extracellular matrix⁸. At Amrita we are exploring different ways of controlling nanostructure and microstructure using electrospinning⁹.

EARLY DIAGNOSTICS AND DRUG DELIVERY

An exciting discovery that propelled the field of nanobiotechnology is that material particles in the nanosize regime have strong interactions with other biological nanomaterials, such as, protein, DNA, enzymes, antigens, antibodies and cellular receptors, allowing them to be used as highly efficient biological probes¹⁰. A particularly attractive choice is a semiconductor nanoparticle in the size regime under 10 nm. Such particles, termed quantum dots, exhibit luminescence of wavelength that is strongly particle size dependent and hence are perfectly suited for diagnostic imaging of specific cells. The Department of Biotechnology, Government of India is supporting a project at ACNS for the development of targeted quantum dots for early detection of oral cancer. The approach we are taking is to biofunctionalize quantum dots with antibodies targeted to known cancer biomarkers either in tumor cells or, more interestingly, in what are known as cancer stem cells – rare pre-cancerous cells with indefinite potential for self-renewal¹¹.

NANOSURFACE BIOENGINEERING

The most well recognized property of the nanoscale is its extremely high surface activity. Indeed a rough calculation will show that at a particle size of about 2 nm 100% of the atoms reside on the surface, and therefore every single atom is capable of reacting with the environment. If this environment is biological, such as, when there are protein molecules or cells with nanoscale receptors on the surface, there is the potential for an unusually strong interaction of the material with the biological environment. Using this principle, at Amrita we have been taking conventional implant materials like Ti and providing nanoscale features on the surface by various methodologies such as, laser treatments, nanochemistry and electrochemistry to provide surfaces ranging from the nanoscale to the microscale and then studying the cell-surface interactions⁵.

THE FUTURE

The benefits of nanotechnology are certainly here to stay in many areas related to the health sciences. These are:

1. Novel nanostructured implants.
2. Tissue engineering using nanostructured scaffolds.
3. Expansion of cells through nanostructuring.
4. Early diagnostics of disease using targeted nanoparticles.
5. Targeted and controlled release of drugs using nanoparticles rather than by systemic treatments.
6. Use of nanoparticle probes for efficient, highly sensitive and high throughput biological assays.
7. Increasing the efficiency of conventional drugs using nanoparticulate versions thereby substantially reducing their dosages and hence the side effects.
8. Development of novel rapid healing wound dressings using nanofibers.

These are only some examples and are not an exhaustive list. At Amrita we are glad to be at the leading edge contributing to an exciting new era where technology and medical sciences are no longer compartmentalized.

REFERENCES

1. Pradeep T. Nano: The Essentials, Tata McGraw Hill Publishing Co. Ltd., 2007, pg. 9.
2. Kumar A, Nair AGC, Reddy AVR, et al. Unique Ayurvedic Metallic Herbal Preparations, Characterization, *Biological Trace Element Research*, vol. 109, No. 3, 2006, pgs. 231-4.
3. Valiathan MS. India's Medical Legacy, 38th Founders Memorial Lecture at the Sriram Institute for Industrial Research, 2002.
4. Charles A. Vacanti. A History of Tissue Engineering and a Glimpse into its Future, *Tissue Engineering*, May 2006, Vol. 12, No. 5, pgs. 1137-42.
5. Divyarani VV, Anitha VC, Manju T, et al. Unpublished work, Amrita Centre for Nanosciences, 2007.
6. Li Z, Yubao L, Aiping Y, et al. Preparation and in vitro investigation of chitosan/nano-hydroxyapatite composite used as bone substitute materials, *J Mater Sc Mater Med*, March 2005, Vol. 16, No. 3, 213-9.
7. Reneker DH, Chun I. Nanometer diameter of fibres of polymer, produced by electrospinning, *Nanotechnology*, Vol. 7, 1996, pgs. 216-33.
8. Ramakrishna S, Fujihara K, Ma Z, et al. An Introduction to Electrospinning and Nanofibers, World Scientific Publishers, 2005, 291.
9. Sajeev US, Menon D, Nair S, et al. Control of Nanostructures in PVA, PVA/Chitosan Blends and PCL through Electrospinning, to be published in the *Bulletin of Materials Science*, 2007.
10. Katz E, Willner I. Integrated Nanoparticle-Biomolecule Hybrid Systems: Synthesis, Properties and Applications, *Angew. Chem. Int. Ed.*, Vol. 43, 2004, pgs. 6042-108. Reya T, Morrison SJ, Clarke MF, et al. Stem Cells, Cancer and Cancer Stem Cells, *Nature*, 414 (6859), Nov. 2001,105-11.

Control Strategies for Rheumatic Fever and Rheumatic Heart Disease in Wayanad, Kerala

L. Krishnan, S. Vasudevan, S. Ajitha, R.K. Kumar*

ABSTRACT

Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) are still an important public health problem in the developing world. The disease burden appears to be closely linked to human development. A recent survey in the Ernakulam District demonstrated that the estimated disease burden of RF and RHD in this region was among the lowest in the developing world. There are parts of Kerala where access to health care and human development indices are much lower than the state average. For this reason the Indian Council of Medical Research (ICMR) has chosen the district of Wayanad for determination of the magnitude of RF and RHD. The services of the entire health care infrastructure of the district (both government and private) including many community volunteers are being used to identify patients with RF and RHD. The results of this study will provide interesting epidemiological insights and help plan specific control strategies.

INTRODUCTION

The incidence of Rheumatic fever and prevalence of Rheumatic heart diseases have declined in the developed countries around the world, although it still remains a major public health problem in developing countries.¹ In India, a study by Padmavati² revealed that the estimated average prevalence of rheumatic heart disease in school surveys during 1984-1995 was 0.18-3.0 per 1000. Another study by Lachandani et al³ revealed the prevalence of RHD to be 4.54 per 1000 in the year 2000. The RF/RHD registry project of Amrita Institute of Medical Sciences and Research Centre (AIMS) at Kochi, Kerala during 2003 – 2004 showed the prevalence of RHD to be 0.12 per 1000, which was the lowest ever reported in India.

The control of Rheumatic fever / Rheumatic Heart disease (RF/RHD) includes a broad spectrum of activities aimed at primary prevention, secondary prevention, health education activities, epidemiological surveillance and creating registry.

The Indian Council of Medical Research (ICMR), New Delhi, under the government of India, which is the apex body for the planning, formulation, coordination, implementation and promotion of biomedical research, initiated The *Jai Vigyan* Mission mode project on RF/RHD control. As part of this project, the ICMR funded the department of Paediatric Cardiology at Amrita Institute of Medical Sciences and Research Centre, Kochi to implement the RF/RHD control programme in the district of Wayanad in Kerala. Its main objectives are to establish a RF/RHD registry, sensitize the community regarding the disease and its prevention and to estimate the prevalence of RHD among school children aged 5-15 years in the district. This paper gives an overview of the ongoing activities of the project being implemented by the Amrita Kripa Charitable Hospital (AKCH), Kalpetta at Wayanad.

PROJECT AREA

The State of Kerala with a population of over 31 million and density of 819 persons per sq.km is located in the southwest part of India. Its achievements in terms of the basic indicators of human development are in par with some of the developed countries.

Kerala continues to rank at the top among Indian States with respect to the human development index, although there are few variations within districts across the state.

Wayanad district, the project area is located in the northern part of Kerala bordering Karnataka and Tamil Nadu and has a population size of nearly 7,87,000. Some of the characteristics of Wayanad include relatively low literacy rates, relative poverty and a high proportion of tribal population as compared to other districts in the State. Given these conditions, the Human Development Report of Kerala⁴, recommends that special attention is needed for implementing policies and programmes to improve the basic well-being indicators such as quality of housing, access to water, good sanitation. This project being implemented at Wayanad could be a stepping-stone in that direction.

CONTROL STRATEGIES

The *Jai Vigyan* Mission mode for control of RF/RHD, adopts a time bound, goal oriented approach and emphasizes on standardized and uniform methodologies. The methodology adopted for this project can be summarized in two components:

Amrita Kripa Charitable Hospital & AIMS, Kochi.
* Dept. of Pediatric Cardiology, AIMS, Kochi.

1. *Passive surveillance*: involves registration of RF/RHD cases in the district, facilitated through a series of workshops for doctors and awareness programs for health workers.
2. *Active surveillance*: involves screening a sample of school children in the district for RHD.

PASSIVE SURVEILLANCE

I. WORKSHOP FOR DOCTORS

The main aim of conducting a series of workshops for the doctors in the region was primarily to sensitize them regarding the project in general and their role in helping to implement the project. It was important that we get all the doctors, both from the government and private sectors to participate in the workshops as they are expected to report all the suspected or established cases of RF/RHD to the project. However, to ensure maximum participation, the doctors in the area were grouped under three block panchayats, based on the geographical area in which they practice. As a result of which a total of three workshops were conducted in the district with the support of professional organizations like the Indian Medical Association and Kerala Government Medical Officers Association. Specific guidelines for patient referrals and the role of doctors in the implementation of the project were highlighted. The doctors were requested to either refer the patients directly to our project office at the AKCH or send the patient details by post through the self-addressed business reply card that was distributed to them during the workshops.

II. AWARENESS PROGRAMS FOR COMMUNITY HEALTH CARE WORKERS

The goal was to involve all the healthcare workers in the district. So we decided to utilize the services of the already existing network of grass root level healthcare workers in the region. It included the Kudumbashree volunteers, Anganwadi workers and primary healthcare workers of the department of health services.

Through these awareness programs they are instructed about the signs and symptoms of RF/RHD, prevention strategies and advised to disseminate this information to other members of their group and the community. Apart from the PowerPoint presentations, an audiovisual documentary exclusively prepared for the project is being screened during the program for better understanding of the disease and the project. They are also taught to identify the suspected or established cases of RF/RHD from the community and motivate them to report to the project office (AKCH) for evaluation and registration under the project registry.

a. Use of Kudumbashree volunteers

Kudumbashree is an innovative, women-centered poverty eradication programme being carried out since 1998

in Kerala State. It gives prime importance for the economic empowerment of the indigent masses, especially the poor women of Kerala. Kudumbashree mainly includes three components micro credit, entrepreneurship and empowerment. Its three-tier organizational structure is the Neighbourhood Groups (NHG) of women who come from poor families and who are identified based on risk indices. Each NHG with about 10 to 20 members selects a five-member volunteer committee having specific responsibilities, such as President, Secretary, Community Health Volunteer, Income Generation Activities Volunteer and Infrastructure volunteer.

Wayanad district has well-organized and networked NHG's, with an average of 350 groups in each Panchayat. Considering the fact that the members are from poor families and literally representing each household, we decided to disseminate information among this group. Since the kudumbashree is closely associated with the Panchayat and has the backing of the bureaucracy, we are conducting awareness classes for these Kudumbashree community health volunteers in each Panchayat.

b. Use of Anganwadi workers

Integrated Child Development Services (ICDS) Scheme is an inter-sectoral programme, which seeks to directly reach out to the community. The ICDS team comprises of the Anganwadi helpers, Anganwadi workers, supervisors, Child Development Project Officers (CDPOs) and District Programme Officers (DPOs). Anganwadi Worker is a lady selected from the local community, and is a community based frontline voluntary worker of the ICDS Programme. She is also an agent of social change, mobilizing community support for better care of young children, girls and women.

Anganwadi workers in Wayanad district have been grouped under three block Panchayats, each consisting of around 200 to 250 workers. Considering the total number and the well-established organization of the workers at the grass root level, we decided to conduct awareness programme in each block Panchayat.

c. Use of primary healthcare workers from the department of state health services

The grassroots level healthcare workers of the government health services constituting Junior Public health Nurses, Junior Health inspectors and health inspectors, were targeted to impart awareness program. This was because; they are the first level contact of the community with formal health care delivery system of the state. The gamut of services they provide is very wide encompassing promotive, preventive and curative services. They are assigned specified population or geographic area to provide comprehensive primary health care to the community and they function closely with the local Grama Panchayat ward members.

The district health services department had grouped these healthcare workers based on the geographical area of work into five groups. Each group consisting of around 60-70 healthcare workers were functioning under one Community Health Center (CHC) in the district. To enable participation of all these healthcare workers, we decided to conduct awareness program in all five CHC's.

ACTIVE SURVEILLANCE

I. School Survey

A cross sectional survey of school children in the age group of 5 – 15 years is being conducted to screen for RHD. We began the survey from September 2006, on a target population of 25,000 school children. In order to generalize the results to the entire school children of the district, we selected the schools at random from the entire district. The schools were stratified based on the type of school (aided, unaided and government) and randomly selected. The number of students screened would be proportional to the total number of children in that particular type of school. Our aim is to survey all students in each selected school. However, anticipating few children to be absent, a total of 60 schools with 27,481 children in the age group of 5 – 15 years were finalized for the survey. These children are screened in two stages:

a. Primary screening

The project team visits the selected school and collects demographic information of each child and records them in a prescribed format (screening form). The children are then called upon in a class wise manner for anthropometric measurement (height, weight and mid arm circumference), blood pressure recording and auscultation. The auscultation is performed by the project medical officer to identify abnormal heart sounds or murmur.

b. Secondary screening

If any child is found to have an abnormal heart sound or murmur from the primary screening, more information is collected regarding the history of Rheumatic fever and about secondary prophylaxis. Later these children are referred to AKCH. All children so referred will undergo detailed clinical examination and echocardiography by a cardiologist to confirm diagnoses. Children confirmed to have RF/RHD would be registered in the project registry.

EVALUATION, REGISTRATION AND FEEDBACK

Following the implementation of the ongoing above-mentioned strategies, patients of suspected or established RF/RHD are reporting to the project office at AKCH directly or through the business reply cards with patient details received from doctors. The patients referred through the cards were contacted by the project field staff and

motivated to visit the project office for evaluation and registration.

Once the patient reports at AKCH directly, a physician initially evaluates the patients and necessary blood tests (ESR, ASO) are done to rule out RF/RHD. Later, suspected or established cases of RF/RHD would be scheduled for cardiologists' evaluation on specified days of a month. Parallely the children short-listed from school survey with abnormal heart sounds would also be scheduled on these days.

A senior cardiologist from AIMS, Kochi would visit AKCH on the first weekend of every month for evaluation and echocardiogram of all patients scheduled under the project. The cardiologist thoroughly examines the patients and if necessary appropriate blood tests and echocardiogram are done. The details of cardiology evaluation, echocardiogram findings and recommendations are recorded in pre-designed format (Form-2). Three copies of Form-2 are made, of which one is retained in the project office; one is given to the patient and one is sent to the referring doctors. In selected cases the cardiologist sends a detailed letter regarding the patient's condition to the referring doctor.

DISCUSSION

The current RF/RHD control strategies being implemented at Wayanad is definitely advantageous for raising the health consciousness of the people. These multifaceted control strategies and awareness programmes targeting individuals in the community belonging to lower socio economic groups maybe effective since, it is known that crowded living conditions and poverty are associated with a high prevalence of RHD.

The major limitation of this project would be the inability to provide treatment despite diagnosis of RF/RHD. Also, the existing government health care services are not equipped enough to provide the required treatment facilities, considering the high cost and the technology driven surgical treatment required for certain RF/RHD cases.

REFERENCES

1. Rheumatic fever Rheumatic Heart disease. Report of a WHO study group, Technical Report Series, WHO, Geneva 1988;764:7-11.
2. Padmavati S. Present Status of Rheumatic heart disease in India. *Indian Heart J* 1995, 47:395-8.
3. Lachandani A, Kumar HRP, Alam SM, et al. Prevalence of rheumatic fever and rheumatic heart disease in rural and urban school children of district Kanpur. *Indian Heart J* 2000, 52:192.
4. Government of Kerala. Human Development Report 2005, Kerala. Centre for Development Studies, Thiruvananthapuram, Kerala.

Adhesive Felt Offloading in the Healing of Diabetic Foot Ulcers

T.S. Mangalanandan, S. Sajith, R. Manoj, Raghavendra, N. Varma, A. Bal, H. Kumar

ABSTRACT

INTRODUCTION

Increased plantar foot pressure is a leading cause of ulceration in the diabetic population. Healing these ulcers requires adequate blood supply, control of infection, excellent wound care and offloading or pressure redistribution of the ulcerative area. As diabetic foot care has evolved over the years, podiatrists have used numerous approaches including complete bed rest, cutout felt pads, specialized footwear and total contact casting to offload these wounds.

AIM

To study the efficacy of medical grade adhesive felt in the healing of diabetic foot plantar ulcers, as compared to conventional techniques.

MATERIALS AND METHODS

The study was carried out from 1st of July '06 to 30th April '07. In both the felt and control groups, patients had relatively clean wounds, and after initial surgical management, the ulcers were in the process of healing. In the felt group, the felt was cut out as per size of the ulcer, and stuck around it, 2 to 3 mm away from the ulcer margins. This was changed once in 10 days, or as per requirement. The patient was ambulant with prescribed diabetic footwear. In the control group, patients were advised orthowedge or rocker bottom outsole diabetic footwear, bed rest, or walker mobilization. Appropriate wound dressings and antibiotics were given in both the groups. In both groups, the wounds were measured once in two weeks using a sterilized, disposable paper scale. End point was complete epithelialisation of the wounds, in both groups.

RESULTS

There were a total of 58 patients; 42 males and 16 females. Each of the 'felt' and 'control' groups had 29 patients.

The ulcer size varied in surface area from 1sqcm to 25 sqcms area in both the groups. Patients in both the groups were followed-up for a minimum period of 3 months, or till complete epithelialisation, whichever was earlier. Wounds in all patients, in both groups had completely epithelialised by the end of the study. There were no dropouts from either group. The mean time taken for wound healing in the felt group was 3.9 weeks (range of 2.6 to 7.2 weeks) and in the conventional group it was 10.3 weeks (range of 6.8 to 13.8 weeks); (p value of 0.0001).

CONCLUSION

The study shows significant reduction in the time taken for wound healing in diabetic foot plantar ulcers where 'felt' was used, as compared to conventional techniques. (p value 0.0001).

It can thus be concluded that felt dressing is an excellent offloading technique in the management of diabetic foot plantar ulcers.

INTRODUCTION

Increased plantar foot pressure is a leading cause of ulceration in the diabetic population. Healing these ulcers requires adequate blood supply, control of infection, excellent wound care and offloading or pressure redistribution of the ulcerated area¹. As diabetic foot care has evolved over the years, podiatrists have used numerous approaches including complete bed rest, cutout felt pads,

specialized footwear and total contact casting to offload these wounds².

However, in order to select an appropriate offloading modality, it is important to be aware of the potential causes of increased plantar pressure in the diabetic foot.

Ground reactive forces (GRF) impact the plantar foot during weight bearing activities in all ambulatory individuals. Ground reactive forces can be perpendicular to the foot (known as vertical stress) or they can work parallel to the foot (known as shear stress). When these forces work to-

gether in a repetitive fashion, ulcers may form on the plantar foot in people with diabetes due to the inability to appreciate the increased stress on the foot^{3,4}.

When people stand, each foot takes on 50 percent of the body weight. However, when people walk, they transfer all of the body weight from one foot to the other. During the stance phase of the gait cycle, the entire foot is only on the ground (foot flat) 23 percent of the time. The heel is in contact with the ground the first 64 percent of the phase while the fore-

foot is in contact the last 59 percent of the phase. This means all of the body weight is on one heel or one forefoot a significant period of time. This pressure can equal 1.2 to 1.5 times the body weight depending on the walking speed⁵.

When a deformity is present, there is increased pressure on the foot. Researchers have shown that diabetes causes a decrease in conduction speed in the tibial and peroneal nerves. This correlates to increased lower extremity muscle weakness. Muscle weakness may lead to foot deformity and subsequently cause areas of increased pressure⁶.

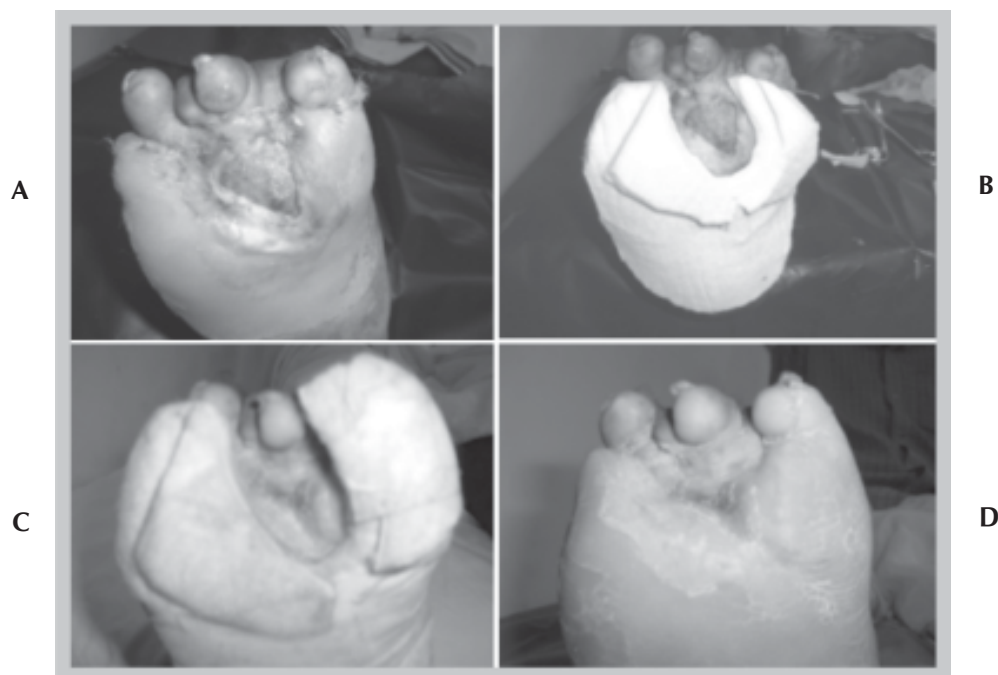
With regard to offloading; some material is usually placed on the foot such as padding or dressings. However, the first and most important offloading technique is to actually take pressure off from the skin of the plantar aspect of the foot. Debriding the hyperkeratotic skin surrounding the wound edge is the one aspect of offloading that one should address^{7,8}. When left untreated, the thick and callused edges of a wound will roll inward and inhibit the wound edges from migrating towards the center. This hyperkeratotic edge may also cause increased plantar pressure. Based upon Dr. Paul Brand's work that demonstrated the greatest amount of pressure placed on a foot ulcer is at the leading edge, Armstrong and Athanasiou later coined the term "edge effect"^{13,16}.

One might think the greatest pressure would be in the center of the wound but many plantar ulcers have such significant depth that the weight bearing forces do not affect the center of the wound. Due to the natural offloading of the central wound cavity, plantar foot pressures intensify at the leading edge of the wound. This is why many plantar foot ulcers need weekly, or at least frequent, debridement for offloading purposes^{9,15}.

Gait modification offers another simple means of offloading the foot. A reduction in walking speed or shuffling-type gait can reduce the pressure on the forefoot. Unfortunately, it is sometimes difficult for patients to change their walking patterns abruptly. Physical medicine can be helpful in retraining patients in gait when needed. All attempts should be made to keep these patients ambulatory with the exception of large wounds. Continued ambulation can reduce other morbidity. Medical grade adhesive felt is an excellent technique for ambulatory offloading of plantar ulcers in diabetic patients^{10,11}.

Felts are a class of fabrics or fibrous structures obtained through the interlocking of wool, fur, cotton, rayon or some hair fibers under conditions of heat, moisture, and pressure. With the exception of felt, nonwoven materials are in the early stages of development. Nonwoven fabrics can be defined as textile fabrics made of a

Plate: 1



A: Shows a forefoot plantar ulcer prior to starting felt offloading treatment. **B:** Shows felt pad applied around the ulcer. **C:** Shows healing ulcer after about 3 weeks of treatment. **D:** Shows epithelialised ulcer.

fibrous layer having randomly laid or oriented fibres or threads.

Felts of the nonwoven class are considered to be the first textile goods produced, and many references may be found to felts and their uses in the histories of ancient civilizations. The nomadic tribes of north central Asia still produce felts for clothing and shelter, utilizing the primitive methods handed down from antiquity¹. Felt is being used at various centers world over, for offloading diabetic plantar foot ulcers

AIM

To study the efficacy of medical grade adhesive felt in the healing of diabetic foot plantar ulcers as compared to conventional techniques.

MATERIALS AND METHODS

The study was carried out from 1st of July '06 to 30th April '07. In both the felt and control groups, patients had relatively clean wounds, and after initial surgical management, the ulcers were in the process of healing.

Inclusion criteria for the study were:

- a) Type 2 & type 1 diabetic patients.
- b) Plantar ulcers below 25 sq cm at study entry.
- c) Non infected ulcers and ulcers with superficial slough.
- d) Ankle Brachial Index (A.B.I) 0.9 to 1.2 at study entry.

Exclusion criteria were:

- a) Ulcers over 25 sq cm surface area.
- b) Deeper/ spreading infections or surrounding cellulites.
- c) Non re-vascularisable Peripheral Occlusive Vascular Disease.
- d) Ulcers encroaching beyond plantar aspect.

The patients who met these criteria were randomly assigned to either felt group or control group.

In the felt group, the felt was cut out as per size of the ulcer, and stuck around it, 2 to 3 mm away from the ulcer margins. This was changed once in 10 days, or as per requirement. The patient was ambulant with prescribed diabetic footwear. Here the footwear did not have an orthowedge or rocker bottom outsole modification. Felt used was 10 mm in thickness and had a 'shore-hardness' of 24. Patients in both groups were followed-up once in two weeks, in the Out Patient Department. (Plate:1)

In the control group, patients were advised orthowedge or rocker bottom outsole diabetic footwear, bed rest, or walker mobilization. Appropriate wound dressing was done by conventional techniques in both the groups. Sharp debridement, enzymatic debriding agents and topical antibiotics were used as per requirement of each patient. Systemic antibiotics were given when required.

Routine investigations were carried out and strict glycaemic control was achieved in all patients.

In both groups, the wounds were measured once in two weeks using a sterilized, disposable paper scale. End point was complete epithelialisation of the wounds, in both groups. Statically, chi-square method was used to compare the two groups.

RESULTS

There were a total of 58 patients; 42 males and 16 females randomized to the two groups. Each of the 'felt' and 'control' groups had 29 patients.

The ulcer size varied in surface area from 1sqcm to 25 sqcms area in both the groups. Mean area of ulcers was 17 sqcm in the felt group and 17.5 sqcm in the control group at the time of entry into the study.

As per the University of Texas (UT) classification (Table 1), ulcers ranged from 1 A to 3 D in both the groups (Table 2).

Table 1: University of Texas Classification of Foot Ulcers

	0	1	2	3
A	no epithelial break	superficial ulcer	ulcer involving tendon, capsule.	ulcer involving Bone, joint
B	infection	infection	infection	infection
C	ischemia	ischemia	ischemia	ischemia
D	ischemia & infection	ischemia & infection	ischemia & infection	ischemia & infection

Table 2: Distribution of patients as per UT classification

	Felt	Control
1A:	4	5
1B:	9	7
1C:	5	7
2B:	7	6
2C:	3	2
3D:	1	2

Peripheral neuropathy was seen in 25 patients of the felt group and 27 of the control group. This was tested by 'vibration perception test' (VPT) using the Biothesiometer. Patients with VPT of 15 volts and above was taken as having peripheral neuropathy.

2 Patients in the felt group and 3 patients in the control group had undergone prior peripheral angioplasty of that lower limb for occlusive vascular disease, confirmed by a peripheral angiogram.

Patients in both the groups were followed-up for a minimum period of 3 months, or till complete epithelialisation, whichever was earlier. Wounds in all patients, in both groups had completely epithelialised by the end of the study. There were no dropouts from either group.

The mean time taken for wound healing in the felt group was 3.9 weeks (range of 2.6 to 7.2 weeks) and in the conventional group it was 10.3 weeks (range of 6.8 to 13.8 weeks); (p value of 0.0001).

DISCUSSION

The felt used in the study had a 'shore hardness' of 24. This is important for equally distributing plantar pressures and preventing build-up of plantar pressure over the area where the felt is stuck. 'Shore hardness' refers to the density of the material. Lesser the shore hardness, softer is the material^{12,14}.

UT classification had shown comparable ulcer size and other parameters in both the groups. Peripheral neuropathy. In the felt group, the time taken for ulcer healing was markedly less, (p value 0.0001), as here the void created under the ulcer provides excellent pressure relief, where as some degree of plantar pressures do act on the ulcer when the patient is using a modified diabetic footwear, or a total contact cast. Since the felt is cut approximately 2 to 3 millimeter away from the margin of the ulcer, and is stuck around it, the material will not shift when the patient is walking. Thus this will obviously give complete relief of plantar pressure at this site. Hence wound healing progresses unhindered despite mobilizing the patient.

In modified footwear this absolute pressure relief will not occur. Modifications of footwear for plantar pressure relief are the 'orthowedge' and 'rocker-bottom' modifications. The orthowedge shoes, which may be anterior, mid or posterior according to whether forefoot, midfoot or the hindfoot is to be offloaded. Rocker-bottom outsole modifications are also commonly prescribed for foot offloading and may be of six different types according to the part of the foot and the degree to which it has to be offloaded. However complete relief of plantar pressure cannot be obtained by these modifications as while walking 15% to 20% or more plantar pressure is bound to be transmitted to the ulcer^{2,5}. Even in a total contact cast, which is a gold standard for plantar ulcer offloading, only about 86% of plantar pressure can be removed¹¹.

Patient compliance may also be a factor, since the felt which is stuck to the plantar skin will remain in position at all times, while a non compliant patient using a modified footwear can walk without it, leading to build-up local pressure and delayed wound healing. Similar studies done by other workers have also shown good results for ulcer healing, and are a proven modality of offloading^{1, 16, 17}. In a prospective clinical trial, by Armstrong DG et al, 63 patients with superficial noninfected, nonischemic diabetic plantar foot ulcers were randomized to one of the commonly used modalities of plantar ulcer off-loading TCC, half-shoe, or RCW and padded felt. Outcomes were assessed at wound healing or at 12 weeks, whichever came first. Primary outcome measures included proportion of complete wound healing at 12 weeks and activity. Results of this study also showed faster healing of plantar wounds, in the group where 'felt' was used.

However as a healed plantar ulcer is also a high risk area for subsequent ulcerations, outsole modifications of footwear like a orthowedge & rocker bottom, or insole modifications will be essential for prevention of ulcer recurrence¹⁷. This is so at the site of healing, the tissue is not as supple as normal tissue, and adhesions of the healed scar to deeper structures will make it less pliable and mobile, leading to a high risk area for injuries. Also the vascularity of these healed ulcers may be lesser than that of the earlier tissue. Hence, this modified diabetic footwear is of paramount importance in the recurrence of healed plantar wounds.

In conclusion, the study shows significant reduction in the time taken for wound healing in diabetic foot plantar ulcers where 'felt' was used, as compared to conventional techniques. (p value: 0.0001).

It can thus be stated that 'felt' is an excellent offloading technique in the management of diabetic foot plantar ulcers.

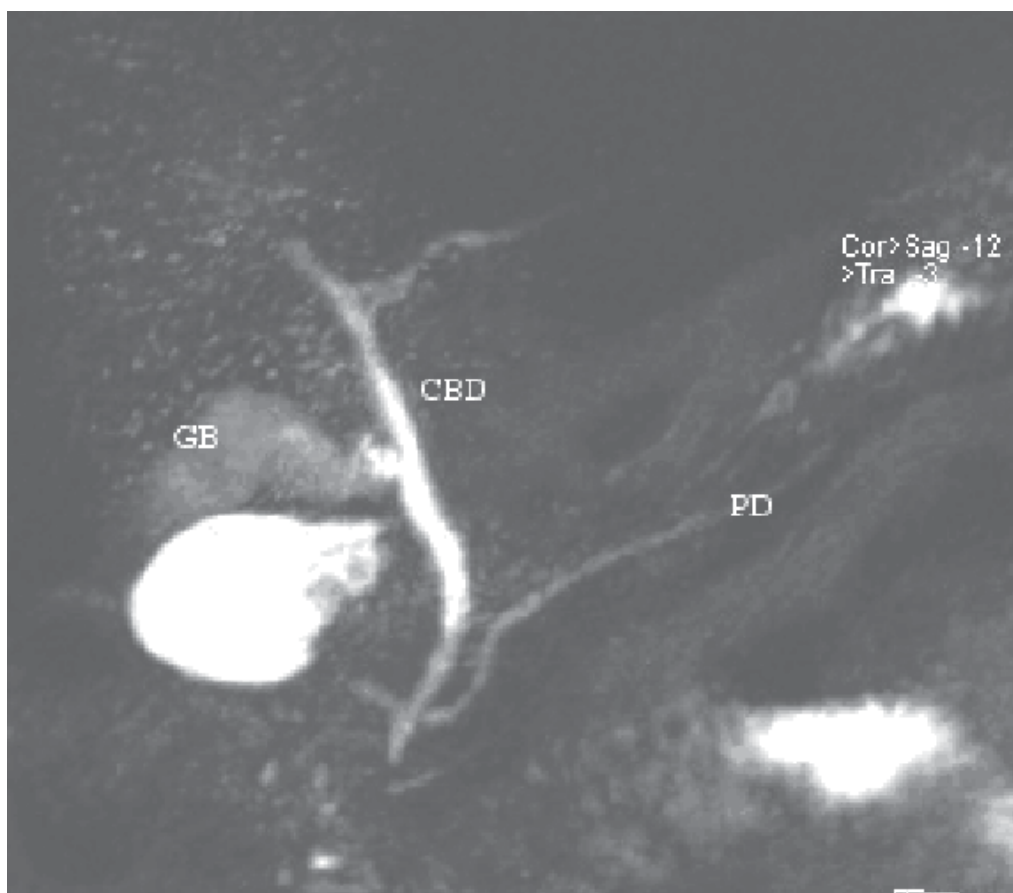
REFERENCES

1. Nubé V, Molyneaux L, Bolton T, et al. The use of felt deflective padding in the management of plantar hallux and forefoot ulcers in patients with diabetes. *The Foot*, Volume 16, 1, 38-43.
2. Off-loading techniques in the treatment of diabetic plantar neuropathic footulceration. *Advances in Wound Care*, Nov/Dec 1999 by Cantanzariti, Alan R, Haverstock, Brent D, Grossman, Jordon P, Mendicino, Robert W.
3. Armstrong DG, Lavery LA, Vela SA, et al. choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. *Arch Intern Med* 1998; 158:289-92.
4. LoGerfo FW. Vascular disease, matrix abnormalities, and neuropathy: implications for limb salvage in diabetes mellitus. *J Vase Surg* 1987; 5:793-6.
5. Payne CB. Biomechanics of the foot in diabetes mellitus: some theoretical considerations. *J Am Podiatr Med Assoc* 1998;88: 285-9.
6. Veves A, Sarnow MR, Giurini JM. et al, Differences in joint mobility and foot pressures between black and white diabetic patients. *Diabet Med* 1995; 12:585-9.
7. Stess RM, Jensen SR, Mirmiran R. The role of dynamic plantar pressures in diabetic foot ulcers. *Diabetes Care* 1997; 20:855-8.
8. Hill MN, Feldman H1. Hilton SC, et al. Risk of foot complications in long term diabetic patients with and without ESRD: a preliminary study. *ANNA J* 1996;23:381-6.
9. Helm PA, Walker SC, Pulliam GE. Recurrence of neuropathic ulceration following healing in a total contact cast. *Arch Phys Med Rehabil* 1991;72:967-70.
10. Moss SE, Klein R, Klein BEK. The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med* 1992; 152:610-6.
11. Mueller MJ, Sinacore DR. Total-contact casting in the treatment of neuropathic ulcers. In: Bowker JH, Pfeifer MA, eds. Levin and O'Neal's the Diabetic Foot. 6th ed. St Louis: Mosby; 2001:301-320.
12. Brodsky JW. Outpatient diagnosis and care of the diabetic foot. In: Heckman JD, ed. Instruction Course Lectures. Rosemont, Ill: American Academy of Orthopaedic Surgeons; 1993;42:121-139.
13. Brand PW. The diabetic foot. In: Ellenberg M, Rifkin H, eds. Diabetes mellitus, theory and practice. 3rd ed. New York; Medical Examination Publishing, 1983, 803-28.
14. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers: diabetic ulcer study group. *J Am Coll Surg* 1996; 183:61-4.
15. American Diabetes Association. Consensus development conference on diabetic foot wound care. *Diabetes Care* 1999; 22:1354-60.
16. Armstrong DG, Lavery LA, Nixon BP, et al. It's not what you put on, but what you take off: Techniques for debriding and offloading the diabetic foot wound. *Clin Inf Dis* 2004;39:S92-9.
17. Armstrong DG, Nguyen HC, Lavery LA, et al. Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 2001;24(6):1019-21.

Radiology Quiz

Chandramohan, R. Kannan, S. Moorthy

A 31 year old male patient was evaluated for recurrent pancreatitis. Figure shows MR cholangiopancreatography(MRCP) image of pancreatic and biliary ducts. What is the diagnosis?



Answer on Page 44

Living Donor Liver Transplantation in Acute Hepatic Failure – viable option in Indian context

S. Sharma, O.V. Sudheer, P. Dhar, S. Sudhindran

ABSTRACT

OBJECTIVE

Acute Hepatic Failure is a medical emergency with a high mortality rate. Worldwide experience has shown that timely liver transplantation can salvage a few of these patients. Cadaveric liver transplantations in India are too infrequent to be considered a viable option in these patients who usually require an emergency liver replacement once medical measures begin to fail. Living donor liver transplantation can be offered to the families of these desperately ill patients. A successful outcome can be expected in centers equipped with experienced surgeons and necessary infrastructure to carry out this major surgical undertaking.

INTRODUCTION

Acute hepatic failure (AHF) is defined as the rapid development of hepatocellular dysfunction – specifically coagulopathy and mental status changes within eight weeks of onset of jaundice in a patient without known preexisting liver disease¹. Advances in intensive medical care and development of artificial liver support systems have only resulted in modest improvements in outcomes with best survival rates of 15% - 30%². Liver transplantation (LT) has revolutionized the treatment of irreversible AHF with 80% short-term salvage and long-term survival rates ranging from 40%-75%³. Yet few actually undergo the procedure due to late referral, lack of suitable donor or the development of contraindications⁴.

We present the case of one fortunate patient with AHF who survived, due to timely referral and readiness of the husband to be a living donor. This report is perhaps the first emergency living related liver transplantation (LDLT) for AHF in South India.

CASE HISTORY

A 46-year-old lady reported to a hepatology centre with progressively increasing jaundice of 21 days. Her etiological workup for viral hepatitis, acetaminophen toxicity, and Wilson's disease was negative. She did confess to taking some ayurvedic preparations for arthralgia for the past 2 years. Despite aggressive supportive measures, the bilirubin levels and coagulation parameters worsened and she developed features of early encephalopathy. At this stage, she was referred to our centre, for liver transplantation.

On arrival, she appeared icteric and confused (Grade II encephalopathy). There were no stigmata of chronic liver disease and her abdominal examination was unremarkable. Her Serum Bilirubin was 34.1 mg% and prothrombin time was prolonged with an INR of 3.1. She was admitted in the ICU for monitoring, and started on antibiotics (Piperacillin and Tazobactam) and antifungal (Fluconazole) agents and was under consideration for possible transplantation. Within 12 hours of admission, she slipped into Grade IV encephalopathy. CT scan of the brain did not reveal intracranial bleed. At

this stage, the pretransplant workup was expedited with the aim of starting the transplant operation within 12 hours. A 64 slice Multidetector CT scan (MDCT) of the donor to assess his anatomic suitability for the proposed right hepatectomy. The total liver volume calculated by CT volumetry was 1114 cm³ while the volume of the right lobe including the Middle Hepatic Vein (MHV) was 675 cm³. No vascular anomalies were identified which would be an impediment to donation. At surgery, a transcystic cholangiogram (IOC) was performed to delineate the biliary anatomy. Though the initial plan was to obtain the right lobe of the donor liver along with the MHV, the parenchymal transection had to be done to the right of the MHV to ensure adequate venous drainage of residual liver segments (particularly segment IV), in the donor. The cold ischaemia time (time from liver retrieval in the cold slush, until rewarming by recipient blood flow including the time spent in graft preparation on the bench table) was 103 minutes and the secondary warm ischaemia time was 61 minutes. The combined operations were completed in 16 hours. The re-

King's College criteria for transplantation in acute liver failure:

Non – acetaminophen cause	Acetaminophen
INR > 6.7	Arterial pH < 7.3 after volume resuscitation
Or any three of	Or concurrent findings of
Unfavorable cause (eg. Drug induced, non A non B hepatitis, Halothane hepatitis)	Encephalopathy grade III/IV
Age < 10 or > 40 years	Creatinine > 300mmol/L
Acute/Subacute presentation	INR > 6.5
Bilirubin level > 300mmol/L	
INR > 3.5	

recipient received 8 units of packed cells and 9 units of plasma. The donor hepatectomy was accomplished without the need for red cell transfusion. The donor was extubated immediately postoperatively while the recipient was extubated the next day.

Initial immunosuppression was with injectable methyl prednisolone alone. Oral steroids, Tacrolimus and Mycophenolate Mofetil were started on the third postoperative day. Tacrolimus dose was adjusted to maintain serum trough levels between 5 and 15ng/ml. The convalescence was rather smooth and she was discharged on 24th postoperative day. At follow up in 3rd month, she is back to near normal life. The donor is back to his routine activities of daily living.

DISCUSSION

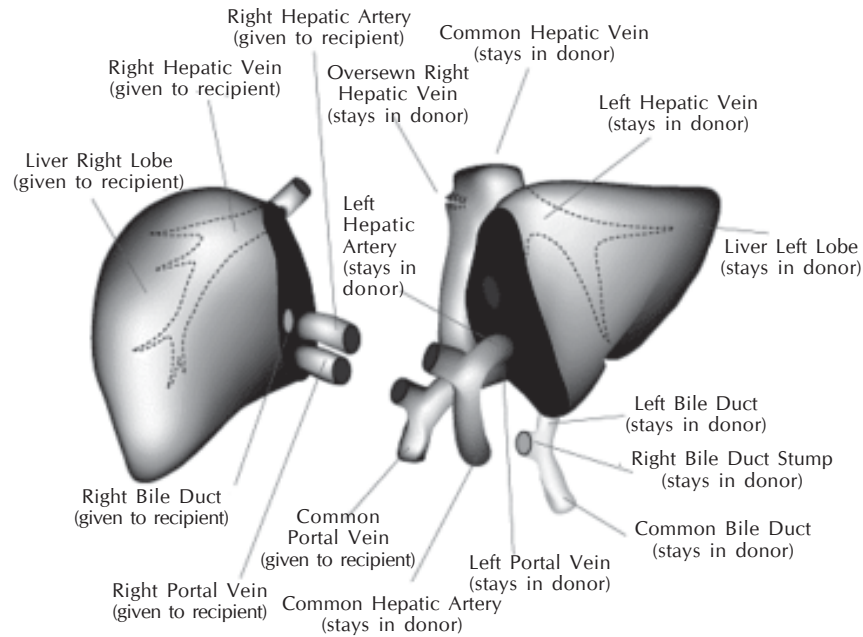
AHF is a clinical syndrome that results from sudden loss of hepatic parenchymal and metabolic functions and manifests as coagulopathy and encephalopathy. The causes differ in various parts of the world. In U.K and USA⁵ acetaminophen and idiosyncratic drug reactions are the most commonly identified etiologic agents while in Japan and India acute hepatitis B is the leading cause of AHF⁶. It is known that spontaneous survival rates from AHF due to acetaminophen toxicity and Hepatitis A are high⁴, while the rates for other viral hepatitis and idiosyncratic drug reactions are low.

AHF constitutes a medical emergency associated with a high mortality due to the development of cerebral edema, coagulopathy and bleeding complications. The role of LT in AHF has been established beyond doubt. The essential challenge is identifying the crucial timing for transplantation. This involves maintaining the fine balance between possible reversibility of the condition through hepatic regeneration versus development of complications, which may either contraindicate transplant or

render the condition irretrievable despite a transplant! A useful tool to assess whether a patient is likely to become irreversible is the Kings college criteria⁷, for early identification of indices with a poor prognosis.

Traditional cadaveric graft if available and in a good condition, is considered ideal because patients with AHF have a huge metabolic demand. However, even in countries with an established cadaveric organ-sharing program, a suitable donor may not be easily available in the emergency setting of AHF. Over the last few years, the use of living donor liver transplantation (LDLT) has been evaluated and the benefits in the setting of AHF are well-established⁸. The advantages are that graft function is usually excellent as cold ischaemia time can be kept to a minimum and the procedure can be completed on an emergency basis before the patient's condition deteriorates irreversibly. The potential disadvantage is possible inadequacy of available liver volume; hence the safer left liver grafts (Fig.1) have given way to the functionally larger right liver, albeit at the cost of significantly higher donor morbidity and mortality⁹.

Donor related complications can be kept to a minimum by careful preoperative estimation of the donor liver volume and a careful delineation of the vascular and biliary anatomy of the two lobes of the liver. The size of the graft required by the recipient is estimated by the graft to recipient weight ratio (GRWR), which is the weight of the graft divided by the weight of the recipient multiplied by 100 (ideal GRWR = 1), and balanced against the 40% of the original liver volume that has to be retained in the donor. CT volumetry is invaluable in this regard¹⁰. It is imperative while planning the parenchymal transection to ensure adequate vascular inflow and outflow and biliary drainage of all the segments in both the lobes of the liver to avoid functional parenchymal loss in either the donor or recipient. The information obtained



with the use of a MDCT and intraoperative cholangiogram greatly facilitate this planning.

The outcome after LDLT is inversely proportional to the degree of liver failure as evidenced by the grade of encephalopathy and degree and number of organ dysfunctions in the recipient. Early referral to a transplant center by the treating physician before irreversible neurologic damage or uncontrollable septic complications have occurred can significantly impact outcome. Soon after arrival our patient slipped into grade IV encephalopathy. Fortunately, we managed an emergency transplantation within hours of deterioration of her neurological status, which probably accounted for her prompt extubation postoperatively.

CONCLUSION

LT has the potential to be a life saving surgery for patients of AHF who deteriorate rapidly and would otherwise have dismal prognosis even with the best medical care. The most important determinant of the outcome of LT is timely referral before end organ damage has occurred. In our country, Gastroenterologists frequently deal with many patients with AHF secondary to viral infections or drug toxicity (due to use of traditional and alternative medicines for various ailments). Too few cadaveric organ donations take place in our country for salvaging these otherwise healthy patients. Lack of a viable donor network for elective supply of organs vitiates against possible reliability in an emergency setting. Living donor liver transplantation performed in experienced centers offers a viable solution to a condition with an otherwise dismal prognosis.

REFERENCES

1. Hoofnagle JH, Carithers RC, Shapiro C, et al. Fulminant Hepatic Failure; Summary of a workshop. *Hepatology* 1995;21:240.
2. Stockman HB, Ijzermans JN. Prospects for the temporary treatment of acute liver failure. *Eur J Gastroenterol Hepatol* 2002; 14:195-03.
3. Lu A, Monge H, Drazan K, et al. Liver transplantation for fulminant hepatitis at Stanford University. *J Gastroenterol* 2002;37:82-7.
4. Bernal W, Wendon J, Rela M. Use and outcome of liver transplantation in acute acetaminophen induced acute liver failure. *Hepatology* 1998;27:1050-55.
5. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary health care centers in USA. *Ann Intern Med* 2002;137:947.
6. Acharya SK, Panda SK, Saxena A, et al. Acute Hepatic Failure in India: A perspective from the East. *J Gastroenterol Hepatol* 2000;15:473.
7. O'Grady JG, Alexander GJ, Hayllan KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; 97:439-45.
8. Uemoto S, Inomata Y, Sukurai T. Living Donor liver transplantation for fulminant hepatic failure. *Transplantation* 2000;233:502-8.
9. Lui CI, Fam ST, Lo CM. Right lobe liver donor liver transplantation improves survival in patients with Acute Liver Failure. *Br J Surg* 2002;89:317-22.
10. Schani TD, Bodian C, Schwartz M. Accuracy and significance of CT scan assessment of hepatic volume in patients undergoing liver transplantation. *Transplantation* 2000;69:545-50.

Transfusion-related Acute Lung Injury: A Case Report and Review of Recent Advances

S. Sharma, A.Gauhar, D.K. VijayKumar, J. Paul*

ABSTRACT

Transfusion-related acute lung injury (TRALI) is an emerging as a common cause of transfusion related adverse events. However the awareness about this entity in medical fraternity is low and consequently it is an under diagnosed and very underreported complication of transfusion therapy. We report a case of 46-year old lady who developed acute hemodynamic and respiratory instability following a single unit blood transfusion in the postoperative period. She responded to symptomatic management with vasopressor and ventilator support. The diagnosis of TRALI relies on excluding other diagnoses such as sepsis, volume overload, and cardiogenic pulmonary edema. All plasma-containing blood products have been implicated in TRALI, with the majority of cases linked to whole blood, packed RBCs, platelets, and fresh-frozen plasma. The pathogenesis of TRALI may be explained by a "two-hit" hypothesis, involving priming of the inflammatory machinery and then activation of this primed mechanism. Treatment is supportive, with a prognosis substantially better than most causes of clinical acute lung injury.

KEY WORDS: Transfusion-related; acute lung injury, blood transfusion, acute respiratory distress syndrome; non-cardiogenic pulmonary edema.

KEY MESSAGES: The article is written with an intention to spread awareness among the medical fraternity to this often missed, misdiagnosed entity that is more frequent than we would like ourselves to believe.

INTRODUCTION

Transfusion related acute lung injury (TRALI) is a frequently misdiagnosed, yet potentially fatal reaction following transfusion of blood products. There is a lot of confusion in the literature regarding this entity because till recently there was no uniform nomenclature, definition or diagnostic features described in relation to it.

We describe a case report of TRALI, not because it is infrequent, unique or has never been described before, but to familiarize our colleagues with it. The intention of this article is to compile available information to self-educate ourselves to a potentially preventable life-threatening condition and the current guidelines for its management.

CASE HISTORY

A 46-year-old lady, who had undergone surgery for ovarian

malignancy, reported breathlessness on the first post-operative day. Her complaints had started within 20-25 minutes of completion of a transfusion of single unit of packed red blood cells (PRBC). She also had chest discomfort and rapidly progressed to become unstable haemodynamically with a falling oxygen saturation (<80%), hypotension with a systolic BP of <80 mm Hg, tachycardia (>140/min), tachypnoea (>30/min), and mild fever (100° F). Immediate investigations done are shown in Table1.

The patient required ventilatory support with a positive end expiratory pressure (PEEP) of 10 for 3 days along with a hemodynamic support with Dopamine, Dobutamine and Noradrenaline (these could be tapered and withdrawn within the next 48 hours).

The initial differential diagnosis was between a transfusion mismatch, myocardial infarction, pulmonary embolism or a fluid overload. Post transfusion recipient and bag blood

sample were sent immediately to the blood bank where a mismatch was ruled out. Also patient had no typical features of a cross match reaction like bronchospasm, rashes, hemoglobinuria, renal shutdown, or falling hemoglobin levels, etc. Fluid overload was ruled out in face of a normal CVP and normal ECHO. A normal ECG, normal ECHO and near normal cardiac enzymes ruled out the possibility of an acute myocardial ischemic event. Pulmonary embolism was eliminated from the differential diagnosis on the basis of bilateral extensive pulmonary infiltrates, normal D-dimer values and no clinical signs of deep vein thrombosis.

In this setting a possibility of TRALI was raised. Patient's clinical features, course of events, response of the acute episode to supportive management, all were supportive of this diagnosis.

The patient eventually recovered from this acute reaction over next 5 days and was discharged to home on the 10th postoperative day.

Dept. of Surgical Oncology, AIMS, Kochi.

* Dept. of Anaesthesia, AIMS, Kochi.

Table 1: Summary of Immediate investigations done at the time of acute symptoms.

S. No.	Investigation	Parameters	Value	Comments
1.	ABG	pH pCO ₂ pO ₂ SpO ₂ Hb Hct	7.447 23.8 30.7 62.2 10.4 32	Measured with O ₂ on flow at a rate of 10 L/min through nasal prongs
2.	Invasive hemodynamic monitoring	Arterial BP CVP	85/48 12	Invasive monitoring instituted in view of the deteriorating hemodynamic status
3.	ECG	Normal sinus tachycardia (HR – 144/min) with no evidence of ischemic changes		
4.	ECHO	Normal study with no evidence of RWMA, normal LA parameters, LVEF – 55%		
5.	Chest X-Ray	Bilateral extensive pulmonary infiltrates, no effusion		
6.	Troponin T		0.352	NR: 0 – 0.2 ng/mL
7.	CK - MB		47	NR: 0 – 23 IU/mL

DISCUSSION

Barnard¹ in 1951 described the first case of fatal pulmonary edema accompanying transfusion therapy. The confusion surrounding TRALI is due to the numerous eponyms that have been used in the past to refer to this clinical entity. The syndrome had previously been referred to as *pulmonary hypersensitivity reaction*^{2,3}, *allergic pulmonary edema*⁴, *non-cardiogenic pulmonary edema*⁵⁻⁷ and *pulmonary leukoagglutinin reaction*⁸.

The term was first coined by Popovsky et al⁹ in 1983 to refer to non-cardiogenic pulmonary edema complicating transfusion therapy in 1985 in a case series report of 36 cases from Mayo clinic, which occurred from 1982 to 1985.

Thus it is still under-recognized and under-reported for a multitude of reasons, which vary from a lack of precise definition to misdiagnosis to lack of awareness.

EPIDEMIOLOGY

TRALI has emerged as one of the most common serious complications of blood transfusion¹⁰⁻¹³. With the reduction of clerical errors and with more effective screening and prevention of the transmission of infectious agents, TRALI has surpassed hemolytic reactions as the leading cause of transfusion-related mortality in developed countries¹¹⁻¹⁴. Published incidence of TRALI ranged from 0.02% to 0.05% per blood product unit transfused and from 0.08% to 0.16% per patient who received a transfusion¹⁵⁻¹⁹. The true incidence of TRALI is not known because there is significant underreporting of cases^{20,21}.

DEFINITION & CLINICAL PRESENTATION

TRALI is defined as non-cardiogenic pulmonary edema temporally related to the transfusion of blood products^{22,23}.

Almost any blood component containing about 50 ml or more of plasma is implicated, use of red blood cells (RBCs), and pooled platelets from several donors seems to have a particularly high risk^{10,12,19,24,25}. Rarely, cryoprecipitate, intravenous immunoglobulin, and stem cell preparations have been implicated and it does not seem to occur with washed RBC^{18,26,27}. Interestingly the incidence is least with Fresh Frozen Plasma (FFP), and maximum with platelet concentrates.

Symptoms of TRALI appear usually within 2 to 6 hours from initiation of transfusion, but cases of presumed TRALI have been described up to 48 hours after transfusion^{28,29}. Clinically the patient presents with features of acute onset respiratory and hemodynamic complications in the absence of features of circulatory overload like dyspnea, tachypnea, frothy sputum, fever, hypotension, or, much more rarely, hypertension^{30,31}. Laboratory findings for TRALI are inconsistent and include acute transient neutropenia³², presence of matching leukocyte antigen-antibody in the donor and recipient³³, and increased neutrophil-priming activity in transfused blood¹⁹. In patients with an endotracheal tube in place, high protein concentration found in edema fluid sampled within the first hour of intubation may help differentiate TRALI from fluid overload and cardiogenic pulmonary edema²³.

Table 2: Proposed scheme of investigations for an adverse event following a transfusion (Adapted from reference no 43)

S. No.	Investigation	Comment
1.	ABO typing	To confirm type
2.	Direct anti-globulin test	To exclude cross match incompatibility
3.	Complete blood counts	Transient neutropenia is seen with TRALI.
4.	Peripheral blood film	Hemolytic cells may be seen in cross match reaction
5.	Chest X-ray	Needed to exclude pulmonary edema, pneumonia, other reasons for hypoxia
6.	Blood cultures	Bacterial contamination is a differential diagnosis
7.	Anti-body panel	Includes anti HLA-1 & HLA-2, anti granulocyte, anti monocyte, anti IgA
8.	D-dimer / FDP	To evaluate for Deep vein thrombosis
9.	ECHO	For cardiac function status and fluid overload
10.	ECG /Cardiac enzymes	For cardiac function status (to exclude Myocardial infarction)
11.	Undiluted pulmonary edema fluid	From endotracheal tube if present – can be diagnostic if fluid to serum protein ratio is >0.75

ETIOLOGY & PATHOGENESIS

The exact etiology of TRALI is unknown, but 2 distinct mechanisms have been suggested. The traditional theory proposes an antibody-mediated reaction between recipient granulocytes and antigranulocyte antibodies from donors who were sensitized during pregnancy (multiparous women) or by previous transfusion^{9,12,34,35}.

Recently, an alternative mechanism has been suggested, implicating pro-inflammatory molecules, predominantly lipid products of cell degradation, known to accumulate during storage of cellular blood products^{19,36,37}.

Both models are based on a two-hit hypothesis wherein a first hit is required as an initial priming event followed by a second initiator event. Of note, the 2 hypotheses of TRALI pathogenesis are not mutually exclusive and even may act synergistically with underlying patient factors to produce acute lung injury.

The first insult (first hit) is priming and adherence of neutrophils to the pulmonary endothelium. Candidate conditions for producing the first insult in TRALI include surgery, sepsis, trauma, massive transfusions, hematologic malignancies, cardiac surgeries, induction chemotherapy and cardiopulmonary bypass²³.

The second insult (second hit) activates these primed neutrophils, resulting in the release of reactive oxygen species that cause capillary leak and pulmonary edema³⁸. For the second hit, parity of the blood donor, relationship to the blood donor, and the age of the blood products can all be potential risk factors²³.

Although the antibody theory remains more widely accepted and published, in some cases there is definite

evidence of biologically active lipids in the etiology of TRALI.

DIAGNOSIS

The first step in management of TRALI is to make a correct diagnosis. It requires a high index of clinical suspicion and awareness about this condition in event of any adverse event temporally related to blood transfusion to diagnose and treat this condition effectively. Figure 1 outlines the algorithm for diagnosis of a suspected case of TRALI. Too often, hypoxia that develops after transfusion therapy is ascribed to volume overload, and diuretics are empirically administered. Mild-to-moderate cases of TRALI may be misdiagnosed as volume overload, and the chance to make a diagnosis of TRALI, and possibly prevent future cases, is lost.

The differential diagnosis of TRALI includes, but is not limited to, transfusion related circulatory overload, anaphylactoid reaction to transfusate, bacterial contamination of transfusate, and hemolytic transfusion reaction³⁹.

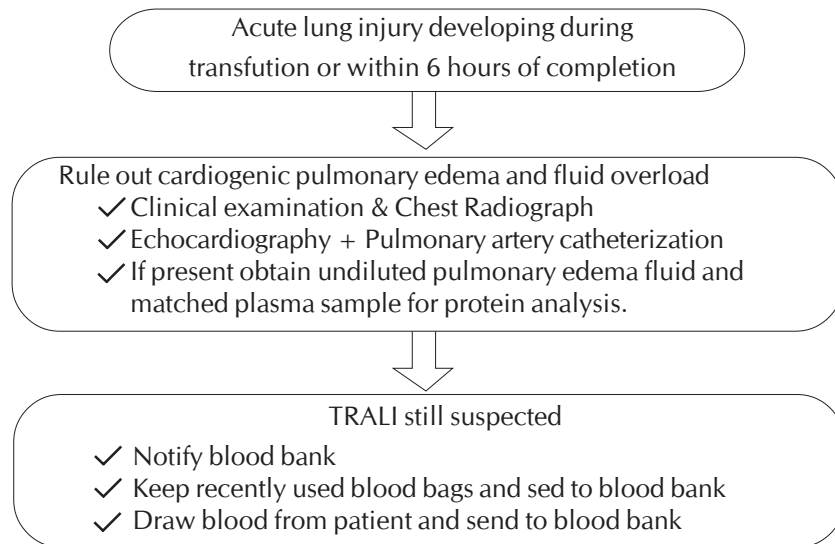
There are no specific investigations since there is no specific abnormality associated with TRALI. However investigations are required to rule out other possibilities of a transfusion related reaction. Thus in regular clinical practice, TRALI is a diagnosis by exclusion because it has no specific symptoms, signs or investigations.

The only routine laboratory parameter that has been associated, albeit infrequently, with TRALI is leucopenia³⁹.

Edema fluid/plasma protein ratio measured by taking matched samples of edema fluid from an endotracheal tube and plasma sample for protein measurements can

Box 1: Criteria for diagnosis of TRALI as per the current consensus (22).

Criteria for ALI (AECC guidelines 1994)	
1.	Timing: Acute onset
2.	Pulmonary artery occlusion pressure \geq 18 mm Hg when measured or lack of clinical evidence of left atrial hypertension.
3.	Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph
4.	Hypoxemia: Ratio of $\text{PaO}_2/\text{FiO}_2 \leq$ 300 mm Hg regardless of the positive end-expiratory pressure level, or oxygen saturation of \leq 90% on room air.
In addition for TRALI	
1.	Onset within 6 hours of transfusion of blood products
2.	No pre-existing ALI prior to transfusion
3.	TRALI still possible if another ALI risk is present
4.	Massive transfusion should not exclude the possibility of TRALI

Fig. 1: Flow chart to evaluate a case of Acute Lung Injury within 6 hours of transfusion

be diagnostic of increased permeability pulmonary edema. In hydrostatic pulmonary edema it is < 0.65 and > 0.75 with increased permeability pulmonary edema⁴⁰. This method is valid only for undiluted pulmonary edema fluid, not BAL.

A scheme of proposed investigations in a case of any adverse clinical event temporally associated with blood or blood product transfusion is given in Table 2

TREATMENT & PROGNOSIS

In majority, TRALI is a self-limiting condition that is believed to have a better short-term prognosis than other causes of acute lung injury²³. Most patients recover with supportive care although about less than 70% patients will require mechanical ventilation with a hospital mortality of 5-15%³⁹.

Management of TRALI is supportive, as it is for any patient with permeability pulmonary edema, and often includes ventilatory support. Patients with TRALI are often normotensive to hypotensive with normal or low filling pressures²³. Diuretics may be contraindicated, and IV fluids should be administered as necessary, titrating with the arterial BP to a mean pressure of 60 mm Hg with appropriate urine output^{39,41}. Invasive hemodynamic monitoring may be necessary in especially severe cases to guide fluid management^{23,39}. For mild TRALI cases, supplemental oxygen and supportive care may be sufficient for treatment. For the more severe case, IV fluids and mechanical ventilation are necessary. Lung protective (low tidal volume with low plateau pressures) ventilatory strategies should be employed when ventilating TRALI patients^{39,41}. There are reports, but no prospective randomized trials, of use of glucocorticoids in the management of TRALI and as of now their role in this setting remains unsettled⁴².

Recurrent TRALI cases have been described⁴², so the indications for future transfusions in a TRALI patient should be scrutinized and the patient monitored carefully if a transfusion is needed at all.

REFERENCES

- Barnard RD. Indiscriminate transfusion: a critique of case reports illustrating hypersensitivity reactions. *N Y State J Med* 1951;51:2399–2402.
- Thompson JS, Severson CD, Parmely MJ, et al. Pulmonary 'hypersensitivity' reactions induced by the transfusion of non-HLA leukoagglutinins. *N Engl J Med* 1971;20:1120–5.
- Wolf CFW, Canale VC. Fatal pulmonary hypersensitivity reaction to HL-A incompatible blood transfusion: report of a case and review of the literature. *Transfusion* 1976; 16:135–40.
- Kernoff PBA, Durrant IJ, Rizza CR, et al. Severe allergic pulmonary oedema after plasma transfusion. *Br J Haematol* 1972;23:777–81.
- Carilli AD, Ramanamurty MV, Chang YS, et al. Noncardiogenic pulmonary edema following blood transfusion. *Chest* 1978;74:310–2.
- Culliford AT, Thomas S, Spencer FC. Fulminating noncardiogenic pulmonary edema: a newly recognized hazard during cardiac operations. *J Thorac Cardiovasc Surg* 1980;80:868–75.
- Hashim SW, Kay HR, Hammond GL, et al. Noncardiogenic pulmonary edema after cardiopulmonary bypass: an anaphylactic reaction to fresh frozen plasma. *Am J Surg* 1984;147:560–4.
- Ward HN. Pulmonary infiltrates associated with leukoagglutinin transfusion reactions. *Ann Intern Med* 1970;73:689–94.
- Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. *Am Rev Respir Dis* 1983;128:185–9.
- Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985;25:573–7.
- Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. *Transfusion* 1990;30:583–90.
- Kopko PM, Marshall CS, MacKenzie MR, et al. Transfusion related acute lung injury: report of a clinical look-back investigation. *JAMA* 2002;287:1968–71.
- Popovsky MA. Breathlessness and blood: a combustible combination. *Vox Sang* 2002;83(suppl 1):147–50.
- Askari S, Nollet K, Debol SM, et al. Transfusion-related acute lung injury during plasma exchange: suspecting the unsuspected. *J Clin Apheresis* 2002;17:93–6.
- Popovsky MA. Transfusion and lung injury. *Transfus Clin Biol* 2001;8:272–7.
- Mariani SM. Conference report—transfusions and TRALI: what are the risks today? Highlights from the 71st Annual Meeting of the American Society for Clinical Laboratory Science, July 22–26, 2003. Philadelphia, PA: Medscape Gen Med 2003; 5:6.
- Silliman CC. Transfusion-related acute lung injury. *Transfus Med Rev* 1999;13:177-86.
- Webert KE, Blajchman MA. Transfusion-related acute lung injury. *Transfus Med Rev* 2003;17:252–62.
- Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 2003;101:454–62.
- Wallis JP. Transfusion-related acute lung injury (TRALI): underdiagnosed and under-reported. *Br J Haematol* 2003; 90:573–75.
- Lee JH. Transfusion-related fatalities: reports to US FDA, 1990–1998. *ABC Newsletter*, 1999.
- Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. *Crit Care Med* 2005;33(4):721–6.
- Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury – a review. *Chest* 2004;126(1):249-58.
- Ennel-friet CP, Reesink HW, Brand A, et al. Transfusion-related acute lung injury (TRALI). *Vox Sang* 2001;81:269-83.
- Gajic O, Rana R, Mendez JL, et al. Acute lung injury after blood transfusion in mechanically ventilated patients. *Transfusion* 2004;44:1468-74.
- Reese EP Jr, McCullough JJ, Craddock PR. An adverse pulmonary reaction to cryoprecipitate in a hemophiliac. *Transfusion* 1975;15:583-8.
- Suassuna JH, da Costa MA, Faria RA, et al. Noncardiogenic pulmonary edema triggered by intravenous immunoglobulin in cancer-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome [letter]. *Nephron* 1997;77:368-70.
- Kopko PM, Holland PV. Transfusion-related acute lung injury. *Br J Haematol* 1999;105:322-9.

29. Levy GJ, Shahot MM, Hart ME, et al. Transfusion associated noncardiogenic pulmonary edema: report of a case and a warning regarding treatment. *Transfusion* 1986;26:278-81.
 30. Toy P, Gajic O. Transfusion-related acute lung injury. *Anesth Analg* 2004;99:1623-4.
 31. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149(3, pt1):818-24.
 32. Yomtovian R, Kline W, Press C, et al. Severe pulmonary hypersensitivity associated with passive transfusion of a neutrophil-specific antibody. *Lancet* 1984;1:244-6.
 33. Kopko PM, Paglieroni TG, Popovsky MA, et al. TRALI: correlation of antigen-antibody and monocyte activation in donor-recipient pairs. *Transfusion* 2003;43:177-184.
 34. Palfi M, Berg S, Ernerudh J, et al. A randomized controlled trial of transfusion-related acute lung injury: is plasma from multiparous blood donors dangerous? *Transfusion* 2001;41:317-22.
 35. Seeger W, Schneider U, Kreisler B, et al. Reproduction of transfusion related acute lung injury in an ex viva lung model. *Blood* 1990;76:1438-44.
 36. Wallis JP, Luhenko A, Wells AW, et al. Plasma and lipids from stored packed red blood cells cause acute lung injury in an animal model. *J Clin Invest* 1998;101:1458-67.
 37. Geelhoed GW, Bennett SH. "Shock lung" resulting from perfusion of canine lungs with stored hank blood. *Am Surg* 1975;41:661-82.
 38. Wyman TH, Bjornsen AJ, Elzi DJ, et al. A two-insult in vitro model of PMN-mediated pulmonary endothelial damage: requirements for adherence and chemokine release. *Am J Physiol Cell Physiol* 2002; 283:C1592-C1603.
 39. Boshkov LK. Transfusion-Related Acute Lung Injury and the ICU. *Crit Care Clin* 21 (2005) 479- 95.
 40. Matthay MA. Pathophysiology of pulmonary edema. *Clin Chest Med* 1985;6:301-14.
 41. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.
 42. Boshkov N, Montgomery J, Sage D, et al. Recurrent transfusion related acute lung injury. *Transfusion* 2001;41:1421-5.
 43. Shander A, Popovsky MA. Understanding the Consequences of Transfusion-Related Acute Lung Injury. *Chest* 2005;128:598S-604S.
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Cases, Evidence and Verdicts

T. Roy, T. Rony, A.N. Babu

The sixth installment of this series reviews three recent articles related to **neuroprotection** in cerebrovascular disease considering either primary or secondary prevention agents.

Y. Lampl MD, M. Boaz, PhD, R. Gilad MD, M. Lorberboym MD, R. Dabby, MD, A. Rapoport MD, M. Anca-Hershkowitz MD, M. Sadeh, MD: Minocycline treatment in acute stroke An open-label, evaluator-blinded study. *Neurology* 2007; 69:1404–1410

BACKGROUND

Ischemic animal model studies have shown a neuroprotective effect of minocycline.

OBJECTIVE

To analyze the effect of minocycline treatment in human acute ischemic stroke.

METHODS

An open-label, evaluator-blinded study was performed. Minocycline at a dosage of 200 mg was administered orally for 5 days. The therapeutic window of time was 6 to 24 hours after onset of stroke. Data from NIH Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Barthel Index (BI) were evaluated. The primary objective was to compare changes from baseline to day 90 in NIHSS in the minocycline group vs. placebo.

RESULTS

One hundred fifty-two patients were included in the study. Seventy-

four patients received minocycline treatment, and 77 received placebo. NIHSS and mRS were significantly lower and BI scores were significantly higher in minocycline-treated patients. This pattern was already apparent on day 7 and day 30 of follow-up. Deaths, myocardial infarctions, recurrent strokes, and hemorrhagic transformations during follow-up did not differ by treatment group.

CONCLUSIONS

Patients with acute stroke had significantly better outcome with minocycline treatment compared with placebo. The findings suggest a potential benefit of minocycline in acute ischemic stroke.

Somchai Laowattana, MD, PhD; and Stephen M. Oppenheimer, MD, PhD

Protective effects of beta-blockers in cerebrovascular disease. *Neurology* 2007;68:509–514

OBJECTIVE

Because activated sympathetic tone is associated with poorer outcome after stroke, we investigated whether beta-blocker treatment was associated with lesser stroke severity and improved outcome.

METHOD

This study prospectively evaluated 111 patients with stroke. Stroke severity on presentation gauged by Canadian Neurologic Scale (CanNS) and medication use verified from medical records. Power spectral analysis of heart rate variability esti-

mated cardiac sympathovagal tone. Coagulation and inflammatory activity were assessed.

RESULTS

On multiple linear regression, betablocker use was the sole independent predictor of less severe stroke on presentation (95% CI: 0.12 to 1.86; $p = 0.03$). When CanNS was dichotomized, multiple logistic regression revealed that beta-blocker use (odds ratio [OR] 3.70, 95% CI: 1.24 to 11.01, $p = 0.02$) and female gender (OR 2.96, 95% CI: 1.14 to 7.69, $p = 0.03$) were independent predictors of CanNS score > 8.5 . There was no difference in blood pressure and blood glucose between these two groups. Beta-blocker treatment was associated with lower sympathovagal tone ($p = 0.001$), thrombin ($p = 0.009$), hemoglobin A1C levels ($p = 0.02$), and erythrocyte sedimentation rate ($p = 0.003$).

CONCLUSION

Beta-blocker use is associated with less severe stroke on presentation and may be cerebroprotective due to a sympatholytic effect associated with decreased thrombin, inflammation, and hemoglobin A1C.

Xiaobin Wang, Xianhui Qin, Hakan Demirtas, Jianping Li, Guangyun Mao, Yong Huo, Ningling Sun, Lisheng Liu, Xiping Xu

Efficacy of folic acid supplementation in stroke prevention: a meta-analysis.

Lancet Vol 369 June 2, 2007

BACKGROUND

The efficacy of treatments that lower homocysteine concentrations in reducing the risk of cardiovascular disease remains controversial. A meta-analysis of relevant randomized trials to assess the efficacy of folic acid supplementation in the prevention of stroke was performed.

METHODS

Data was collected from eight randomized trials of folic acid that had stroke reported as one of the endpoints. Relative risk (RR) was used as a measure of the effect of folic acid supplementation on the risk of stroke with a random effect model. The analysis was further stratified by factors that could affect the treatment effects.

FINDINGS

Folic acid supplementation significantly reduced the risk of stroke by 18% (RR 0.82, 95% CI 0.68–1.00; $p=0.045$). In the stratified analyses, a greater beneficial effect was seen in those trials with a treatment duration of more than 36 months (0.71, 0.57–0.87; $p=0.001$), a decrease in the concentration of homocysteine of more than 20% (0.77, 0.63–0.94; $p=0.012$), no fortification or partly fortified grain (0.75, 0.62–0.91; $p=0.003$), and no history of stroke (0.75, 0.62–0.90; $p=0.002$). In the corresponding comparison groups, the estimated RRs were attenuated and insignificant.

INTERPRETATION

The findings indicate that folic acid supplementation can effectively reduce the risk of stroke in primary prevention.

COMMENTARY

The first article by Lampl et al suggests that administration of minocycline at the acute stage of stroke is associated with better clinical outcome as measured by three standard scales for neurological disability. Minocycline, a semisynthetic second generation derivative of tetracycline, was shown to have a clear beneficial neuroprotective effect in animal models of a variety of conditions. The proposed mechanisms of minocycline include its anti-inflammatory effect, reduction of microglial activation¹ matrix metalloproteinase reduction² nitric oxide production³, and inhibition of apoptotic cell death⁴.

There are, however, a number of limitations to the study. The trial was neither double-blinded nor controlled and the total number of patients was quite small. It also remains to be defined whether differing routes of administration of the drug, changes in dosing or treatment window might have led to changes in the result. Nevertheless, the study shows that minocycline has promise and warrants further study.

The second article by Somchai Laowattana et al concluded that Beta-blocker use was associated with less severe stroke on presentation and may be cerebroprotective due to a sympatholytic effect associated with decreased thrombin, inflammation, and hemoglobin A1C. Acute stroke has been associated with sympathetic activation⁵ and higher norepinephrine levels have been correlated with more severe functional impairment. In this study, beta-blocker treatment correlated with lower cardiac sympathovagal tone, indicating that a potential mechanism may be the antisymphathetic effect of these medications. The protective effect may also be related to anti-inflammatory mechanism as suggested by the lower ESR values in these patients. Stroke patients on beta-blockers also had lower thrombin levels and hemoglobin A1C levels. It is interesting that this study suggests a decrease in severity of stroke for patients on beta-blockers, while other reports have raised concerns of a greater incidence of stroke in patients taking beta-blockers for hypertension control compared to other medications. If one assumes that both of these findings are legitimate, then the clinician is left with a dilemma – weighing both, it may best to go with the option that decreases incidence as opposed to reducing severity.

Finally, the meta-analysis by Wang et al suggests that folic acid supplementation may reduce the risk of stroke through primary prevention in certain subsets and clinical circumstances. It showed that a decrease of less than 20% in the concentration of homocysteine did not significantly affect the relative risk of stroke, whereas a significant reduction in the risk of stroke occurred with a decrease in homocysteine concentration of 20% or more.

Wang concluded that folic acid supplementation significantly reduces the risk of stroke by 18% (95% CI 68–100, $p=0.045$), and that the benefit was greater in those trials with a longer treatment duration (> 36 months), larger homocysteine-lowering effects (> 20%), no or partial grain fortification, and no history of stroke. However, it should be noted that the non-stratified analysis only attained marginal statistical significance, and this meta-analysis has inherent limitations due to its inability to adjust for individual variables (such as differences in supplement composition between studies)⁶. These findings should be viewed in light of the current controversy about the role of homocysteine reduction for cardiovascular disease – a number of trials such as the HOPE – 2 study failed to find any benefit on cardiovascular endpoints through folate supplementation. Interestingly, this same study did show a decrease in stroke by roughly 25%⁷.

In conclusion, stroke remains a potentially devastating clinical event for which preventive therapies remain suboptimal. The reviewed studies provide some promising approaches to consider in pharmacological neuroprotection. Further studies are needed for more definitive insights.

REFERENCES

1. Stirling DP, Khodarahmi K, Liu J, et al. Minocycline treatment reduces delayed oligodendrocyte death, attenuates axonal die-back, and improves functional outcome after spinal cord injury. *J Neurosci* 2004;24:2182–90.
2. Ryan ME, Usman A, Ramaurthy NS, et al. Excessive matrix metalloproteinase activity in diabetes: inhibition by tetracycline analogues with zinc reactivity. *Curr Med Chem* 2001;8:305–16.
3. Amin AR, Attur MG, Thakker GD, et al. A novel mechanism of action of tetracyclines: effects on nitric oxide synthesis. *Proc Natl Acad Sci USA* 1996;93:14014–9.
4. Lee SM, Yune TY, Kim SJ, et al. Minocycline reduces cell death and improves functional recovery after traumatic spinal cord injury in the rat. *J Neurotrauma* 2003;20:1017–27.
5. Hachinski VC, Smith KE, Silver MD, et al. Acute myocardial and plasma catecholamine changes in experimental stroke. *Stroke* 1986;17:387–90.
6. Mark SD, Wang W, Fraumeni JF Jr, et al. Lowered risks of hypertension and cerebrovascular disease after vitamin/mineral supplementation: the Linxian Nutrition Intervention Trial. *Am J Epidemiol* 1996;143:658–64.
7. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567–77.

Radiology Quiz (Answer)

DIAGNOSIS: Pancreas divisum

DISCUSSION:

MR cholangiopancreatography(MRCP) image shows the main pancreatic duct(PD) crossing the common bile duct(CBD) and entering into minor papilla proximal to CBD insertion suggestive of Pancreas divisum. Minor duct joins with the CBD.

Embryologically pancreas develops from two components namely the dorsal and ventral pancreas. When the rotation of bowel occurs, the main pancreatic duct in the dorsal pancreas combines with the ventral component to form the main duct of Wirsung, which enters through the main papilla and ampulla of Vater. In most instances, the minor duct of Santorini becomes atretic or if patent, it enters into minor papilla.

Pancreas divisum, the most common congenital variant of the pancreatic anatomy, the ventral and dorsal pancreatic ducts fail to fuse in utero, resulting in drainage of the bulk of pancreatic fluid (80-95%) via the duct of Santorini through the relatively small minor papilla and predispose for pancreatitis.

ERCP is the standard of reference for imaging the pancreaticobiliary system because of its high image resolution and the advantage of allowing therapeutic intervention¹. ERCP, however, is expensive and invasive, with a reported complication rate of 5%.

CT scan findings of pancreatic divisum include: the increase in the craniocaudal length of pancreas and the occasional presence of a fat cleft separating the dorsal and ventral elements².

MR cholangiopancreatography(MRCP) has been described as providing direct cholangiography and pancreatography noninvasively and without use of contrast medium³. With use of a heavily T2-weighted pulse sequence, solid organs and moving fluids have low signal intensity, and stationary fluids such as bile and pancreatic juice have high signal intensity. Nonfusion of ventral and dorsal pancreatic ducts in pancreas divisum can be recognized more readily after secretin-stimulated MRCP. Exogenous administration of secretin stimulates the secretion of fluids and bicarbonates by the exocrine pancreas, with a consequent increase in the volume of fluid inside the pancreatic ducts. This increase in fluid content is used to improve the visualization of pancreatic ductal anatomy on MRCP.

Various endoscopic approaches used for the treatment of pancreas divisum with acute recurrent pancreatitis include endoscopic sphincterotomy of the minor ampulla, with or without sphincterotomy of the major ampulla; ductal balloon dilatation; and pancreatic duct stent placement.

REFERENCES

1. Frank HM, Ana L. K., Anubha W., et al. MRI of Pancreatitis and Its Complications: Part 2, Chronic Pancreatitis. *AJR* 2004; 183:1645-52.
2. Soulen MC et al: Pancreatic divisum: CT scanning and ERCP correlation. *Radiology* 1986;161;145.
3. Patrice MB, Caroline R, Patrice T, et al. Pancreas Divisum: Evaluation with MR Cholangiopancreatography. *Radiology* 1996; 199:99-103.
4. Manfredi R, Costamagna G, Brizi MG, et al. Severe chronic pancreatitis versus suspected pancreatic disease: dynamic MR cholangiopancreatography after secretin stimulation. *Radiology* 2000; 214(3):849-55.