Applied Nutrition
PGND- 2nd semester

World Health Organization

International Food Safety Authorities Network (INFOSAN)

9 June 2006
INFOSAN Information Note No. 3/2006 – Food Allergies

Food Allergies

SUMMARY NOTE

- A food allergy is an adverse reaction to food involving an immunological mechanism.
- The clinical symptoms of food allergies range from mild discomfort to severe or life-threatening reactions, which require immediate medical intervention.
- The prevalence of food allergies has been estimated to be around 1-3% in adults and 4-6% in children.
- More than 70 foods have been reported as causing food allergies.
- The only way for allergic individuals to manage food allergies is to avoid eating the food that causes the allergy.
- The foods, which cause the most severe reactions and most cases of food allergies are: cereals containing gluten, crustacean, eggs, fish, peanuts, soybeans, milk, and tree nuts.
- The Codex Alimentarius Commission Committee on Food Labelling recommends always declaring these foods and ingredients derived from them.
- Awareness about food allergies among public food and health officials, and those supplying and preparing food is the first step in protecting individuals with food allergies.
- This note contains links to examples of guidelines with advice to the food industry and caterers on managing food allergen risks.

Why are food allergies important health issues?

Individuals with food allergies develop symptoms by eating foods that for the vast majority of the population are part of a healthy diet. Even small amounts of the offending food can cause serious and even fatal reactions in susceptible individuals. Fortunately in most instances the outcome is not death but various symptoms affecting the skin, gastrointestinal tract, respiratory tract, eyes, and/or central nervous system. The only way for the allergic individual to manage food allergy is to avoid eating the food that causes the allergic reaction. In practice avoiding the offending food can be difficult. Food allergies influence the life quality and economy of the food-allergic individual and the economy of the food industry. Consequently, food allergies are a concern for both the food allergic individual and all those involved in supplying and preparing food including family and friends, caterers, restaurants and the food industry.

Food allergy remains the principle safety concern for foods derived from recombinant-DNA. These genetically modified foods contain newly expressed proteins that may present a risk for the food-allergic individual. The Codex Alimentarius Commission's Principles and guidelines on food derived from biotechnology[1] recommends a procedure to assess newly expressed proteins for potential allergenicity. The procedure is designed to screen out newly expressed proteins that are likely to cause allergy. This INFOSAN note on food allergies will provide some basic information about food allergies as well as links to more information.

What are food allergies?

In 2003 the World Allergy Organization proposed a revised nomenclature for allergic and allergic-like reactions[2]. According to this proposal (figure 1), adverse non-toxic reactions to food should be termed food hypersensitivity. When an immunologic mechanism has been demonstrated the appropriate term is food allergy. Food allergy can further be characterized by whether the immunological mechanism involves IgE antibodies or not. Other reactions to food, previously referred to as "food intolerance", should be called non-allergic food hypersensitivity.

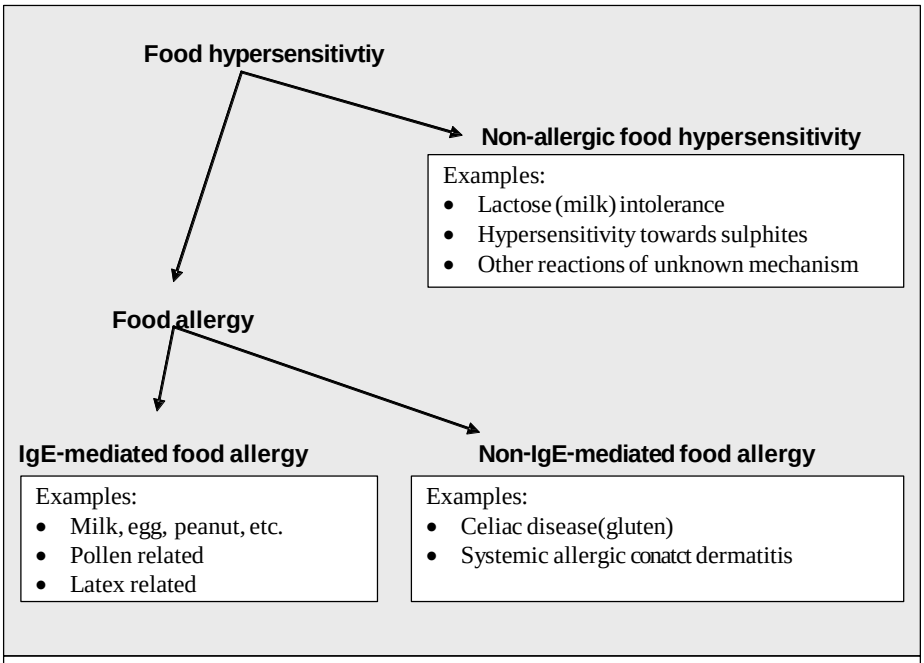

Figure 1. Terms used for adverse reactions to food and some examples.

What are the symptoms of food allergies?

The symptoms of food allergies range from mild discomfort to severe, life-threatening reactions, which require immediate medical intervention. Symptoms may be triggered in the skin (e.g. itching, redness, swelling), gastrointestinal tract (e.g. pain, nausea, vomiting, diarrhoea, itching and swelling of oral cavity), respiratory tract (e.g. itching and swelling of the nose and throat, asthma), eyes (e.g. itching and swelling), and/or cardiovascular system (e.g. chest pain, abnormal heart rhythm, very low blood pressure causing fainting, and even loss of consciousness).

Allergic reactions to foods generally occur within a few minutes to one hour after eating the offending food. Symptoms can last for days or even weeks. The specific symptoms and severity of an allergic reaction are affected by the amount of the allergen consumed and by the sensitivity of the allergic person.

How many individuals are affected by food allergy?

The prevalence of food allergies in the general population has been roughly estimated to be around 1-3% in adults and 4-6% in children[3]. It is however difficult to estimate the prevalence of food allergies because different studies use different methodologies and the occurrence of food allergies changes with age. Egg and milk allergies are the most common food allergies among infants but are often outgrown. Shellfish allergy is more common among adults than children, while peanut allergy is equally common among children and adults.

Which foods can cause allergies?

More than 70 foods have been described as causing food allergies[8]. Several studies indicate that 75% of allergic reactions among children are due to a limited number of foods, namely egg, peanut, milk, fish and nuts[3]. Fruits, vegetables, nuts and peanuts are responsible for most allergic reactions among adults. Individuals with pollen or latex allergy often experience allergic symptoms when they eat certain fruits, vegetables or nuts[4]. This "cross-reactivity" occurs because the body cannot distinguish between the allergens in pollen or latex and related proteins in food and reacts to both. In Europe and the US peanut and nuts are the foods most commonly reported to cause life-threatening reactions.

The Codex Alimentarius Commission Committee on Food Labelling has listed the foods and ingredients that cause the most severe reactions and most cases of food hypersensitivity. In section 4.2.1.4 of General Standards for the Labelling of Prepackaged Foods[6] it states: "The following foods and ingredients are known to cause hypersensitivity and shall always be declared:

- Cereals containing gluten; i.e., wheat, rye, barley, oats, spelt or their hybridized strains and products of these;
- Crustacea and products of these;
- Eggs and egg products;
- Fish and fish products;
- Peanuts, soybeans and products of these;
- Milk and milk products (lactose included);
- Tree nuts and nut products; and
- Sulphite in concentrations of 10 mg/kg or more."

While the Codex list contains the major allergens on a world-wide basis, the prevalence of food allergies varies in different geographical areas. Some countries have chosen to include additional foods on their national list of foods and ingredients that must be declared on food labels. The EU for example has chosen to add celery, mustard and sesame seeds and products thereof to the list of allergens, which must appear on food labels.

Processing and preparing food as well as the food matrix may increase or decrease allergenicity. However, currently, the data are insufficient to give general advice on how to process and prepare food and what food matrix should be used to make a food safe for an allergic person.

From food challenge studies some information is available regarding the amounts of an allergen that may trigger an adverse effect in an individual. Generally doses range from hundred microgram to grams of protein[3, 7]. However, for ethical reasons people who have experienced life- threatening reactions to foods are often not tested. These people may include some of the most sensitive individuals. Case reports have described food-induced life-threatening reactions following kissing or exposure to airborne food particles. However, the amounts, which provoked the reactions, were not established. Hence, with the available studies, it is impossible to draw firm conclusions about the highest dose of an allergen that it is safe to consume for all persons allergic to a particular food.

How can food allergic people be protected?

Awareness about food allergy among public food and health officials, and everybody supplying and preparing food is an important first step in protecting food allergic people. In order to manage allergen risks, manufacturers need to have a thorough knowledge of the ingredients and possible contaminants in a food product. Allergens may contaminate an otherwise allergy-safe food if, for example, the product is made on the same processing equipment as products containing allergens, without adequate cleaning between products. Guidelines for the food industry about key areas they need to consider to manage allergen risks are available[9, 10]. Eating away from home is often risky for an allergic person. Advice for caterers on what to do to limit the risk of one of their customers getting an allergic reaction is available[11]. The main advice for the caterer is never to guess whether a dish contains a certain food but always to check the ingredients carefully before giving advice to a food allergic customer.

Studies are ongoing in the United States and Europe[5] to obtain a better understanding of the true prevalence of food allergies. The results of these studies will aid in developing better guidelines for the protection of the food allergic individual. The food allergic individuals need to know what to avoid eating. They are dependent on reliable and easy to find information about ingredients in the foods they buy. Intake of even very small amounts of an ingredient, to which they are allergic, may be fatal.

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Progress in Nutrition 2018; Vol. 20, Supplement 2: 29-35 DOI: 10.23751/pn.v20i2-S.6970

Overview on eating disorders

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Summary. There is a commonly held view that eating disorders are lifestyle choice. Eating disorders are actually serious and often fatal illnesses, obsessions with food, body weight, and shape may also signal an eating disorders. Common eating disorders include anorexia nervosa, bulimia nervosa, night-eating syndrome, eating disorders not otherwise specified and binge-eating disorders. Eating disorders occur in men and women, young and old, rich and poor and from all cultural backgrounds; they result in about 7000 death a year as of 2010, making them the mental illnesses with the highest mortality rate. The chance for recovery increases the earlier they are detected, therefore, it is important to be aware of some of the warning signs of an eating disorder. In this review, different types of eating disorder, their side effects, complications and treatments are discussed.

Key words: eating disorders, types, side effects, complications, treatments

Introduction

Whether it is the effect of the media, family or friends, the number of eating disorders has significantly increased and they are becoming more and more prevalent. There are five classifications of eating disorders: anorexia, bulimia, binge eating disorder (BED), eating disorders not otherwise specified (EDNOS) and night eating syndrome (1). Over seven million girls and women and one million boys and men will suffer from an eating disorder in their lifetime. Up to 3.7% of females will be diagnosed with anorexia nervosa and an estimated 4.2% will have bulimia nervosa (2). The majority of adolescent patients seen in referral centers fit into a third category (EDNOS) and does not fit strict criteria for either anorexia or bulimia (3). Nineteen percent of college-aged females are bulimic; many go undiagnosed until much later. At the other end of the spectrum, 1% to 5% of the population falls into the category of binge eating disorder, not yet an approved psychiatric diagnosis (4). Anorexics are more likely to be female (90%-95%); 80% of bulimics are female and 60% of BEDs are female (5). Eating disorders begin early, with 10% being diagnosed in children less than 10 years of age. One third of patients are diagnosed as preteens and adolescents up to age 15. In total, 86% of patients are diagnosed with eating disorders before the age of 20 (6).

Etiology of Eating Disorders

The eating disorders have traditionally been viewed as sociocultural in origin. However, recently it was found that genetics tend to have a strong influence on these disorders (7). Current research demonstrates that eating disorder symptoms may be as common or more common among certain ethnic groups (Asians, blacks, and Hispanics) when compared with whites (8). There was no difference found in dieting and restraint scores between Asian, Latino, and white adolescent girls and boys (9) and no difference in binging or BED in obese patients who sought to lose weight with bariatric surgery (10). However, an analysis of 18 studies (1987-2001) concluded that African-American women were less likely than white women to have an eating disorder (11). As well, a study in school age girls dem-

onstrated that Native American girls had higher rates of restricting/purging and dieting than white or nonwhite/ non-Native American populations (12).

Types of Eating Disorders

1. Anorexia nervosa (AN)

Anorexia nervosa is a highly distinctive serious mental disorder. It can affect individuals of all ages, sexes, sexual orientations, races, and ethnic origins; however, adolescent girls and young adult women are particularly at risk (13, 14). The disorder involves the fear of gaining weight, having a distorted body im- age, a refusal to maintain normal weight, and the use of extreme measures to keep the weight off. Anorexia is typically diagnosed after a person is 25-30 percent below the normal weight for three months or more (15). Additionally, cognitive and emotional functioning are markedly disturbed in people with this disorder (16).

Typically, two sub-types of anorexia are identified. First, restricting-type anorexics (R-AN) lose weight purely by dieting and exercising without binge eating or purging. Second, binge-eating/purging-type anorex- ics (BP-AN) also restrict their food intake and exercise to lose weight, but periodically engage in binge eating and/or purging (17).

Anorexia is often associated with denial of illness and resistance to treatment. Consequently it is difficult to engage individuals with AN in treatment, including nutritional restoration, and weight normalization (18). The physical signs and effects of anorexia are presented in figure 1.

2. Bulimia nervosa (BN)

Bulimia nervosa is a serious, potentially life-threatening eating disorder. It is characterized by a cycle of bingeing and compensatory behaviors such as self-induced vomiting designed to undo or compensate for the effects of binge eating (19). Patients diagnosed with bulimia nervosa follow closely with patients diagnosed with binge-purge anorexia (1). Bulimia is diagnosed if the binge-purge cycle occurs at least two times a week. The act of purging can cause severe damage to the esophagus and teeth and it can also cause the gag reflex to be less sensitive (1).

Non-Purging type of bulimia is also diagnosed and is characterized by using other inappropriate methods of compensation for binge episodes, such as excessive exercising or fasting. In these cases, the typical forms of purging, such as self-induced vomiting, are not regularly utilized (20). The physical signs and effects of bulimia nervosa are presented in figure 2.

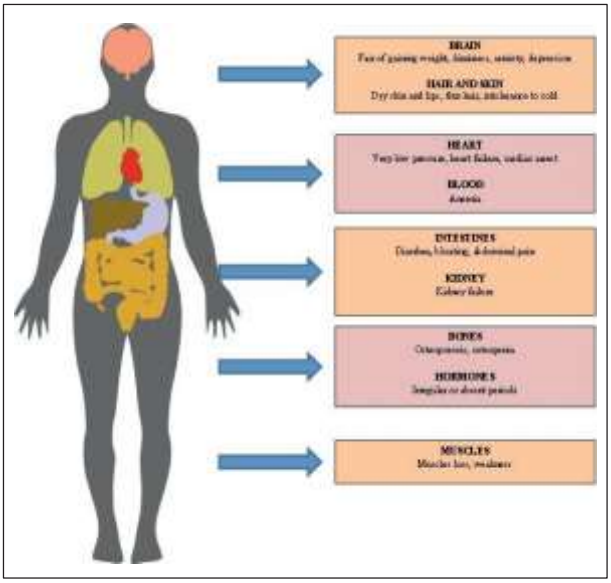

Figure 1. Physical signs and effects of anorexia nervosa

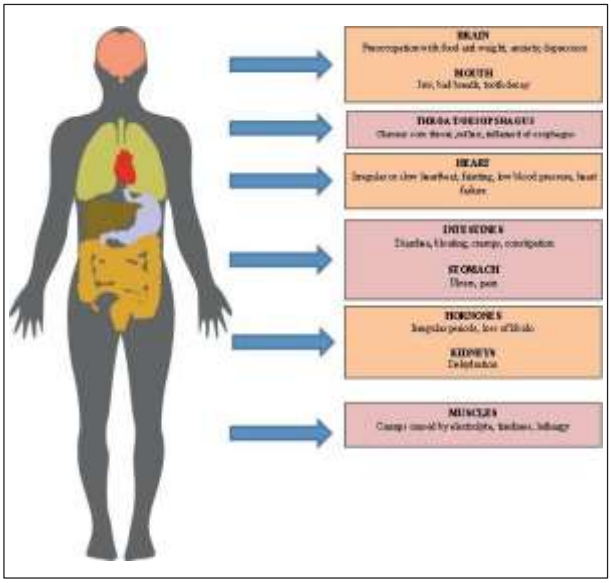

Figure 2. Physical signs and effects of bulimia nervosa

3. Binge-eating disorders (BED)

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th edition, binge-eating disorder is defined by several criteria (21). Individuals must report consuming an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances in addition to experiencing a loss of control over one's eating behavior during this time (21). In addition, at least three of the following characteristics must also be present: summing food much more rapidly than normal; eating food until uncomfortably full; consuming large amounts of food when not feeling physically hungry; consuming food alone to avoid embarrassment; or feeling disgusted, depressed, or guilty after the eating event (22). The diagnosis also requires that a significant amount of distress be associated with the binge episodes, which must occur at least once per week for 3 months or more. Lastly, the disorder must not be accompanied by any regular compensatory behavior, nor should the binge eating occur solely during an episode of bulimia nervosa or anorexia nervosa (22). The physical signs and effects of binge-eating disorder are presented in figure 3.

4. Eating disorders not otherwise specified (EDNOS)

Eating disorders not otherwise specified is much used by clinicians yet largely ignored by researchers. It

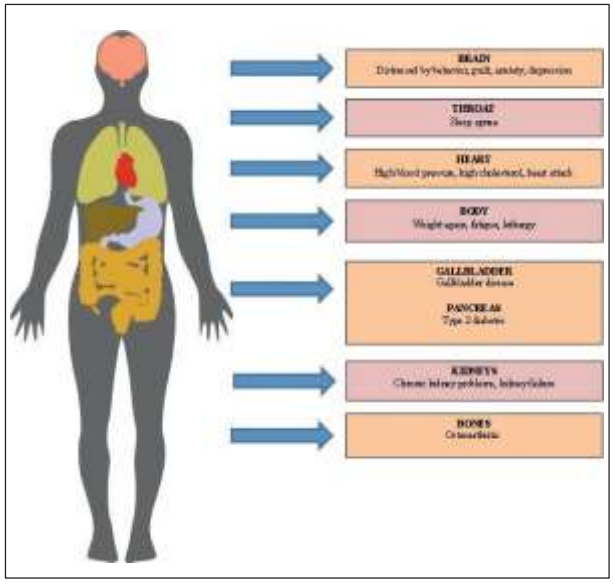

Figure 3. Physical signs and effects of binge eating disorder

is the category for disorders that do not meet the criteria for any other specific eating disorder and accounts for about 50% of eating disorders (23, 24). Although patients with EDNOS do not meet the diagnostic criteria for either AN or BN, if the disordered behaviors continue, they may progress to frank AN or BN. For example, some patients may have met all criteria for AN with the exception of missing three consecutive menstrual periods, or they may be of normal weight and purge without bingeing. Although patients may not present with medical complications, they often present with medical concerns and treatment modality depend on the severity of impairment and the symptoms (24).

Fairburn and Bohn described two subtypes as particularly common for EDNOS. The first are instances where the individual's presentation closely resembles AN or BN nervosa, but he or she just fails to meet the diagnostic thresholds. The second subtype are cases in which the clinical features of AN and BN are combined in ways other than in the two recognized syndromes (25).

5. Night-eating syndrome (NES)

The other prominent form of disordered eat- ing related to overweight and obesity is NES. NES was first described by Stunkard et al. among a group of individuals with obesity seeking weight loss treatment (26). They reported that those with the syndrome consumed a large majority of their caloric intake (25% or more) at a time when individuals without obesity would not be eating. In addition, the patients experienced insomnia and morning anorexia. Attention to NES was neglected until the late 1990's, when the focus of eating-related research shifted in response to the growing prevalence of obesity in the United States (27). Since this time, the definition of NES has varied. For example, in later years, Stunkard's definition was expanded to include nocturnal ingestions (28).

NES is characterized by recurrent episodes of night eating, which is described as either excessive food consumption in the evening (after dinnertime, i.e., evening hyperphagia) or eating after awaken- ing from sleep (i.e., nocturnal ingestions). NES is also characterized by at least three of the following symptoms: morning anorexia, the presence of a strong urge to eat between dinner and sleep and/or during

the night, sleep onset and/or maintenance insomnia, frequently depressed mood or mood worsening in the evening, and a belief that one cannot get back to sleep without eating (28, 29). In order to be diagnosed with NES, individuals must be aware of and be able to recall the eating episodes. These symptoms must also cause significant distress and/or impairment in functioning and not be better explained by external factors or another disorder, such as a sleeping disor- der or other disordered eating pattern (30). NES is classified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5) as an "other specified feeding or eating disorder."

Side effects of eating disorders

1. Osteoporosis

Anorexics are at increased risk of osteoporosis due to lowered intake, being under- weight, and decreased estrogen related to amenorrhea. Calcium supplementation in pubertal girls may increase peak bone mass (31). Calcium supplementation may increase the beneficial effects of physical activity on bone (32). Deficiency of vitamin D in young people can affect their ability to reach peak bone mass (33). Special risks in eating disorder patients for osteoporosis include the following:

- Anorexic girls (aged 13-23 years) who also suffer from depression may be at higher risk for osteoporosis than those without depression; the reason for this finding is not known (34).
- Amenorrhea in anorexic women and young girls may indicate the onset of estrogen deficiency, which can have a negative effect on bone density and peak bone mass.
- Under-nutrition can affect bone density through deficiency of anabolic hormones such as insulin like growth factor I; in addition, low weight is also a risk factor for lowered bone mass (35).
- Data indicate that osteoporosis could be considered a risk factor for periodontal disease progression, especially in subjects with preexisting periodontitis (36).

2. Taste receptors damaged

For all four taste stimuli (sweet, salty, sour, and bitter), intensities on the palate have been found to be lower in bulimic subject than in control subject (37), reduced taste sensitivity affected only the palate and not the whole mouth. Specifically, taste receptors located on the palate may become damaged because vomit is directed toward the roof of the mouth during purging (37, 38).

3. Oral Health

The association between oral pathology and eating disorders is most clearly established in cases with frequent self-induced vomiting, regardless of whether the diagnosis is anorexia or bulimia, and is characterized by dental erosion on palatal surfaces. Dental caries and dry mouth secondary to salivary gland dysfunction also occur (39). Gingival inflammatory changes due to vitamin C deficiency/scurvy are also observed (40).

4. Others

There were other side effects as well, including decreased concentration and other cognitive changes; physical changes that included decreased need for sleep; gastrointestinal problems; dizziness; headaches; noise and light sensitivity; weakness; fluid retention; cold intolerance; and difficulties with hearing and sight. There was a 40% slowing of basal metabolic rate, low body temperature, decrease in heart rate, and respiration (41).

Complications of eating disorders

No rehabilitation works 100% every time and a risk of relapse is always present. Re-feeding is one of the most prevalent complications characterized by the inability of the body to cope with the extreme change in metabolic function. The main signs of the re-feeding syndrome are (42):

- Hypophosphatemia, hypokalemia and hypomagnesaemia
- Heart failure
- Salt and water retention
- Depletion of vitamins such as B1, B6

These symptoms are caused by the change in metabolism in the body from fat to carbohydrates. When an anorexic patient starves themselves they are using stored fat as the primary source of energy. But when they start eating again their bodies can switch from using stored fat as energy to using carbohydrates from food again. This change will lead to insulin being released from the pancreas to aid in the uptake of glucose. When the insulin is released cells will start to increase the amount of glucose, phosphate, potassium, magnesium and water that they take in (43).

To avoid re-feeding syndrome, levels of phosphorus, magnesium, potassium and calcium should be determined for the first 5 days and every other day for several weeks; electrocardiogram should be also performed (18). If indicated, during the first days of refeeding, large amounts of multi-vitamins and minerals, in particular potassium, thiamine, phosphate and magnesium, should be provided. Again, strict monitoring is needed to prevent vitamin A and D toxicity in case of excessive supplements (44).

Types of treatment on eating disorders

1. Pharmacological treatments

Medications are generally useful for patients with bulimia nervosa and BED. Common forms of pharmacotherapy include antidepressants, antiepileptic medications, anti-obesity, and stimulant medications (45). For bulimia nervosa, antidepressant medications are the primary pharmacologic treatment (46). The evidence for the use of fluoxetine in the treatment of bulimia nervosa comes in the form of various case reports, systematic studies, and double-blind, randomized placebo controlled trials (47). Tricyclic antidepressants and monoamine oxidase inhibitors are also found to be effective were also found to be more effective than placebo in decreasing the binging and vomiting in patients with bulimia nervosa (48). Ondansetron at 24mg/day is also reported to reduce binge eating and self-induced vomiting in a small placebo-controlled study of 29 patients with bulimia nervosa (49).

For BED, lisdexamfetamine is reported to be generally well tolerated and effective, and is the first medication to be indicated by the FDA for treatment of BED (46). The anticonvulsant topiramate administered at a dose of 25 to 600mg daily is found to significantly reduce binge frequency and weight (50).

For anorexia nervosa, there is limited evidence supporting benefits of medications and different treatments were used for treating the accompanying symptoms. Olanzapine appears to demonstrate some benefit for weight gain and transdermal administration of hormonal agents is also being explored for improving bone health in anorexia nervosa (46).

2. Family-based treatment (FBT)

Although early models of family therapy for AN focused on addressing problematic aspects of the family that were believed to contribute to the development and maintenance of AN (51, 52), more recent models have focused on reducing blame and utilizing the family as a resource for recovery (53). In FBT, parents play a central role in restoring their child's health, and siblings are encouraged to provide emotional support to their ill sibling. The FBT should happen in the home during parental meal and needs the support of both parents. If parents do not have a shared understanding of how to undertake these tasks, they may unintentionally undermine each other (54).

3. Inpatient

Inpatient treatment is usually for very seriously ill patient who are usually the ones with cardiac or severe psychological issues that might need special medical attention throughout their treatment. These patients are fed by nasogastric feeding in order to reduce the risk of re-feeding syndrome and insulin spikes that can cause serious problems (55). Patients have also shown that they have less abdominal distention, nausea, and bloating (55). By being fed this way, doctors are able to add in more necessary fat to the diet without the patient objecting leading to a decreased hospital stay.

4. Outpatient

The standard nutritional treatment for outpatient is progressive bolus oral feeding (55). This is when the patient has a nutritionist set up a plan for what they need to eat to meet their goal caloric intake as well as nutritional needs. But some patients have had digestive issues such as nausea, bloating and pain from re-

turning to normal eating too quickly (55). The biggest consequence of this form of treatment is that it can lead to re-feeding syndrome and refusal to eat altogether. Many patients will struggle with the idea of eating solid food again especially enough to meet the caloric intake goal needed to make them healthy.

Conclusion

Eating disorders affect not only the diagnosed patients, but the families surrounding them. They can be triggered by society trends, genetics, and family and can develop during any stage in life, classified as a medical illness. Although these conditions are treatable, the symptoms and consequences can be detrimental and deadly if not addressed. They commonly coexist with other condition, such as anxiety disorder, substance abuse, or depression. Eating disorders can lead to heart and kidney problems and even death. Treatment involves monitoring, talk therapy, nutritional counseling, and sometimes medicines. People with eating disorder suffer of osteoarthritis, Kidney failure, high blood pressure, diarrhea, dizziness, etc. There are many complications that can arise with treatment such as refeeding syndrome and hypophosphatemia, which can lead to patient distress or fatality. Eating disorders are a lifelong battle even after treatment is completed.

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PERSPECTIVE

Early Diagnosis of Febrile Illness: The Need of the Hour

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In clinical practice, children presenting with high grade fever of few days duration is a common scenario. The clinician is frequently faced with a situation where, clinical clues are subtle or minimal and a plethora of diagnostic modalities are available, and choosing the best option is a challenge. Herein, we briefly discuss the various rapid diagnostic tests (RDTs) or point of care tests (POC), available in the Indian scenario, that help elucidate the etiology of short duration fever in children.The significance of a detailed clinical history and physical examination cannot be overemphasized, and forms the basis for selecting from the battery of tests available.

THE NEED FOR EARLY DIAGNOSIS

Infectious diseases are responsible for an enormous burden of death and disability in developing countries, especially in children, thereby leading to a huge loss of healthy life-years [1]. Many people in developing countries do not have access to health care and laboratory facilities, and the diagnosis rests on the availability of RDT or POC tests [2]; so that treatment can be initiated at the earliest, to prevent complications and mortality.

Characteristics of an ideal POC test have been described as 'ASSURED' [3]:

Affordable; Sensitive; Specific; User-friendly (simple to perform in a few steps with minimal training); Robust and rapid (can be stored at room temperature and results available in <30 minutes); Equipment free or minimal equipment that can be solar-powered; and Deliverable to those who need them.

Epidemic dengue has spread to many new areas and has increased in the already affected South East Asia, which is home to 70% of the global at-risk population, with case fatality rates of 1-5% [4]. Typhoid fever continues to be a serious public health problem in many developing countries. It may lead to serious complications in 10-15% of cases with a case fatality rate of 1-4%. Global estimates range from 17 to 22 million cases per year and 216,000 to 600,000 deaths [5]. Half of the world's population is at risk of malaria, and as per WHO estimates, 243 million cases led to nearly 863,000 deaths in 2008 [6]. In India, around 1.5 million confirmed cases are reported annually by the National Vector Borne Disease Control Programme [NVBDCP], of which about 50% are due to *Plasmodium falciparum* [7].

All these conditions present diagnostic challenges as many clinical features are overlapping and non specific. There is no test available that can predict the progression of these illnesses to their life-threatening severe forms. Making the correct diagnosis is thus, crucial to prevent significant delay in starting appropriate therapy, reduce hospital stay and expenses, and prevent complications [8]. Early laboratory diagnosis is valuable, as some patients progress rapidly to severe disease and death, and also for surveillance activities, outbreak control, academic research, vaccine development, and clinical trials. The need for rapid diagnostic techniques has increasingly been felt to overcome this challenge. ***Table* 1** lists the various available RDTs.

DIAGNOSIS OF DENGUE FEVER

Dengue virus belongs to the family Flaviviridae, whose members share common cross-reactive antigens, complicating laboratory diagnosis. Virus isolation and PCR methods require sophisticated

TABLE 1: VARIOUS RDT'S AVAILABLE FOR DIAGNOSIS OF DENGUE, MALARIA AND ENTERIC FEVER

S. No.	Disease	Test	Type of Sample	Method Report	Time to of positivity	Earliest day of positivity	Latest day	Trade name (Rupees)	Cost	Sensitivity	Specificity
1	Dengue	NS1 Antigen	Serum	A ICT	1 hour	1	9	NS1 (Panbio ICT)	775/-	70-97%	1
2	Dengue	Duo Ag-Ab	Serum	A ELISA	Same day	1 (Ag)5(Ab)	9(Ag) 5 mths(Ab)	Dengue Ag-Ab Duo Rapid Screening Test	950/-	45-100%	57-100%
3	Dengue	IgM,IgG (qualitative)	Serum	A/R/F ICT	Same day			Dengue IgM, IgG Qualitative test	1450/-		
4	Dengue	IgM (quantitative)	Serum	A/R/F EIA	Same day	3-5 days	3 months	Dengue IgM	1350/-	83% (52-100%)	85% (53-99%)
5	Dengue	IgG (quantitative)	Serum	A/R/F EIA	Same day	10-12 days	lifelong	Dengue IgG	1350/-		
6	Enteric	Rapid IgM	Serum	A/R/F ICT	Same day	3-5 days	2 weeks	Typhickeck, Typhidot	350/-	75%-92%	75-90%
7	Enteric	Widal	Serum	A HA	24 hours	week2	3 weeks	Widal	300/-	40%-70%	60-75%
8	Malaria	Falciparum Ag	WB-EDTA/ Heparin	A/R Chromatography	Same day	Anytime		Parachek F	525/-		
9	Malaria	Malaria Pan/Pf	WB-EDTA/ Heparin/ Citrate	A/R ICT	Same day	Anytime		EZ Dx	600/-		
10	Malaria	IgG Ab	Serum	A/R/F ICT	Same day			Malaria IgG	550/-		
11	Malaria	QBC	WB-EDTA	A Fluorescent microscopy	Same day	Anytime		QBC	475/-	75-96%	82-98.4%

Legend: NS - non structural, Ag – Antigen; Ab – Antibody; ICT – Immunochromatography; ELISA - Enzyme linked immunosorbent assay; WB- Whole blood; EIA - Enzyme immunoassay; Ig –Immunoglobulin; HA–Haemagglutination; A – Ambient; R –Refrigerated; F –Frozen.

laboratories, are expensive, and are not widely and easily available. Antibody-based tests [hemagglutination inhibition (HI) and IgM antibody capture ELISA (MAC-ELISA)] are approved for diagnosis of dengue infection. Both tests fail to discriminate between infections by other flaviviruses. The HI test is simple, sensitive, and reproducible but requires paired sera at least 1 week apart and thus is not very useful for clinical management. MAC-ELISA can measure a rise in dengue-specific IgM and IgG even in serum samples collected at 2-day intervals. This helps diagnose acute primary or secondary dengue infection. However, the need for proper timing of sample collection, false positive reactions, the long persistence of IgM antibodies, and limited availability are a few shortcomings [8].

In a recent meta-analysis of rapid (<60 minutes) diagnostic immunochromatographic test (ICT) for dengue, it was shown that the ICT can both rule in and rule out disease but is more accurate in samples collected in the late acute phase of infection [9]. The sensitivity of the ICT to differentiate between primary and secondary infection was suboptimal (66-71%) but the specificity, odds ratio and positive likelihood ratio indicated that it is an acceptable test for differentiating between the two [9].

Until recently, detection of dengue antigens in acute-phase serum was rare in patients with secondary infections because such patients had pre-existing virus-IgG antibody immune complexes. New developments in ELISA and dot blot assays directed to the envelop/membrane (E/M) antigen and the non-structural protein 1 (NS1) demonstrated that high concentrations of these antigens in the form of immune complexes could be detected in patients with both primary and secondary dengue infections up to nine days after the onset of illness. After day five, dengue virus and antigens disappear from the blood coincident with the appearance of specific antibodies. NS1 antigen may be detected in some patients for a few days after defervescence [4]. In a study by Kumarasamy, *et al*. [10], the dengue NS1 antigen-capture ELISA gave an overall sensitivity of 93.4% and a specificity of 100%. The sensitivity was significantly higher in acute primary dengue (97.3%) than in acute secondary dengue (70%). The positive predictive value of the dengue NS1 antigen-capture ELISA was 100% and negative predictive value was 97.3%. NS1 antigen ELISA was superior to virus isolation and RT-PCR for the laboratory diagnosis of acute dengue infection based on a single serum sample [10].

DIAGNOSIS OF ENTERIC FEVER

While the gold standard for definitive diagnosis of enteric fever is the bacteriological culture, the long time to availability of reports may limit its use. Widal test, though extensively used, cannot give a reliable diagnostic result in endemic regions due to difficulty in establishing a steady-state baseline titre, cross-reactivity with other organisms, effect of previous immunisation, inability to differentiate paratyphoid from typhoid, and lack of reproducibility of the result [11]. The timing of the widal test in a febrile illness is also important. It can give falsely positive results with other conditions such as malaria, immunological disorders and chronic liver diseases [12]. Even culture-positive typhoid patients may not produce detectable antibody levels, resulting in a false-negative serology [13,14].

Antibody-dependent tests [Multi-Test Dip-S-Ticks, TyphiDot, and TUBEX to detect IgG, IgG and IgM, and IgM, respectively] can be falsely-positive, particularly in endemic areas. Antigen-based tests become positive earlier in the illness before antibodies are identified or culture report becomes available. They can also help in the early detection of treatment failures and the carrier state. Narayanappa, *et al.* have reported that Typhidot-M was positive in 97% of cases who presented with fever of <7 days among blood culture positives as compared to Widal, which was positive in 24.2%, the overall sensitivity of the test was 92.6% [15]. In patients with fever >7 days duration, the IgM levels start declining and the IgG starts taking over, which can give rise to false negative results. Typhidot-M is easy to perform, sensitive, early, rapid [16], and requires minimal training, thus is an ideal screening test, though the higher cost is a limitation.

Enzyme immunoassays, counter-immune electrophoresis and co-agglutination tests to detect serum or urinary somatic/flagellar/Vi antigens of *Salmonella typhi* have also been evaluated. The suboptimal and

variable sensitivity and specificity estimates, inability to detect *Salmonella paratyphi* infection and Vi antigen negative strains of *S. typhi* are serious limitations of the Vi antigen detection tests [17]. The nested PCR-based diagnosis of typhoid could be a more useful tool than either blood culture or Widal test, owing to its greater discriminatory ability [18-20]. Case definitions based on combinations of serological tests can detect additional cases while maintaining 100% specificity [21].

With the sequencing of the entire serotype Typhi genome, it is possible to identify other antigens, such as fimbrial antigens, that may produce an antibody response specific to serotype Typhi [22].

DIAGNOSIS OF MALARIA

The increasing burden of the disease, the emergence of resistance to antimalarials, and availability of expensive artemesinin-combination therapies, especially in highly endemic regions, are increasing the need for rapid accurate diagnosis of patients with suspected malaria. WHO recommends that all case of fever clinically suspected as malaria should be confirmed either by microscopy or rapid diagnostic tests (RDTs) [6]. Despite being the "gold standard", the most important shortcoming of microscopic examination is its relatively low sensitivity, particularly at low parasite levels. The Quantitative buffy coat smear (QBC) technique is simple, reliable, and user-friendly, but it requires specialized instrumentation, is more expensive than conventional light microscopy, and is poor at determining the species and the number of parasites.

RDTs detect malaria antigen in blood flowing along a membrane containing specific anti-malaria antibodies (immunochromatographic lateral-flow-strip technology); they do not require laboratory equipment, are easy to perform and provide results within half an hour. Characteristics of a RDT vary based on regional malaria epidemiology and the goals of a malaria control programme [23]. The ideal test should be able to detect a response to therapy, and detection of recrudescence or relapse. Most products target a *P. falciparum*-specific protein, e.g. histidine-rich protein II (HRP-II) or lactate dehydrogenase (LDH). Some tests detect *P. falciparum* specific and pan-specific antigens (aldolase or panmalaria pLDH), and distinguish non-falciparum infections from mixed malaria infections. Despite their ability to discriminate between different species of malaria, the dipstick methods are poor at detecting mixed infections when one species is present at a significantly lower parasitemia than the other. The World Health Organisation (WHO) has recommended a minimal standard of 95% sensitivity for *P. falciparum* density of 100/μl, and a specificity of 95% [23,24]. Indian Academy of Pediatrics recommends the use of RDT'S in India in far away communities with poor access to health care facilities and non-availability of microscopic diagnosis; malaria in immunocompromised; in areas of multidrug resistance; and in severe and complicated cases [25].

The rapid diagnostic tests and microscopy can be utilized as complementary tools for maximum benefit; with RDTs providing a rapid or screening diagnosis, and microscopy reserved for resolution of confusing cases and verification of negative cases.

Contributors' credit: BD conducted the literature search and drafted the manuscript. DM conceptualised the topic and made intellectual contribution to the manuscript.
Funding: None.
Competing interests: None stated.

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Food allergy and intolerance

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Abstract: Allergic reactions to foods represent severe actual problems for mankind having increased global character. Adverse food reactions are divided to food allergy, an immunological response to food, and food intolerance, a non-immune reaction with allergy-like symptoms. It is estimated that 6—8 % of children and 1—2 % of adults suffer from food allergy. The prevalence of food intolerance in adults is no more than 5—6 %, however in infants and young children, it is varied from 0.3 % to 20 %. Allergy is caused by different food allergens (milk proteins, cereals, nuts, fruits and vegetables), while there is frequent cross-allergy among them. Food intolerance is adverse reaction resulting from enzyme deficiencies, pharmacological reactions, and response to toxic or irritant components of food. Focusing on dairy products and cereals, the impact of fermentation in reducing food intolerance or allergenicity is reviewed in this paper.

Keywords: food allergy, food intolerance, allergens, lactic acid bacteria, fermentation

Introduction

The concept that certain foods can produce adverse reaction in sensitive individuals has been gradually revealed for a long period. Food allergy and food intolerance have been known since antiquity Hippocrates (460—370 BC) reported that cow's milk could cause gastric upset and urticaria. Galen (131—210 BC) described a case of intolerance to goat's milk (David, 2005; Kayserová, 2004). For instance, the observations on the cause of food allergens as fishes and eggs or clams in the development of asthma and dermatitis were expanded, respectively in the 17th and 18th centuries. Other food allergy milestones were carried out in 1656 when, P. Borel introduced a skin test with egg white in France and probably in 1919 when C. Richet summarized all up to date knowledge in his paper on Food Anaphylaxix (cit. Hefle, 2001). Demonstrations of food antigens that were rapidly absorbed from the gastrointestinal tract and transported to the various organs of the human body were provided by Prausnitz and Kustner in 1921. In 1959, Burnet proposed a theory describing the recognition of foreign antigens by lymphocytes and the subsequent induction of immune response (cit. Hayakawa et al., 1999). Further investigations of food allergy finished in 1972 and 1984 understood the intestinal and common mucosal immune systems by Tomasi and Bienenstock (cit. Hefle, 2001).

In the past, food allergy and intolerance were considered as minor health problems. Scientific research and interest are focused on food adverse reactions only in last decade of 20th century (Smith, 1997).

The terms food allergy and food intolerance are often mixed up, but there are some differences between them (Mills and Breiteneder, 2005). Food allergy is only certain part of adverse food reactions. These reactions can be toxic or non-toxic. Bacterial toxins or high content of biogenic amines may activate a toxin reaction. Non-toxic reactions are caused by immune or non-immune mechanisms (food allergy or intolerance) (Ispano et al., 1998; Halken, 1997). Immunologic reactions to food are mediated by the immune system, while all other reactions fall into the non-immunologic category (Davis, 2009). Cereals and milk cause most food allergies and intolerances in our country.

The production of fermented foods is one of the oldest food processing technologies known to man. Lactic acid bacteria are used in food fermentation for longer preservation and improving textures, flavours and tastes. Moreover, proteolysis during fermentation can lead to reduction of immunoreactivity of food proteins. Hence, it could be expected that fermentative transformations with suitable lactic acid bacteria could produce hypoallergenic products (El-Ghaish et al., 2011).

Food allergy

Food allergy is defined as an adverse immunological (hypersensitivity) response to food (food proteins) and as such it is not a single disease, nor is it caused by one pathophysiologic disturbance (Sicherer, 2002; Sicherer and Sampson, 2006; Sicherer and Sampson, 2010; Macdougall and Etuwewe, 2005; Madsen, 1997; Halken, 1997; Crevel et al., 2007). This is manifested only in hypersensitive individuals (Rimárová, 2008), who have so-called predisposition (Hefle, 1996) and where symptoms appear rapidly following exposure to macromolecules (Mills and Breiteneder, 2005). Food allergic reaction can be

divided into IgE mediated and non IgE mediated (Ispano et al., 1998; Halken, 1997; Ortolani and Pastorello, 2006; Davis, 2009).

The number of patients suffering from food allergy has increased during recent decades, and allergic diseases have become a major clinical and public problem (Sicherer and Sampson, 2010; Macdougall and Etuwewe, 2005; Emmett, 1996).

There are several factors, which are responsible for development of food allergy: especially genetic allergy predisposition, early "foreign" food protein exposure (time, dose, and frequency), allergen uptake and handling (Halken, 1997).

The prevalence of specific food allergies is dependent on regional dietary habits and methods of food preparation (Sampson, 2004; Davis, 2009).

The risk of developing allergies is significantly influenced by genetic disposition. The changes in lifestyle and environmental factors result in increases of adverse food reactions. Complex factors include socioeconomic impacts, impacts of external and internal environment, exposure to new allergens, stress, use of antibiotics, infectious diseases, climate change, and others (Rimárová, 2008; Samartín et al., 2001).

Food allergy affects 2—4 % of the population (Fuchs, 2008). The highest prevalence observed in children between 1.5 to 3 years (25 % of all food reactions). According to various studies suffer from food allergy 6—8 % of children and 1—2 % of adults (Altman and Chiaramonte, 1997). Only about 20 % of all food allergies persist into adulthood, others resolve spontaneously within three years of age (Svačina, 2008).

This is probably due to delayed onset of the mechanisms of oral tolerance to food proteins (Fuchs, 2008). Some studies indicated only 11 % resolved egg and 19 % resolved milk allergy by age 4 years (Sicherer and Sampson, 2010; Savage et al., 2007; Skripak et al., 2007).

Symptoms range from mild and tolerable (slight abdominal pain) to anaphylaxis which can result in physical collapse and death. The symptoms are divided into three main groups: immediate (within 1h of ingestion), delay or late (more than 1h after ingestion), and remote (Gray and Chan, 2003).

In Table 1, there is a summary of symptoms caused by food, which contains allergens. These symptoms involving the skin, gastrointestinal tract, respiratory tract, the motoric system, cardiovascular system, genitourinary tract and central nervous system, or can be shown by overall reaction (life threatening anaphylactic reaction —in rare instances).

Symptoms of food allergy vary depending on several factors, such as the age of the subject, the allergen involved and the amount of food eaten, physical exercise, stress, coexisting medical problems, among others (Samartín et al., 2001; Gray and Chan, 2003).

The food allergens can be defined as chemical, physical and biological substances occurring in environmental, which in sensitive individuals produce allergic reactions. The ability of allergen provoke this reaction depends on the type of allergen, the amount, duration of operation, points of entry and the degree of hypersensitivity of a particular organism (Rimárová, 2008). The allergic reaction can be caused by different amount of protein, from perhaps a tenth of a milligram up to grams, and sometimes tens of grams (Crevel et al., 2007).

The major food allergens are water- or salt-soluble proteins or glycoproteins with molecular weights of 10—60 kD that are stable to heat, acid, and proteases (Sicherer and Sampson, 2006; Sicherer, 2002; Hayakawa et al., 1999; Smith, 1997, Sampson, 1999; Davis, 2009). Allergens, which are stable against denaturation and degradation during food processing, are mostly responsible for causing food allergies (Davis, 2009).

Tab. 1. The most common clinical manifestations of food allergies (Svačina, 2008; Sicherer and Sampson, 2006; Macdougall and Etuwewe, 2005; Fuchs, 2008; Halken, 1997; Ring et al., 2001; Carter, 2003; Muraro et al., 2014).

Location	Manifestations
Gastrointestinal	abdominal cramps, flatulence, blood in the stools, nausea, abdominal distension, colic, pain, vomiting, meteorism, diarrhea, constipation, malabsorption
Skin	atopic dermatitis, contact dermatitis, eczema, skin rashes, itching or flushing, tingling, swelling of the lips, palate, tongue or throat erythema, urticaria, angioedema,
Respiratory	recurrent wheezing, nasal congestion, itchiness or sneezing, asthma, laryngeal edema, stridor, cough, rhinoconjunctivitis cold, shortness of breath, dyspnea
mouth, neck, ears	stomatitis, otitis, pharyngitis
nervous system	irritability, restlessness, fatigue, migraine
blood count	anemia, eosinophilia, thrombocytopenia
other signs	enuresis, nephrotic syndrome, arthritis

More than 200 proteinaceous allergens have been identified and characterized, and over 100 different foods or food components may cause adverse reactions (Hayakawa et al., 1999; Astwood and Fuchs, 1996).

The eating habits and socio-cultural background are responsible for differences in foods most commonly involved in allergy. Variations of occurrence are between age groups as well as countries (Madsen, 1997; Ring et al., 2001).

The main allergens, which according to recommendation of European Union subject to mandatory marking on the food are:

- cereals containing gluten (i.e. wheat, rye, barley, oats, spelt, kamut or their hybridised strains) and products thereof,
- crustaceans and products thereof,
- eggs and products thereof,
- fish and products thereof,
- peanuts and products thereof,
- soybeans and products thereof,
- milk and products thereof (including lactose),
- nuts i. e. Almond (*Amygdalus communis L.*), Hazelnut (*Corylus avellana*), Walnut (*Juglans regia*), Cashew (*Anacardium occidentale*), Pecan nut (*Carya illinoiesis (Wangenh.) K. Koch*), Brazil nut (*Bertholletia excelsa*), Pistachio nut (*Pistacia vera*), Macadamia nut and Queensland nut (*Macadamia ternifolia*) and products thereof,
- celery and products thereof,
- mustard and products thereof,
- sesame seeds and products thereof,
- sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/litre expressed as SO_2 (DIRECTIVE 2003/89/EC).

These so-called main allergens are responsible for almost 90 % of allergic reactions and intolerance (Rimárová, 2008; Macdoughal and Etuwewe, 2005; Hayakawa et al., 1999). Reactions to fruits (apples, peaches, apricots, cherries, kiwi and citrus fruits) and vegetables (celery) are common (approximately 5 %) but usually not severe (Sicherer, 2002, Sicherer and Sampson, 2006; Svačina, 2008) and the allergens are often sensitive to cooking (Hayakawa et al., 1999). Also, some food additives —colours, preservatives, flavorings, colorings, antioxidants, can be implicated in food allergies and intolerances (Smith, 1997; Ring et al., 2001).

It is generally assumed that sensitization to the classical food allergens such as milk, egg, peanut and fish occurs via the gastrointestinal tract, although other types of food allergy occur as a consequence of prior sensitization to inhaled allergens such as pollen (Mills and Breiteneder, 2005; Sampson, 2004; Breiteneder and Ebner, 2000).

Cereals are the major plant food, which cause adverse food allergies. Cereals contain a range of allergens (Mills and Breiteneder, 2005). IgE mediated reactions to wheat have been demonstrated as early as the beginning of the 20th century (Scibilia et al., 2006). The prevalence of cereal allergy has increased among the children as well as among the adults. More than 0.5 % of children and 3 % of adults suffer from an allergy to wheat (Battais et al., 2005; Zuidmeer et al., 2008). Some cereal allergens: water soluble albumins and globulins (lipid transfer proteins, inhibitors of trypsin and α-amylase), and water insoluble gliadins and glutenins, known as prolamins were described in scientific studies (Battais et al., 2005; James et al., 1997; Walsh et al., 1985).

Prolamins are responsible for food-dependent exercise-induced anaphylaxis and atopic dermatitis, inhibitors of proteases and α-amylases have also been described as both inhalant and food allergens (Mills and Breiteneder, 2005). Glycosylated subunits of tetrameric α-amylase inhibitors from wheat (CM16), and its homologs from barley (CMb), and *rye Sec c1* have the highest allergenic activity. Inhibitors of enzymes have been described as major allergens in rice and buckwheat (Mills and Breiteneder, 2005).

From the animal origin foods, milk is the food, which is often responsible for formation of allergies.

Cow's milk is one of the most common causes of adverse reactions in foods and it contains about 20 proteins, which are considered to be an allergens. Allergy is frequently induced by casein and whey proteins. Casein is fractionated into α-, β-, and κ-casein. Whey proteins include: α-lactalbumin (α-la), β-lactoglobulin (β-lg), bovine serum albumin (BSA) and immunoglobulin (Igs) (El-Agamy, 2007; Cocco et al., 2003; Jarvinen et al., 2002). The most common allergens are β-lactoglobulin, α-casein and serum albumine (Besler et al., 2001; Mills and Breiteneder, 2005). Allergy to cow milk can be observed in about 2.5 % of children below 3 years of age (El-Ghaish et al., 2011).

Food intolerance

Food intolerance is abnormal non-immune reaction with allergy-like symptoms after ingesting of food (Kayserová, 2004; Madsen, 1997; Halken, 1997; Ortolani and Pastorello, 2006). It results from enzyme deficiencies, pharmacological reactions, and response to toxic or irritant components of food (Gray and Chan, 2003).

Estimates of the prevalence of food intolerance vary widely from 2 % to over 20 % of the population (Nelson and Ogden, 2008). The prevalence of food intolerance in adults are no more than 5—6 %, in infants and young children is varying from 0,3 % to 20 % (Gray and Chan, 2003).

Symptoms of food intolerance include skin rashes, urticaria, angioedema and eczema, nasal congestion, sinusitis, pharyngeal irritations, asthma and an unproductive cough, mouth ulcers, abdominal cramp, nausea, gas, intermittent diarrhea, constipation, irritable bowel syndrome, and may include anaphylaxis (Ortolani and Pastorello, 2006; Ozdemir et al., 2009; Cardinale et al., 2009; Gray and Chan, 2003).

Intolerance to lactose

The lactose intolerance is a result of lactase deficiency and is a form of carbohydrate malabsoption. Lactose is hydrolyzed by lactase in the intestinal mucosa. The by-products of lactose hydrolysis are the monosacharides, glucose and galactose (Wilson, 2005).

The lactase deficiency has been described as primary, secondary, or congenital ones. Primary lactase deficiency is the normal gradual reduction in lactase production seen as an individual matures from infancy into adulthood and is expressed variably across populations (Wilson, 2005). Approximately 25 % of the human population maintains a high level of lactase activity and therefore a large capacity to digest lactose throughout life (Suarez et al., 2003). Secondary lactase deficiency occurs because of gastroenteritis, bowel surgery, cystic fibrosis, or immune disorders. Congenital lactase deficiency is a rare hereditary disorder in which lactase activity is absent (Wilson, 2005).

The prevalence of lactose intolerance is lowest in people of Northern European descent (15 %) and highest in many Asian populations (near 100 %). The prevalence lactase deficiency in individuals of African descent is approximately 70—80 %. Similar level is reported for Latinos and those of Eastern and South American ancestry (Paige, 2005).

The symptoms of lactose intolerance include, for example flatulence, loose, stools, abdominal pain, diarrhea, vomiting, skin irritation (Suarez et al., 2003; Wilson, 2005; Paige, 2005). Not all individuals with a reduce level of the enzyme lactase exhibit symptoms with the ingestion of dietary lactose. The presence or absence of symptoms varies with amount and type of food consumed, intestinal transit time, and the level of residual intestinal lactase (Paige, 2005).

Intolerance to gluten

Gluten is a protein, which is rich in amino acids proline and glutamine. These amino acids are collectively known as prolamins. Gluten is found mainly in foods (wheat, rye and barley) but may also be found in everyday products such as drugs or vitamins (Rimárová, 2008; El-Ghaish et al., 2011).

Consumption of gluten can lead to development of celiac disease (gluten enteropathy) in subjects with genetic predisposition (Rimárová, 2008; Hybenová et al., 2013). It causes inflammation of the small intestine, leads to numerous abdominal as well as non-gastrointestinal symptoms and interferes with absorption of nutrients from food (Counts and Sierpina, 2006; El-Ghaish et al., 2011).

Celiac disease has a four sub-phenotype:

- classic celiac disease — dominated by symptoms and sequelae of GI malabsorption,
- celiac disease with atypical symptoms — few or no GI symptoms, extraintestinal symptoms predominate
- silent celiac disease —patients are asymptomatic but have a positive serologic test
- latent celiac disease —persons are asymptomatic but are at increased risk for later development of symptoms and/or histologic changes (Counts and Sierpina, 2006).

Celiac disease (CD) affects 1 % of the children and adults in the United States and Europe with similar prevalence rates in many other countries worldwide (Hadithi and Peña, 2010).

Symptoms of celiac disease occur when dietary proteins in wheat, barley, and rye are ingested by susceptible patients, activating an abnormal mucosal immune response that damages the small intestine by inducing chronic inflammation. The most common gastrointestinal (GI) symptoms of celiac disease include diarrhea, weight loss, vomiting, abdominal pain (with or without distention), anorexia, and constipation. The most common non-GI symptoms include iron-deficiency anemia (up to 5 % of celiac patients are anemic), failure to grow, short stature, delayed puberty, infertility, recurrent fetal loss, osteoporosis, vitamin deficiencies, fatigue, protein-calorie malnutrition, recurrent aphthous stomatitis, elevated transaminase levels, and dental enamel hypoplasia. The presence of obesity does not preclude a diagnosis of celiac disease. Several neuropsychiatric conditions have been reported to accompany celiac disease, including depression, anxiety, ataxia, seizures, peripheral neuropathies, and migraines (Counts and Sierpina, 2006; Van Heel and West, 2006; Berti et al., 2006; Freeman et al., 2002).

Reduction of allergenicity by lactic acid bacteria

Fermentation by lactic acid bacteria (LAB) is one of the oldest and most economic methods of manufacture and storage of food. It represents a natural way of increasing nutritional and sensory value of foods and reducing of antinutritional factors. In addition, fermentation leads to reduction of allergenicity of foods.

It is well-known that LAB release more or less proteolytic enzymes. Because allergens are proteins, LAB may degrade them during fermentation. The proteolytic system of LAB is composed of proteinases, peptidase and peptide transport systems. It is essential for their growth (Kleber et al., 2006; Pescuma et al., 2011).

Most studies revealed that allergy to cow milk is caused mainly by casein and β-lactoglobulin (El-Ghaish et al., 2011). The reduction of milk protein antigenicity depends on the species of LAB and on condition of fermentation. Bu et al. (2010) chose three LAB strains for fermentation of milk (*Lb. bulgaricus, S. thermophilus* and *Lb. helveticus*) and determined the protein allergenicity after 12 h fermentation. They found out that whey protein allergenicity decreased significantly, by 53—87 % for α-lactalbumin and 86—95 % for β-lactoglobulin as compared with unfermented milk. It was demonstrated that combination of two LAB strains (*Lb. helveticus* and *S. thermophilus*) leads to the reduction of antigenicity of both whey proteins (α-lactoalbunim and β-lactoglobulin) during fermentation (Bu et al., 2010).

Pescuma et al. (2011) found out decreasing of β-lactoblobulin antigenicity during fermentation by *Lb. delbrueckii* subsp. *bulgaricus* CRL 656 and they showed for the first time that a *Lactobacillus* proteinase was able to degrade allergenic response of human sera towards this protein.

Kleber et al. (2006) observed the potential of some lactic acid bacteria in combination with *S. thermophilus* subsp. *salivarius* for the reduction of β-lactoglobulin antigenicity in sweet whey and skim milk. Reduction of more than 70 % in sweet whey and more than 90 % in skim milk was detected.

In addition to all probiotic effects associated with the consumption of yoghurt, one may expect modification of allergenic properties of milk due to the process of fermentation. Hydrolysis of β-lactoglobulin and α-lactalbumin (allergenic whey protein of milk) by lactic bacteria may decrease (99 % of antigenicity) their allergenicity (Besler et al., 2001; Bertrand-Harb et al., 2003).

Bu et al. (2010) found that at the beginning of the fermentation, the antigenicity decreased gradually but at longer fermentation time it slightly increased.

It was demonstrated that LAB have a capacity to hydrolyze the wheat gliadin fraction improving their digestibility. De Angelis et al. (2006) showed that probiotic commercial preparation VSL#3 was able to hydrolyze gliadin polypeptides during dough fermentation. They also found out that pool of lactic acid bacteria (*Lb. alimentarius* 15M, *Lb. brevis* 14G, *Lb. sanfranciscensis* 7A and *Lb. hilgardii* 51B) was able to hydrolyse 109 of 129 ethanol-soluble polypeptides during fermentations of rye flour (De Angelis et al., 2006).

Gobbetti et al. (2007) demonstrated the hydrolysis of gliadin during long-time fermentation of dough, which was made from wheat (30 %) and non-toxic oat, millet and buckwheat flours started with the selected *Lb. alimentarius* 15M, *Lb. brevis* 14G, *Lb. sanfranciscensis* 7A and *Lb. hilgardii* 51B.

Rizzello et al. (2006) showed the capacity of the same pool of LAB to hydrolyzed wheat and rye allergens. Lactic acid fermentation caused a certain hydrolysis of albumins/globulins, and especially of gliadins.

Beyond proteolysis activity of LAB during fermentation, they may aid in the host protection against allergenic sensitization by degradation of potentially allergenic epitopes in the intestinal lumen.

Several pathologies of the gastrointestinal tract, particularly food allergy, are due to an exaggerated and imbalanced response of the gut mucosal immune system (Weid et al., 2002).

At the beginning of last century, it was observed that the consumption of fermented foods could be beneficial to health. Further, it was proposed that the health-promoting properties of such foods were imparted by fermentative microbes. It is now understood that lactic acid bacteria present in fermented foods are primarily responsible for imparting health benefits (Cross et al., 2001).

Lactic acid bacteria present in the human gut play a beneficial or probiotic role including the improvement of the local immune system. The intestinal barrier consists of physiologic and immunologic factors that restrict mucosal colonization by pathogens, prevent foreign antigens and pathogens (including food allergens) from penetrating the mucosa and regulate the antigen-specific immune responses (Rautava et al., 2005; Weid et al., 2002). Local damage may cause increasing macromolecular absorption resulting in increased systemic food allergen load, particularly in patient suffering from gastrointestinal pathology (Houben et al., 1997). Indeed, the balance of bifidobacteria versus clostridia in the neonatal flora appears to determine the allergic status in infants (Weid et al., 2002; Kalliomaki et al., 2001). In addition to bifidobacteria, several epidemiological studies clearly support the beneficial effects of lactobacilli against food allergy (Weid et al., 2002).

Scientists have attempted to select strains of LAB with immuno-stimulatory properties to use against gut diseases or to improve gastrointestinal mucosal immunity (Ortolani and Pastorello, 2006).

Also, Majamaa and Isolauri (1997) hypothesized that oral introduction of probiotics may prove to be

a useful tool for the treatment of food allergy by alleviating intestinal inflammation.

It was demonstrated that probiotic bacteria such as *Lactobacillus GG* may promote endogenous barrier mechanisms in patients with atopic dermatitis and food allergy, and by alleviating intestinal inflammation may act as a useful tool in the treatment of food allergy (Hayakawa et al., 1999; Chalk and Chalk, 2003).

On the contrary, Muraro et al. (2014) stated that the evidence that probiotic supplements have preventative or therapeutic activity for food allergy is lacking, and further research is needed to make recommendations in this area.

The mechanisms by which allergies might be reduced by consuming fermented foods is uncertain. Several theories exist, including the ability of LAB to enzymatically hydrolyze allergenic food molecules or to stabilize the gut mucosa sufficiently to reduce systemic uptake of food-borne allergens (Cross et al., 2001; Sutas et al., 1996). It is also possible that fermented foods containing LAB could serve to limit the establishment of an allergic phenotype during neonatal development (Matricardi et al., 1999).

One mechanism by which specific strains of lactobacilli may aid in host protection against allergic sensitization is the degradation of potentially allergenic epitops in the intestinal lumen. However, only proteolysis of allergenic epitopes is not sufficient to explain the clear anti-allergic effects of certain strains of LAB that have been demonstrated (Weid et al., 2002). The permeation of antigens across the gut lining may be the primary factor in food hypersensitivities which manifest as allergic disease (Chalk and Chalk, 2003).

Most of the current probiotic foods are mainly dairy based; there is a growing interest in the development of non-dairy probiotic products due to problems such as lactose intolerance in many people and the unfavourable cholesterol content of fermented dairy products. Cereals contain water-soluble fiber (such as β-glucan and arabinoxylan), oligosaccharides (such as galacto- and fructooligosaccharides) and resistant starch, and thus have been suggested to fulfill the prebiotic concept (Rivera-Espinoza and Gallardo-Navarro, 2010).

Conclusion

Recent changes in eating habits and in the environment are thought to be connected to the recent rapid increase in food and other allergies. Food allergies are common, result in both acute and chronic disease, might be increasing in prevalence, affect quality of life, and can be severe and potentially fatal. Effective management of food allergy is dependent on complete avoidance of the food allergen, patient education, and emergency treatment of anaphylaxis. Elimination diets can be expensive, are socially disruptive, and run the risk of being nutritionally inadequate.

Theory that fermented foods can benefit health has been extrapolated to the possibility that fermentative LAB could present a dietary means of anti-allergy treatment (and possibly prophylaxis), through a mechanism of immunoregulation.

Probiotic bacteria don't have only immunomodulatory effect, but they are able to reduce food allergens during the fermentation of food with allergenic potential. There is evidence that they are able to reduce the gluten content of cereals, by proteolysis they reduce albumin and globulin content in milk and prolamins in cereals.

Now, there is a challenge before us to enrich the market with ferment and probiotic foods, because our manufacture's offer is limited to dairy foods. Because milk is one of the major allergens, we have to focus on other substrates that are suitable carriers of probiotic bacteria.

Acknowledgement

This work was supported by courtesy of the Slovak Grant Agency (VEGA 1/0495/13).

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AIDS and nutrition in patients

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ABSTRACT

Introduction: AIDS is a viral infection that particularly affects the nutritional status of patients by complicating the absorption of nutrients and their metabolism.
Purpose: The purpose of this retrospective study is to highlight the contribution of nutrition to the wellness of people with HIV in all stages of the disease.
Review Methods: The methodology used to select the information used in this study includes review studies and research in leading databases such as PUBMED, MEDLINE, and IATROTEK. The selection criterion of the articles was the Greek and English language.
Results: The real goal of the nutritional assessment of patients with AIDS is to improve their ability to consume a sufficient quantity and variety of foods in order to meet their nutritional needs. The evaluation of dietary intake assesses the adequacy of food and nutrients consumed. It includes assessing the dietary patterns, frequency of meals, and the factors that affect food choice.
Conclusions: Maintaining a good nutritional status has a significant impact on the functioning of the immune system and the overall health of people living with HIV / AIDS.
Key words: AIDS, nutrition, immune system infection, immunosuppressant

DOI: 10.5604/01.3001.0010.1881

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Received: 02.04.2017
Accepted: 25.05.2017
Progress in Health Sciences
Vol. 7(1) 2017 pp 182-186

INTRODUCTION

In 1983, HIV was first isolated by Francis Barre-Sinnousi and Luc Montagnier at the Pasteur Institute in Paris on suspicion that it could be the cause of AIDS. This initial discovery was confirmed a year later by researchers at the National Institutes of Health, headed by Robert C. Gallo [1].

In 1986, the International Commission on the Classification of Viruses attributed the name human immunodeficiency virus (HIV) to the retrovirus. Globally, it is estimated that 35.3 (32.2 to 38.8) million people were living with HIV in 2012. There has been an increase in people receiving antiretroviral therapy from previous years; an overwhelming number of men, 31.8 million, compared with women, 16 million. New infections have dropped by 33% since 2001, with the reduction being more pronounced among children. At the same time, the number of deaths from AIDS has also decreased from 2.3 million in 2005 to 1.6 million 2012 [2, 3].

In 1987, the first antiretroviral agent, AZT (zidovudine), was launched as a treatment for HIV. Even though the long-term viral suppression treatment doesn't cure HIV, it still provides temporary relief from symptoms and clinical manifestations by slightly delaying the onset of AIDS [4]. Although the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s until today has led to a significant reduction in morbidity and mortality, a complete elimination of the virus has not been achieved. It is estimated that HAART has reduced mortality by 80% in industrialized countries [5].

Deaths from AIDS have declined by 30% from 2005, when it was recorded and was the highest percentage in history. The total number of people who have died from AIDS rose then to 30 million [6].

In 2012, about 9.7 million people with HIV had access to antiretroviral therapy in low- and middle-income countries, which represents 34% of people that received treatment, according to 2013 WHO guidelines [6].

It is estimated that the average time from the moment of infection with the virus until death is 9.4 years for patients who do not receive any kind of treatment. However, there is a very small percentage (<1%) of patients who are able to suppress the virus naturally without the use of antiretroviral drugs [7].

The onset of AIDS is characterized by the collapse of the immune system after a long asymptomatic period. CD4 cell levels continue to fall (<200 cells / ML) to levels that can increase the risk of opportunistic infections by bacteria, viruses, fungi, and parasites such as Microcystis Carinii, cytomegalovirus and enteropathic parasites, which could be threatening life diseases [8].

Nutrition has always been an important aspect of HIV care. Maintenance of a good nutritional status has a significant impact on the functioning of the immune system and the overall health of people living with HIV / AIDS [9].

The purpose of this study is to highlight the contribution of nutrition to the wellness of people with HIV in all stages of the disease, helping patients with AIDS to live a long and healthy life.

MATERIALS AND METHODS

The study material consisted of recent articles on the subject that were found mainly in the electronic database Medline and the Association of Greek Academic Libraries (HEAL-Link), with the following keywords: diet, HIV, and nutrition intervention. The exclusion criterion for articles was a language other than Greek or English.

Generally about AIDS

AIDS is an abbreviation of the English scientific term «Acquired Immune Deficiency Syndrome». It is a viral infection that can lead to serious and currently irreversible damage to the immune system [10].

The classic definition of AIDS includes patients with a definite diagnosis of opportunistic infection (pneumonia Karinio Pnefmonysti (PC) is the most typical) or with a tumor (mainly Kaposi's Sarcoma (KS)), which is a sufficient indicator of cellular immune deficiency, but with no other known causes or factors responsible for the immune deficiency [11].

A disease carrier is a person who is infected with the virus but not yet sick (that does not show any symptoms), also might be called HIV (+) person or HIV seropositive. This person transmits the virus to others through sex, blood, or birth [12].

Concerning the complications of the disease, malnutrition is a major complication of HIV infection, and has been recognized as an important predictor of the disease. Even if malnutrition occurs more often at the final stage of the disease, it can also occur at its onset, before severe immunosuppression is triggered [13].

Malnutrition is described as an imbalance between intake and the body's needs that leads to metabolic disorder, decreased body function and body mass loss, or as a state of nutrition in which a deficiency or imbalance of energy, protein and other nutrients causes measurable negative effects in tissues and / or body shape [14].

Moreover, the virus particularly affects the nutritional status of the patient, increasing the energy requirements, and negatively affecting the absorption of nutrients and metabolism, which lead

to cytokine activity and diarrhea [15]. Malnutrition enhances the viral effects in the person by weakening immune response and worsening immunosuppression, which adversely affects the overall outcome of the disease [16].

Diet of patients with AIDS

The goal of nutritional assessment is to understand the patient's nutritional status in order to develop a nutritional care plan that should consist of nutritional goals, nutritional services, and medical care. Nutritional assessment involves gathering information about the socio-economic characteristics, medical history, eating habits, anthropometric, clinical, and biochemical measurements, and current treatment [17]. The assessment of dietary intake evaluates the adequacy of food and nutrients consumed. It includes evaluating the dietary patterns, frequency of meals, and factors affecting food choice. The real goal is to improve the AIDS patient's ability to consume a sufficient quantity and variety of foods that covers their nutritional needs [18].

There are a number of factors that influence the nutritional needs of people living with HIV e.g. age, physical activity, clinical stages of health, metabolism, and viral load. For example, the absence or presence of symptoms such as fever, diarrhea, weight loss, and wasting can alter appropriate uptake. People with HIV need a diet that will provide them with nutrients that meet their increased nutritional needs [5].

People with HIV have higher energy requirements. While there is no definitive answer regarding the appropriate increase of energy intake, there is strong justification for increasing energy intake for those at an advanced stage or for supporting medical interventions [19].

There is no evidence for increased protein requirement above and beyond that required in balanced nutrition to meet total energy needs. For the nutritional care of people with HIV and infectious diseases, the goal for protein intake should be 1.2 g/kg of body weight per day in the stable phases of the disease, and can be increased to 1.8 g/kg in acute situations [20].

The recommended intake of fat is the same as for uninfected individuals, specifically no more than 30-35% of total energy needs. However, HIV patients who take certain antiretroviral drugs or with certain infection signs, such as diarrhea, may require changes in the time or amount of fat intake [21].

Also the use of vitamins and mineral supplements is considered a popular adjunctive therapy [22]. Vitamin A supplement administration has been shown to reduce diarrhea-associated mortality [23]. But also vitamin E supplements (800 mg/day) reduce oxidative stress, promote the reduction of viral load, and may enhance cell viability in individuals receiving anti-retroviral therapy [24]. Vitamin D supplements may also provide additional benefits regarding the reduction of HIV transmission, disease evolution, and immunological benefits [25]. It should be noted that taking vitamin D and calcium supplements prevents the appearance of secondary hyperparathyroidism that usually occurs in HIV patients treated with Tenofovir [26].

Furthermore, the physical, psycho-social and environmental context in which people with HIV live may affect their nutritional status [27]. For example, an HIV patient suffering from occasional infections may show difficulty in buying, preparing and consuming food while poverty, lack of refrigeration or lack of appropriate facilities may limit food choice. The amount of food consumed can also be limited by factors such as substance/alcohol abuse, depression, or senile dementia [18].

Nutrition counseling of patients with AIDS

The goal of nutritional intervention is the prevention or inversion of weight loss. This is achieved by improving appetite and nutrient absorption, treating all the direct causes of anorexia and malabsorption such as mouth ulcers and diarrhea, improving the intake of calories from high fat diets in protein and low fat content, with or without adding micronutrient supplements and by rectifying psychosocial problems such as poverty and depression by providing social and psychological support [28].

The supply of nutrients through diet or parenteral nutrition can reverse metabolic disorders. However, in the wasting syndrome associated with AIDS, dietary intervention is not effective until the underlying causes of wasting are corrected [29].

Nutritional counseling is vital to ensure that patients have balanced nutrition, paying special attention to macronutrients and micronutrients. The goal of dietary counseling is to improve food quality in order to cover the required needs for energy, protein and minerals, as well as to increase intake due to changes in REE [30].

Finally, general dietary recommendations should be provided to patients so that they can overcome the various problems affecting food intake and consequently weight [31]. It is useful for patients to keep a detailed diary of foods, drinks and snacks consumed in order to assess their nutritional status [32].

Patients may benefit from small frequent meals with foods of their choice while large portions may discourage intake [5]. Pureed foods and liquids are indicated in patients with dysphagia. In patients with nausea and vomiting symptoms, the consumption of small and dry meals, without a

strong flavor, is recommended [33]. In people with diarrhea, a lactose-free diet, low in fiber and semi-solid foods is recommended [34].

CONCLUSIONS

Diet has always been an important aspect of HIV care. The treatment of people with HIV infection should include the optimum dietary intervention in order to help them live a long and healthy life [35]. Maintaining a good nutritional status has a significant impact on the functioning of the immune system and the overall health of people living with HIV/AIDS [36]. It has also been suggested that good nutrition can contribute to the wellbeing of people with HIV at all stages of the disease and may even extend life expectancy [37].

There are several tools that are used to make dietary intake assessments, such as: food diaries, dietary history, and the 24-hour recall and food frequency questionnaire. The method should be chosen according to the particular characteristics of the patients. It is better to use a combination of methods that will adequately reflect normal intake, dietary preferences, food intolerances, and any changes that may undermine the nutritional intake of each patient.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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1 OrganicResponse to Stress

Maria Isabel Toulson Davisson Correia

contents

Introduction

The organic response to stress, first described as the metabolic response to trauma, in 1942, by Sir David Cuthbertson, is a physiologic phenomenon secondary to any insult to the body. Cuthbertson [1] introduced the terms *ebb* and *flow* to describe the phases of hypo- and hypermetabolism that follow traumatic injury. Such phenomenon is triggered by multiple stimuli, including arterial and venous pressure derangements, changes in volume, osmolality, pH, and arterial oxygen content. Also, pain, anxiety, and toxic mediators from tissue injury and infection trigger the organic response (Table 1.1). These stimuli reach the hypothalamus stimulating the sympathetic nervous system and the adrenal medulla. This physiological response to an insult might become pathological depending on the intensity and duration of injury. The organic response can be seen as the "fight or flight" response to adverse phenomena that can become highly associated with increased morbidity and mortality if perpetuated for long periods. The ultimate goal of the organic response is to restore homeostasis. Intermediate goals are to limit further blood loss; to increase blood flow, allowing greater delivery of nutrients and elimination of waste products; and to debride necrotic tissue and to initiate wound healing.

Currently, with the development of medical sciences, the once "simple" metabolic response to stress (represented by the ebb and flow phases) has evolved into a complicated and intricate web of responses. Therefore, a better appropriate denomination such as the organic response to stress that encompasses several body compartments should be used. Although, one cannot fully go against

table 1.1
organic response to stress: triggering Factors

- Body temperature (hypo and hyperthermia)
- Excessive bleeding (shock)
- Fluid and electrolyte derangements
- Infection
- Inflammation
- Pain
- Poor nutritional status
- Prolonged fasting
- Psychological problems

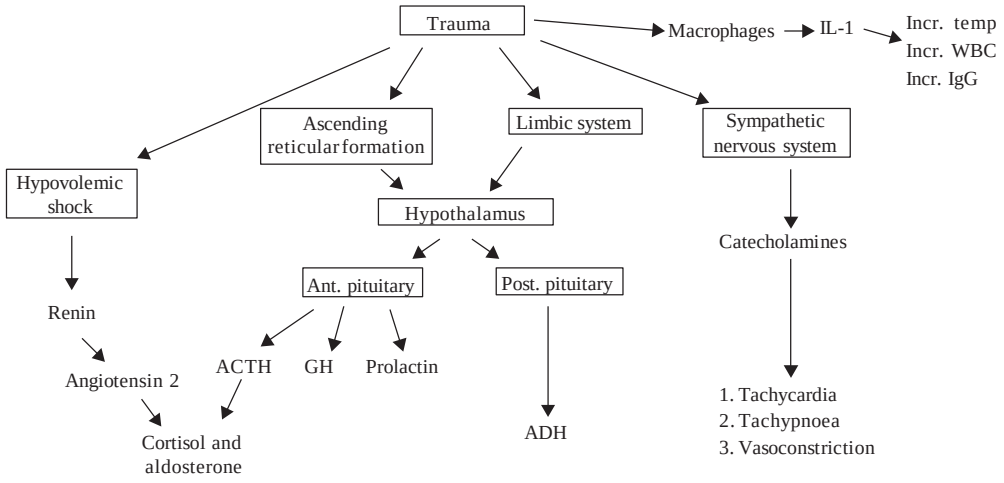

Figure 1.1 Organic Response to Stress.

its development, recognizing its magnitude and knowing its different particularities might help minimize the risks of perpetuating its duration, leading to the reduction of morbidity and mortality related to it. In surgical stress, especially under major elective conditions, it's important for surgeons to be aware that a perfect anatomic operation maybe followed by a disastrous outcome if patients are not metabolically conditioned. Undernutrition, pain control, and fluid and electro- lyte balance, among others, are of paramount importance and should be dealt in a multimodal approach to decrease the organic response to trauma [2–6]. Therefore, it is extremely important to be acquainted with the complex mechanisms of the organic response (Figure 1.1) in order to act early and, maybe, prevent some of its deleterious effects.

The magnitude of the response and the adequate initial approach are determinant factors that might influence the patient's outcome [2,5,7–9]. The severity of the hypermetabolic phenomena thereafter might lead to the systemic inflammatory response syndrome (SIRS), the amplified generalized body response, which may culminate with multiorgan dysfunction and death.

stress

Stress is a term applied to the fields of physiology and neuroendocrinology and refers to those forces or factors that cause disequilibrium to an organism and therefore threaten homeostasis [10]. The stressors might be a consequence of physical injury, mechanical disruptions, chemical

changes, or emotional factors. The body's response to these factors will depend on their magnitude, duration, as well as the nutritional status of the patient. Complex sensory systems trigger reflex nervous system responses to the stressors that alert the central nervous system (CNS) of the disturbance. In the CNS, neurons of the paraventricular nucleolus of the hypothalamus elaborate corticotropin-releasing hormone (CRH) and activate the hypothalamic–pituitary–adrenal axis (HPA). In addition, other areas of the brain also signal the peripheral autonomic nervous system. These two latter systems elicit an integrated-response, referred collectively as the "stress response," which primarily controls bodily functions such as arousal, cardiovascular tone, respiration, and intermediate metabolism [1]. Other functions such as feeding and sexual behavior are suppressed, while cognition and emotion are activated. In addition, gastrointestinal activity and immune/inflammatory responses are altered.

Historical Perspective

Sir David Cuthbertson, a chemical pathologist in Glasgow, was the first physician studying the metabolic response to injury in the early part of the twentieth century, by following patients with long bone fractures [1]. However, long before Cuthbertson's studies, John Hunter, in his *Treatise on the Blood, Inflammation and Gunshot Wounds* [11], was the first to question the paradox of the response to injury by saying: "Impressions are capable of producing or increasing natural actions and are then called *stimuli*, but they are likewise capable of producing too much action, as well as depraved, unnatural, or what we commonly call diseased action." He must have intuitively perceived that nature might have created these responses in order to have some advantages in terms of recovery, but he also noticed that if the responses were overexaggerated, life could be jeopardized.

The concept that illness was associated with an increased excretion of nitrogen leading to negative nitrogen balance was defined in the late nineteenth century. During the First World War, studies carried out by DuBois [12] showed that an increase in 1°C in temperature was associated with a 13% increase in the metabolic rate.

Cuthbertson's findings were derived from questions aroused by orthopedic surgeons who were eager to find out why patients with fractures of the distal third of the tibia were slow to heal. His studies were negative in the sense that he could not offer the exact explanation to the question, but at the same time, he came up with something much more interesting and fundamental. He measured the excretion of calcium, phosphorus, sulfate, and nitrogen in the urine and found that the amount of excreted phosphorous and sulfate in relation to calcium was higher than expected if all these elements had come from the bone. He went on to show that this was a catabolic phenomenon related to breakdown of protein, reflecting an increase in metabolic rate. The association between the systemic metabolic response and hormonal elaboration was soon sought, but this approach was initially hampered by methodological problems. The investigations carried out by Cannon [13] on the autonomic nervous system suggested the increased catecholamine response to illness as one of the explanations of the physiologic responses seen by Cuthbertson. Later, Selye proposed corticosteroids as the main mediators of the protein catabolic response [14]. However, the following question still remained unanswered: what was the signal that initiated and propagated the immediate elaboration of the adrenal cortical hormones? Hume [15] and Egdahl [16] showed that in injured dogs (operative injury or superficial burn to the limbs) with intact sciatic nerves or spinal cords, there was an increase of adrenal hormones, contrary to what happened in those animals with transected nerves or spinal cords, in whom the response was abated. From the investigated setting, it was possible to identify afferent nervous signals as essential components to trigger the HPA stress response.

Allison et al. [17] showed that such organic response was also associated with suppression of insulin release, followed by a period of insulin resistance and with high glucagon and growth hormone (GH) levels. Recently, the organic response has been associated not only

with neuroendocrine alterations but it is also accompanied by inflammatory responses and mediators as well as immunologic dysfunctions.

organic response to stress (table 1.2)

Ebb and Flow Phases

Cuthbertson [1] originally divided the organic response into an ebb and a flow phase. The ebb phase begins immediately after injury and typically lasts 12–24 h, if the initial injury is under control. However, this phase may last longer depending on the severity of trauma and the adequacy of resuscitation. The ebb phase may equate with prolonged and untreated shock, a circumstance that is more often seen in experimental animals than in clinical practice. It is characterized by tissue hypoperfusion and a decrease in overall metabolic activity. In order to compensate this, catecholamines are discharged with norepinephrine being the primary mediator of the ebb phase. Norepinephrine is released from peripheral nerves and binds to $beta_1$ receptors in the heart and alpha and $beta_2$ receptors in peripheral and, to a lesser degree, splanchnic vascular beds. The most important effects are the cardiovascular, because norepinephrine is a potent cardiac stimulant, causing increased contractility and heart rate and vasoconstriction. These phenomena are attempts to restore blood pressure and increase cardiac performance and maximal venous return.

Hyperglycemia may be seen during the ebb phase. The degree of hyperglycemia parallels the severity of injury. Hyperglycemia is promoted by hepatic glycogenolysis secondary to catecholamine release and by direct sympathetic stimulation of glycogen breakdown.

Some authors have investigated the ebb phase in experimental animals and human beings [18] and have noticed important aspects, such as that after sustained long fractures, with concomitant great loss of blood, there is an impairment of vasoconstriction, which is not seen in bleeding events alone, such as that seen in duodenal ulcer bleeding. In another study, Childs et al. [19] showed an effect of injury on impairing thermoregulation in injured subjects who presented with reduced vasoconstriction in response to cold stimulus.

The onset of the flow phase that encompasses the catabolic and anabolic phases is signaled by high cardiac output with the restoration of oxygen delivery and metabolic substrate. The duration of this phase depends on the severity of injury or the presence of infection and development of complications (Table 1.3). It typically peaks around the third to the fifth day, subsides by 7–10 days, and merges into an anabolic phase over the next few weeks. During this hypermetabolic phase, insulin release is high but elevated levels of catecholamines, glucagon, and cortisol counteract most of its metabolic effects.

table 1.2
organic response to stress

The organic response is related to

- Magnitude (severity)
- Duration (the longer the more severe)
- Nutritional status of the patient (malnourished patients do worse)
- Associated diseases (increase morbidity and mortality)
  - Diabetes
  - Heart disease
  - Pulmonary
  - Immunologic
  - Others

table 1.3
Metabolic response to stress

- The ebb and flow phases
  - Glucose and protein metabolism
- Fluid and electrolyte response
- Endocrine response
  - HPA
  - Thyrotropic axis
  - Somatotropic axis
  - Lactotropic axis
  - Luteininizing hormone-testosterone axis
- Inflammatory response
- Immunologic response

Increased mobilization of amino acids and free fatty acids from peripheral muscles and adipose tissue stores result from this hormonal imbalance. Some of these released substrates are used for energy production—either directly as glucose or through the liver as triglyceride. Other substrates contribute to the synthesis of proteins in the liver, where humoral mediators increase production of acute phase reactants. Similar protein synthesis occurs in the immune system for the healing of damaged tissues. While this hypermetabolic phase involves both catabolic and anabolic processes, the net result is a significant loss of protein, characterized by negative nitrogen balance and also decreased fat stores. This leads to an overall modification of body composition, characterized by losses of protein, carbohydrate, and fat stores, accompanied by enlarged extracellular (and, to a lesser extent, intracellular) water compartments.

Glucose and Protein Metabolism

Glucose is always fundamental independently of which organic response phase the patient is in. Dr. Jonathan Rhoads pointed out that providing 100 g of glucose guarantees energy to cells that solely rely on this substrate such as neurons and red cells and allows the body to use fat stores and some muscle protein for the remaining energy needs [20]. During simple starvation without any stress condition, glucose infusion inhibits hepatic gluconeogenesis, but after injury, despite the high con- centration of circulating glucose, gluconeogenesis prevails. AQ1

The amino acids released from protein catabolism in muscle are largely taken up by the liver for new glucose production, rather than being used as fuel to meet energy demands. The latter are provided by the fat reserve (about 80%–90%) [21]. The reason why injured patients need such a high rate of endogenous glucose production may be explained by the high demand of injured tissues for glucose. Wilmore et al. showed that patients with severe burns in one leg and with minor injury to the other had a fourfold increase of glucose uptake by the burnt limb [22]. At the same time, the burnt leg produced higher amounts of lactate, suggesting anaerobic respiration. The lactate is then returned to the liver for gluconeogenesis, in the so-called Cori cycle, which is metabolically expensive. One mole of glucose yields two ATP through glycolysis, but via gluconeogenesis costs three ATP. This may contribute to the underlying increase in the metabolic rate (Figure 1.2).

Insulin has an anabolic or storage effect by synthesizing large molecules from small molecules and inhibiting catabolism. It also promotes glucose oxidation and glycogen synthesis, whereas it inhibits glycogenolysis and gluconeogenesis. On the other hand, the catabolic hormones, such as catecholamines, cortisol, and glucagons, enhance glycogenolysis and gluconeogenesis.

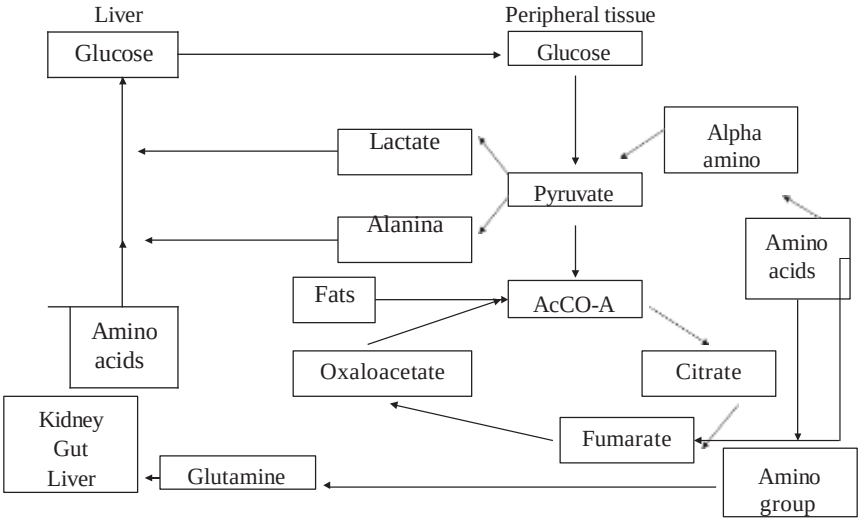

Figure 1.2 Aerobic glycolysis and Cori cycles.

Fluid and Electrolyte Response

Hypovolemia prevails in the ebb phase and is entirely reversible with appropriate fluid administration. However, in the absence of volume resuscitation, within 24 h, mortality is nearly uniform [23]. The patient's initial response to hypovolemia is targeted to keep adequate perfusion to the brain and the heart in detriment of the skin, fat tissue, muscles, and intra-abdominal structures. The oliguria, which follows injury, is a consequence of the release of antidiuretic hormone (ADH) and aldosterone. Secretion of ADH from the supraoptic nuclei in the anterior hypothalamus is stimulated by volume reduction and increased osmolality. The latter is mainly due to increased sodium content of the extracellular fluid. Francis Moore coined the terms "the sodium retention phase" and "sodium diuresis phase" of injury to describe the antidiuresis of both salt and water in the flow phase [24]. Volume receptors are located in the atria and pulmonary arteries, and osmoreceptors are located near ADH neurons in the hypothalamus. ADH acts mainly on the connecting tubules of the kidney but also on the distal tubules to promote reabsorption of water. Aldosterone acts mainly on the distal renal tubules to promote reabsorption of sodium and bicarbonate and increase excretion of potassium and hydrogen ions. Aldosterone also modifies the effects of catecholamines on cells, thus affecting the exchange of sodium and potassium across all cell membranes. The release of large quantities of intracellular potassium into the extracellular fluid is a consequence of protein catabolism and may cause a rise in serum potassium, especially if renal function is impaired. Retention of sodium and bicarbonate may produce metabolic alkalosis with impairment of the delivery of oxygen to the tissues. After injury, urinary sodium excretion may fall to 10–25 mmol/24 h and potassium excretion may rise to 100–200 mmol/24 h. Intracellular fluid and exogenously administered fluid accumulate preferentially in the extracellular third space because of increased vascular permeability and relative increase in interstitial oncotic pressure. This is the reason most patients become so edematous after the first days following injury and resuscitation.

Endocrine Response

Hypothalamic–Pituitary–adrenal axis

The hypothalamus secretes CRH in response to the stress stimuli. CHR stimulates the production, by the pituitary, of adrenocorticotropic hormone (ACTH), also known as corticotropin, which as its name implies, stimulates the adrenal cortex. More specifically, it triggers

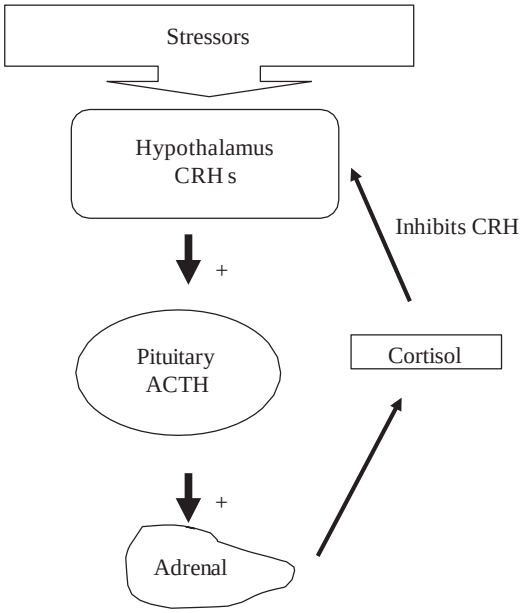

Figure 1.3 The hypothalamic–pituitary–adrenal axis.

the secretion of glucocorticoids, such as cortisol, and has little control over the secretion of aldosterone, the other major steroid hormone from the adrenal cortex. CRH itself is inhibited by glucocorticoids, making it part of a classical negative feedback loop (Figures 1.1 and 1.3). It seems that the secretion of aldosterone is most likely under the control of an activated renin–angiotensin system.

Hypercortisolism acutely shifts carbohydrate, fat, and protein metabolism, so that energy is instantly and selectively available to vital organs such as the brain, and anabolism is thus delayed. Intravascular fluid retention and the enhanced inotropic and vasopressor response to catecholamines and angiotensin II offer hemodynamic advantages in the "fight and flight" response. This hypercortisolism can be interpreted as an attempt of the organism to mute its own inflammatory cascade, thus protecting itself against over-responses [25].

Serum ACTH was found to be low in chronic critical illness, while cortisol concentrations remained elevated, suggesting that cortisol release may be driven through alternative pathways, possibly involving endothelin [26].

thyrotropic axis

Serum levels of T3 decrease, within 2 h after surgery or trauma, whereas T4 and TSH briefly increase. AQ2
Apparently, low levels of T3 are due to a decreased peripheral conversion of T4. Subsequently, circulating levels of TSH and T4 often return to "normal" levels, whereas T3 levels remain low. It is important to mention that the magnitude of T3 decrease has been found to reflect the severity of illness. Several cytokine mediators, mainly tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6), have been investigated as putative mediators of the acute low T3 levels [27].
Teleologically, the acute changes in the thyroid axis may reflect an attempt to reduce energy expenditure, as in starvation.

A somewhat different behavior is seen in patients remaining in intensive care units for longer periods. It has been seen that there is a low-normal TSH values and low T4 and T3 serum concentrations. This seems to be reduced due to reduced hypothalamic stimulation of the thyrotropes, in turn leading to reduced stimulation of the thyroid gland. Endogenous dopamine and prolonged hypercortisolism may play a role in this phenomenon. When exogenous dopamine and glucocorticoids are given, hypothyroidism is provoked or aggravated, in critical illness [28].

somatotropic axis

Circulating levels of GH become elevated, and the normal GH profile, consisting of peaks alternating with virtually undetectable troughs, is altered with peak GH and interpulse concentrations being high and the GH pulse frequency being elevated. This happens throughout the first hours or days of an insult, be it surgery, trauma, or infection. In physiological situations, GH is released from the pituitary somatotropes in a pulsatile fashion, under the interactive control of the hypothalamic GH-releasing hormone (GHRH), which is stimulatory, and somatostatin, which exerts an inhibitory effect. Apparently, after stress, it seems that withdrawal of the inhibitory effect of somatostatin and the increased availability of stimulatory GH-releasing factors (hypothalamic or peripheral) could hypothetically be involved. It has also been suggested that there seems to be acquired peripheral resistance to GH, and these changes are brought about by the effects of cytokines, such as TNF alpha, IL-1, and IL-6 [29]. GH exerts direct lipolytic, insulin-antagonizing, and immune-stimulating actions. Such changes prioritize essential substrates such as glucose, free fatty acids, and amino acids toward survival rather than anabolism.

In chronic illness, the changes in the somatotropic axis are different. GH secretion is chaotic and reduced compared with the acute phase. Although the nonpulsatile fraction is still elevated and the number of pulses is high, mean nocturnal GH serum concentrations are scarcely elevated and substantially lower than in the acute phase of stress. One of the possibilities that explain this situation is that the pituitary is taking part in the "multiple organ failure syndrome" becoming unable to synthesize and secrete GH [29]. Another explanation could be that the lack of pulsatile GH secretion is due to increased somatostatin tone or to reduced stimulation by endogenous releasing factors, such as GHRH.

lactotropic axis

Prolactin was among the first hormones known to have increased serum concentrations after acute physical or psychological stress [29]. This increase might be mediated by oxytocin, dopaminergic pathways, or vasoactive intestinal peptide (VIP). Inflammatory cytokines may be the triggering factor. Changes in prolactin secretion in response to stress might contribute to altered immune function during the course of critical illness. In mice, inhibition of prolactin release results in impaired lymphocyte function, depressed lymphokine-dependent macrophage activation, and death from normally nonlethal exposure to bacteria [30]. It remains unclear if hyperprolactinemia contributes to the vital activation of the immune cascade, after the onset of critical illness. In the chronic setting of critical illness, serum prolactin levels are no longer as high as in the acute phase.

luteinizing Hormone–testosterone axis

Testosterone is the most important endogenous anabolic steroid hormone. Therefore, changes within the luteinizing hormone–testosterone axis in the male may be relevant for the catabolic state in critical illness, in which there are low testosterone levels. The exact cause is unclear, but cytokines may once again be enrolled in this phenomenon [31]. Hypothesizing over the low testosterone levels, it may be important to switch off anabolic androgen secretion, in acute stress, in order to conserve energy and metabolic substrates for vital functions [32].

In chronic states, circulating testosterone levels become extremely low, in fact almost undetectable. Endogenous dopamine, estrogens, and opiates might be the cause for the low levels.

Inflammatory response

The local inflammatory response is part of the body's attempt to restore homeostasis, particularly healing, which in most situations after injury is successful (Figure 1.4). However, at times, this is not the case and deviations occur, leading to a perpetuated response that may jeopardize survival such as in the SIRS. In the latter, inflammation is triggered at sites remote from the site of initial injury. In some cases, SIRS progresses to multiple organ dysfunction syndrome (MODS), which is associated with high mortality rates.

The physiologic inflammatory response to trauma is a complex cellular and molecular event, in which inflammatory cells such as polymorphonuclear cells (PMNs), macrophages, and lymphocytes

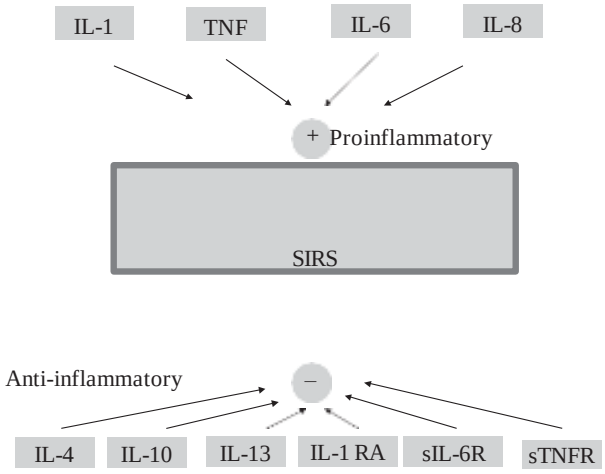

Figure 1.4

AQ3

are recruited to the site of injury and secrete inflammatory mediators. The endothelium at the site of injury also participates. PMNs are the first cells arriving at the site of injury and release potent oxidizing molecules, including hydrogen peroxide, hypochlorous acid, oxygen-free radicals, proteolytic enzymes, and vasoactive substances, such as leukotrienes, eicosanoids, and platelet-activating factor (PAF). There is evidence that PAF is partially responsible for the increased permeability in sepsis and shock [33]. Oxygen-free radicals are proinflammatory molecules causing lipid peroxidation, inactivation of enzymes, and consumption of antioxidants. PMNs release proteolytic enzymes, which activate the kinin/kallikrein system. In turn, this system stimulates the release of angiotensin II, bradykinin, and activated plasminogen. Bradykinin causes vasodilatation and mediates increased vascular permeability.

Macrophages are activated by cytokines and engulf invading organisms. They also debride necrotic host tissue and elaborate additional cytokines. TNF alpha (synthesized by macrophages) and IL-1 beta (synthesized by macrophages and endothelial cells) are the proximal proinflammatory mediators. These cytokines initiate the elaboration and release of other cytokines, such as IL-6. Monocytes, macrophages, neutrophils, T and B cells, endothelial cells, smooth muscle cells, fibroblasts, and mast cells secrete this cytokine. It is probably the most potent inductor of acute phase response, although its exact role in the inflammatory response remains unclear. On the other hand, it is considered to be the most reliable prognostic indication of outcome, particularly in sepsis because it reflects the severity of injury [34].

Il-8 belongs to a group of mediators known as chemokines because of their ability to recruit inflammatory cells to the sites of injury. It is synthesized by monocytes, macrophages, neutrophils, and endothelial cells. It is also used as an index of magnitude of systemic inflammation and it seems to be able to identify those patients who will develop MODS [35]. High levels of IL-6 and IL-8 in alveolar washouts, 2 h after injury, have been reported, suggesting that the alveoli might be the first structures suffering with the metabolic response to stress [36]. These high levels might be used, in the future, as prognostic factors to the development of multiorgan dysfunction syndrome.

IL-4 and IL-10 are anti-inflammatory cytokines, synthesized by lymphocytes and monocytes and exert similar effects. They inhibit the synthesis of TNF alpha, IL-1, IL-6, and IL-8.

Nitric oxide (NO) is elaborated by various cell types, including endothelial cells, neurons, macrophages, smooth muscle cells, and fibroblasts. NO mediates vasodilatation and regulates vascular tone. NO is probably a key mediator in the pathophysiology of stress and shock.

Acute-phase reactants are produced in the liver in response to injury in order to maintain homeostasis. Its production is induced by cytokines. These proteins function as opsonins (C-reactive protein), protease inhibitors ($alpha_1$-proteinase), hemostatic agents (fibrinogen), and transporters (transferring). Albumin is a negative acute phase protein and its synthesis is curtailed by inflammation.

Immunologic response

The inflammatory mediators (TNF-α, IL-1, and IL-6) release substrates, from host tissues, to support T and B lymphocyte activity and, therefore, create a hostile environment for invading pathogens. This is an integral part of the body's response to infection and injury. Such inflammatory mediators raise body temperature and produce oxidant substrates that initiate downregulation of the process once invasion has been defeated. Nonetheless, this mechanism poses considerable cost to the host and according to its magnitude and duration might lead to the SIRS. The latter might cause the MODS, in some patients. The majority of patients survive SIRS without developing early MODS and, after a period of relative clinical stability, manifest a compensatory anti-inflammatory response syndrome (CARS) with suppressed immunity and diminished resistance to infection.

The interaction between the innate and adaptive immune systems seems to be important inductor of both SIRS and CARS. T cells from the adaptive immune system play a role in the early SIRS response to injury and in CARS. Other possible mediators of CARS include prostaglandins of the E series. Also, products of complement activation seem to induct TNF alpha production. In summary, the SIRS, which regularly occurs after serious injury and in some cases proves fatal to the individual, has been partially characterized by both clinical and animal researches. However, the triggering mechanisms and signaling systems involved in inducing and maintaining it are incompletely understood and defined.

conclusIons

The organic response consists of the complex hydroelectrolytic, hematological, hormonal, metabolic, inflammatory, and immunologic changes that follow injury or trauma. It is the body's life-saving process that will definitely impact on patients' outcomes according to the way it is approached. Therefore, it is currently accepted that the best way to face such situation is by providing a series of multimodal attitudes, which encompass good nutrition status, short preoperative fasting time, intraoperative body temperature control, adequate fluid administration, pain control and early oral or enteral nutrition, as well as early mobilization among others. Most of these recommendations are easily accomplished at very low cost.

In summary, the organic response is a physiological phenomenon that tries to protect the body against any aggression. However, when it is too intense and lasts for longer periods, it is associated with higher morbidity and mortality. In order to avoid such situation, it is of utmost importance to be aware of the different facets and comply with the several attitudes that might be able to decrease the magnitude of the response. Nonetheless, these interventions, especially those that have tried to abrogate it, should be seen with caution and under protocol control because attenuating or abolishing the organic response may not be without risk, with the latter placing responsibility on the care provider to be fully aware of the possible side effects. Future research, especially in the area of genetics and molecular biology, will no doubt help understand several aspects not currently known.

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Nutrition Therapy in Sepsis

Paul E. Wischmeyer, MD, EDIC

KEYWORDS

• Protein • Parenteral nutrition • Enteral nutrition • Calories • Lean body mass
• Lipids

KEY POINTS

- Sepsis is characterized by early massive catabolism, lean body mass (LBM) loss, and escalating hypermetabolism persisting for months to years.
- Early enteral nutrition should attempt to correct micronutrient/vitamin deficiencies, deliver adequate protein (**w**1.0 g/kg/d), and moderated nonprotein calories (**w**15 kcal/kg/d), as well-nourished patients can generate significant endogenous energy for a limited period.
- After resuscitation, increasing protein (1.5–2.0 g/kg/d) and calories is needed to attenuate LBM loss and promote early mobility and recovery.
- Following ICU, significant protein/calorie delivery for months to years is required to facilitate functional and LBM recovery, with high protein oral supplements being essential to achieve adequate nutrition (>3000 kcal/d and higher protein [>1.5 g/kg/d] likely needed).
- Screening for preillness malnutrition is essential, with supplemental parenteral nutrition added if the protein/calorie goals are not met with timeliness, depending on the preillness nutrition/LBM status.

INTRODUCTION

Sepsis, requiring care in the intensive care unit (ICU), is characterized by an acute catabolic response leading to rapid mobilization of energy stores, as muscle, glycogen, and lipid stores are broken down to drive glucose production.[1,2] This catabolism contributes to rapid loss of lean body mass (LBM) contributing to muscle wasting, weakness, and loss of physical function commonly known as ICU-acquired weakness (ICU-AW) or post-ICU syndrome (PICS).[3] This LBM loss is exacerbated by sepsis-induced anorexia

Disclosure Statement: P.E. Wischmeyer is an associate editor of *Clinical Nutrition* (Elsevier), has received grant funding related to this work from the NIH NHLBI R34 HL109369, Canadian Institutes of Health Research, Baxter, Fresenius, Lyric Pharmaceuticals, Isomark LLC, and Medtronics. He has served as a consultant to Nestle, Abbott, Fresenius, Baxter, Medtronics, Nutricia, Lyric Pharmaceuticals, and Takeda for research related to this work. He has limited ownership shares in Isomark for his consulting work with Isomark, which has otherwise been unpaid in nature. He has received honoraria or travel expenses for lectures on improving nutrition care in illness from Abbott, Fresenius, and Medtronics.
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Crit Care Clin 34 (2018) 107–125
http://dx.doi.org/10.1016/j.ccc.2017.08.008 criticalcare.theclinics.com

and the inability to take nutrients by mouth volitionally for days to months.[4] Unless nutrition therapy is provided via enteral or parenteral routes, patients also accumulate a rapidly evolving energy deficit, which further contributes to muscle wasting and worsened outcomes.[5–7] This illness and, unfortunately, iatrogenic starvation are superimposed on the marked inflammatory and endocrine-mediated acute-phase stress response. Critically ill (burns) patients can lose as much as 1 kg of LBM per day.[8] Other ICU patients also have significant LBM loss, much of it in the first 7 to 10 days of their ICU stay.[9] Patients often regain weight after the ICU stay, but much of this is only fat mass rather than functional LBM.[10] This finding is not surprising, as data from burn ICU patients demonstrate that catabolism and subsequent increasing hypermetabolism following injury can persist for up to 2 years following discharge from the hospital; this can markedly hinder recovery of LBM and function.[8]

This evolutionarily conserved stress response allows the injured or septic human to generate energy to escape an attacker and recover from initial illness in a period when food gathering and consumption would initially be limited. Before the relatively recent (evolutionarily) development of ICU and hospital care, this period of cachexia and catabolism was self-limited, likely to a few days. The injured or infected (septic) human escaped its attacker and then either improved and reinitiated volitional nutrition intake or death occurred. However, modern ICU care now allows prolonged survival from sepsis via the ability to provide vital organ support for extended periods of time, making previously unsurvivable septic insults now survivable. In fact, innovations in ICU care have recently led to an almost yearly reduction of hospital mortality from sepsis.[11] However, these same data reveal many patients with sepsis are not returning home to functional lives after ICU discharge but instead to rehabilitation settings where it is unclear if they ever returned to a meaningful quality of life (QoL). In fact, in the same period that in-hospital ICU mortality seems to be declining, there has been a tripling in the number of patients going to rehabilitation settings.[11] Up to 40% of mortality within the first year of ICU stay occurs following ICU discharge.[12] Unfortunately, for those who do survive, nearly half will not return to work in the first year after discharge,[13] often because of PICS and ICU-AW.[3]

A growing body of data indicates that persistent underfeeding throughout the ICU stay, particularly protein underfeeding, may significantly contribute to long-term mortality and QoL impairment months later.[5,14–16] If we are to optimize recovery from sepsis and critical care, we need to consider basic metabolism and a historic understanding of starvation and recovery to use targeted nutritional care to our critically ill patients with sepsis. The focus of modern ICU nutrition therapy and research efforts should emphasize the realization that nutritional needs change over the course of a septic illness, as catabolism persists and increasing hypermetabolism evolves and persists, often for months to years.[9] Finally, screening for preillness malnutrition and the presence of nutritional risk (as defined by scores, such as the NUTRIC (Nutrition Risk in the Critically Ill) score,[17,18] or computed tomography [CT] LBM analysis[19]) is essential at diagnosis of sepsis. In patients found to have preexisting sarcopenia or malnutrition, parenteral nutrition (PN), with adequate protein delivery and modern balanced lipids, can be safely added when enteral nutrition (EN) is failing.

MANAGEMENT GOALS FOR NUTRITION IN SEPSIS

Acute Catabolic Phase of Sepsis

Acute phase: adequate protein and moderated nonprotein calories

As stated earlier, the early or acute phase of sepsis is characterized by massive mobilization of the body's calorie reserves as muscle, glycogen, and lipid stores are broken

down to generate glucose to support ATP production (Figs. 1 and 2, Table 1A).[1,2] This metabolic response to stress can generate 50% to 75% of glucose needs during illness[2] and is not suppressed by feeding or intravenous glucose infusion.[16] Further, the early acute phase of sepsis and trauma are not hypermetabolic states; rather, patients have a total energy expenditure (TEE) to resting energy expenditure (REE) ratio of 1.0 and 1.1 for sepsis and trauma, respectively.[20] Thus, caloric need does not consistently increase in the early phases of sepsis. In fact, the more severe the septic shock, the lower the REE, as the body hibernates and reduces metabolism in response to severe sepsis.[21] This idea is shown in Table 1 in the context of caloric needs from the World Health Organization in health and the landmark Minnesota Starvation Study.[7] Data from Uehara and colleagues[20] demonstrate that REE in the first 2 to 5 days (acute phase) in elderly patients with sepsis (mean age: 67 years) is approximately 1850 kcal/d with a TEE of approximately 1920 kcal/d (giving a TEE of 25 kcal/kg). These data and other recent trials[22] suggest we should consider feeding less nonprotein calories early in the acute phase (first 24–96 hours) of critical illness and markedly increase calorie delivery during recovery as illustrated in Fig. 1. At the same time, it is well known that protein losses increase 4-fold in the first 24 hours of critical illness[23] and health carers are exceedingly poor at meeting these needs.[23] Unfortunately, large international surveys indicate ICU practitioners deliver an average of 0.6 g/kg/d of protein for the first 2 weeks following ICU admission.[6] This amount is 33% to 50% of the latest ICU guideline-recommended protein delivery of 1.2 to 2.0 g/kg/d.[24] In contrast to conventional teaching, the delivery of additional nonprotein calories does not significantly improve nitrogen balance in illness beyond delivery of 50% of predicted REE.[16] A secondary analysis of the pediatric PEPANIC (Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit) trial by the Vanhorebeek[25] group demonstrates that very early higher protein delivery may be associated with adverse outcomes, related possibly to inhibition of autophagy. Of note, increased lipid delivery early in critical illness was associated with earlier ICU

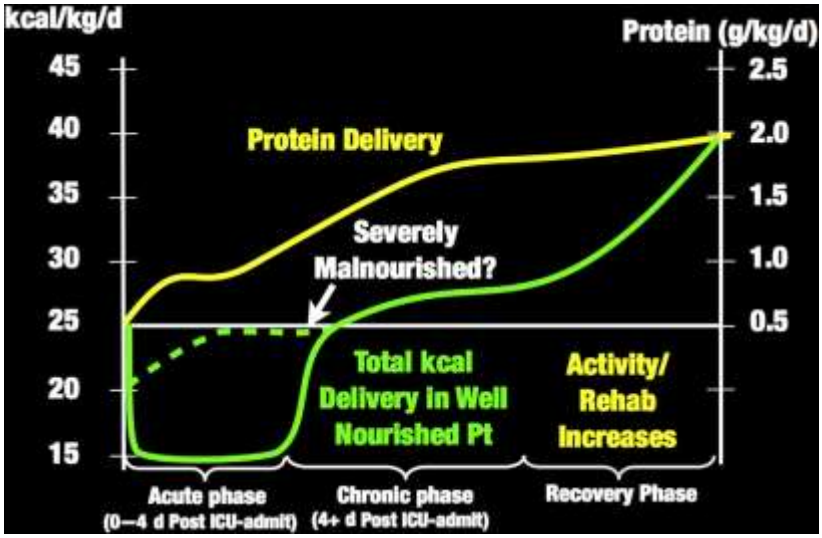

Fig. 1. Proposal for targeted nutrition delivery in sepsis. Pt, patient.

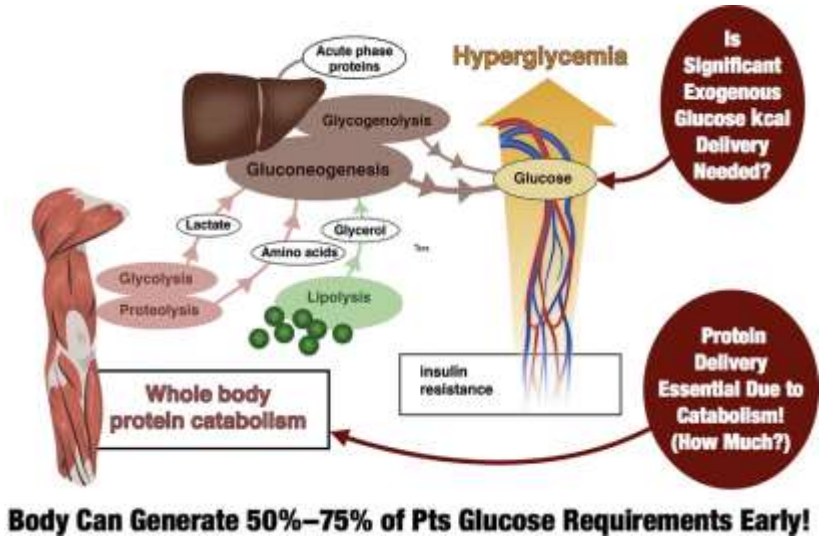

Fig. 2. Early acute-phase catabolic response to sepsis. Pts, patients. (*Adapted from* Gillis C, Carli F. Promoting perioperative metabolic and nutritional care. Anesthesiology 2015;123(6): 1455–72.)

discharge. These hypothesis-generating findings from this study leave the clinician in a challenging position with an essential need to provide protein during ICU recovery, yet it remains unclear currently how much to give and when to escalate protein delivery to guideline goals. Thus, an ideal targeted feeding strategy may perhaps be approximately 15 kcal/kg/d of total energy needs during the early ICU stay (acute phase: day 1–4), while ensuring patients receive an optimal lower protein delivery (**w**1.0 g/kg/d) as early as possible after ICU admission (see Fig. 1). Reduced calorie/protein delivery during the acute phase may not, however, be applicable in severely malnourished patients (ie, patients with significant pre-ICU weight loss or NUTRIC score [without interleukin 6 (IL-6) levels] **≤**5) who are unlikely to have the metabolic reserve to generate endogenous energy needs.[18,24] Ironically, the most recent guidelines from the Society of Critical Care Medicine (SCCM)/American Society for Parenteral and Enteral Nutrition (ASPEN) emphasize these points suggesting hypocaloric PN (**≤**20 kcal/kg/d or 80% of estimated energy needs) *with adequate protein (**≤**1.2 g protein per kilogram per day)* be considered in patients requiring PN over the first week in critical care.[24] In early sepsis, they suggest provision of trophic feeds (defined as 10–20 kcal/h, up to 500 kcal/d) for the initial phase of sepsis, advancing as tolerated after 24 to 48 hours to greater than 80% of the target energy needs with early delivery of *1.2 to 2.0 g of protein per kilogram per day*.[24] These data for moderated nonprotein calorie delivery are driven by recent large randomized controlled trials (RCTs) showing equivalent outcomes from trophic versus higher-energy feeding (nonprotein kilocalorie delivery).[26,27] The need for additional protein intake has been well described by Hoffer and Bistrian[14,15,28] in several recent publications questioning whether it is actually protein deficit and not calorie deficit that is important in improving outcomes in critical illness. Given the limited higher protein, lower kilocalorie EN options, total PN (TPN) or EN protein supplements may be required. TPN is now a significantly more viable option to achieve this goal, as 3 recent large trials of both

Table 1
Nutritional interventions in sepsis

Nutritional Intervention	Recommended Delivery/Dose	Rationale/Recent Evidence	References
A. Nutritional interventions in sepsis: acute phase (first 24–96 h in ICU until resuscitated)			
Early EN	Protein: **w**1.0 g/kg/d Nonprotein kcal: **w**15 kcal/kg/d (in well-nourished pts) • Benefit for key role of elevating lipid dose in nonprotein kcal delivery in day 1–4?	• Prevent LBM wasting, weakness, and infections to improve recovery • Concern for ↑↑ protein dose (>1.2–1.5 g/kg/d?) (day 1–4?) creating risk due to impaired autophagy	9,14,16,24–28
PN	• Well nourished: consider delay until day 3–7 if <60% EN protein/kcal goal • Malnourished pts: start at ICU admit goal: **w**1.2 g/kg/d protein total kcal **w**15–20 kcal/kg/d	• Prevent caloric deficit early to reduce LBM loss, enhance recovery, physical function, and QoL • Signal of benefit in pts failing EN, EN contraindications, or pre-ICU malnutrition • No increased risk of infection over EN or other IV fluid delivery from TPN	2,5,9,15–18,22,24,25,29–31
Prokinetics and/or postpyloric feeding	Consider metoclopramide or erythromycin for GRVs >500 or feeding intolerance symptoms Consider postpyloric feeding for GRVs >500, feeding intolerance symptoms; may reduce silent aspiration if the tube is past third portion of duodenum?	• Inconclusive: may be reduced aspiration with postpyloric feeding in meta-analysis; however, postpyloric feeding equivalent to gastric feeding in recent RCT on aspiration risk and EN delivery • Need future new efficacious and low side-effect prokinetics	24,36–38
Supplemental parenteral feeding during first week in ICU	• Well nourished: consider a delay until day 3–7 if <60% EN protein/kcal goal • Malnourished pts: Start at ICU admit goal: **w**1.2 g/kg/d **w**15–20 kcal/kg/d Start at ICU admit in malnourished pts with NUTRIC >5 (w/o IL-6) and/or NRS≤5	• Prevent caloric deficit early to enhance recovery • No clear benefit of higher kcal dosages (>25 kcal/kg/d) in well-nourished ICU pts receiving dextrose-predominant, low protein PN in first 3 d • Potential benefit in pts with contraindication to EN or failing EN, especially malnourished pts at ICU admit	2,5,6,9,15–18,24,25,29–31

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Table 1
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Nutritional Intervention	Recommended Delivery/Dose	Rationale/Recent Evidence	References
More protein (>1.2 g g/kg/d) early (day 1–4 in ICU)	Protein: ≥1.0 g/kg/d Until further research is completed on effects of very early protein delivery	Key area of controversy • Spare endogenous protein to reduce LBM loss, facilitate early mobility, and enhance recovery • Concern for ↑↑ protein dose (>1.2–1.5 g/kg/d?) (day 1–4?) creating risk due to impaired autophagy	2,5,6,14,15,23–25,28,40
Thiamine	Strongly consider repletion all pts in septic shock requiring vasopressors: dosage: 200 mg IV thiamine twice daily for 7 d	• ≥35% of pts with septic shock potentially thiamine deficient • In thiamine-deficient pts: mortality from septic shock reduced by thiamine replacement • Potential for thiamine, vitamin C, and low-dose steroids to reduce mortality	51–53
Vitamin D	• Vitamin D level measured at ICU admit in ALL pts • Vitamin D <20: should receive 100,000 units of vitamin D_2 or D_3 for 5 d in first week and then 1–2× weekly (monitoring levels) for ICU stay	• Many vitamin D–deficient pts worldwide; vitamin D essential to immune function and muscle restoration and function • Data in ICU: significant relationship between vitamin D deficiency and adverse ICU outcomes • Recent large RCT in ICU: mortality benefit to repletion	58–63
Balanced TPN lipids (fish/olive oil)	• Recommend use of balanced lipid solutions containing fish oil and/or olive oil to minimize soy lipid content • Should not use pure soy lipid in sepsis or critical care setting for PN nutrition delivery	Soy lipids are • Immune suppressive • Associated with increased infections and LOS • Have elevated phytosterols, which increase cholestasis risk Meta-analysis data and recent RCTs: support use of balanced lipids with reduced infections and LOS	32,33,71,72
Antioxidants	Possible role for vitamin C in septic shock with thiamine and low-dose steroids (vitamin C: 1.5 g IV q 6 h for 4 d or until discharge from the ICU)	• Prevent organ failure/fluid leak • No clear benefit; for selenium or cocktail use possibly depends on dose and preillness deficiency status; more confirmatory literature needed for vitamin C	53–57

Trace element/ micronutrients	Routine administration of IV micronutrients/vitamins plus electrolyte replacement justified during acute phase of ICU until full enteral intake reached	• Many pts potentially deficient in trace element at ICU admit • Depletion can lead to refeeding syndrome, with thiamine, Mg, K, and PO_4 deficiencies and potentially fatal complications (ie, cardiac failure, lactic acidosis, and respiratory failure)	22,48
Glutamine	Do not use early in shock, on vasopressors, or in renal failure (especially predialysis?) • Continued safety and use in TPN pts not in shock or renal failure at appropriate doses (<0.35 g/kg/d) supported by multiple meta-analyses	• Resupply conditional deficiency to improve outcomes • Inconclusive and potentially harmful in higher doses (>0.5 g/kg/d EN/oral and >0.35 g/kg/d IV), early in shock or renal failure • Safety of EN/oral GLN and potential benefit indicated in ongoing trials in burn injury	56,66–70
B. Nutritional interventions in sepsis: chronic and recovery phase: (postresuscitation to hospital discharge)			
EN	Protein: 1.2–2.0 g/kg/d Nonprotein kcal: 25–30 kcal/kg/d (ideally guided by indirect calorimetry) In recovery phase: greater kcal and protein delivery likely required	• Prevent ongoing LBM wasting, weakness, and infections to improve recovery • Facilitate early mobility and physical therapy • Minnesota Starvation Study: >4000 kcal/d required for recovery	7,9,14–16,24,28
PN	• Well nourished: consider delay until d 3–7 if <60% EN protein/kcal goal • Malnourished pts: start at ICU admit goal: **w**1.2 g/kg/d protein total kcal **w**15–20 kcal/kg/d	• Prevent caloric deficit early to reduce LBM loss, enhance recovery, physical function, and QoL • Signal of benefit in pts failing EN, EN contraindications, or pre-ICU malnutrition • No increased risk of infection over EN or other IV fluid delivery from TPN	2,5,9,15–18,22,24,25,29–31
Oral nutrition	Should not provide high protein oral nutrition supplements to all pts 2–3 × d when oral nutrition initiated	• Exceedingly poor oral intake in ICU pts • Recent large RCT, large database observational data, and meta-analysis: reduced mortality, complications, LOS, and hospital costs • Minnesota Starvation Study: >4000 kcal/d required for recovery	4,7,9,42–47

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Table 1 (*continued*)

Nutritional Intervention	Recommended Delivery/Dose	Rationale/Recent Evidence	References
Supplemental parenteral feeding	• Well nourished: consider delay until day 3–7 if <60% EN protein/kcal goal • Malnourished pts: Start at ICU admit goal: **w**1.2 g/kg/d protein total kcal **w**15–20 kcal/kg/d Start at ICU admit in malnourished pts with NUTRIC >5 (w/o IL-6) and/or NRS **≤**5	• Prevent caloric deficit early to enhance recovery • No clear benefit of higher kcal dosages (>25 kcal/kg/d) in well-nourished ICU pts receiving dextrose- predominant, low-protein PN in first 3 d • Potential benefit in pts with contraindication to EN or failing EN, especially malnourished pts at ICU admit	2,5,6,9,15–18,24,25,29–31
Vitamin D	• Vitamin D level measured at ICU admit in ALL pts • Vitamin D <20: should receive 100,000 units of vitamin D_2 or D_3 for 5 d in first week and then 1–2× weekly (monitoring levels) for ICU stay	• Many vitamin D- deficient pts worldwide, and vitamin D essential to immune function and muscle restoration and function • Data in ICU: significant relationship between vitamin D deficiency and adverse ICU outcomes • Mortality benefit to repletion shown in recent large RCT in ICU	58–63
Balanced TPN lipids (fish/olive oil)	• Recommend use of balanced lipid solutions containing fish oil and/or olive oil to minimize soy lipid content • Should not use pure soy lipid in sepsis or critical care setting for PN nutrition delivery	Soy lipids are • Immune suppressive • Associated with increased infections and LOS • Have elevated phytosterols, which increase chole- stasis risk Use of balanced lipids with reduced infections and LOS supported by meta-analysis data and recent RCTs	32,33,71,72

Glutamine	Do not use early in shock, on vasopressors, or in renal failure (especially predialysis?) • Support from multiple meta-analyses for continued safety and use in TPN pts not in shock or renal failure at appropriate doses (<0.35 g/kg/d)	• Resupply conditional deficiency to improve outcomes • Inconclusive and potentially harmful in higher doses (>0.5 g/kg/d EN/oral and >0.35 g/kg/d IV), early in shock or renal failure • Safety of EN/oral GLN and potential benefit indicated in ongoing trials in burn injury	56,66–70
C. Nutritional interventions in sepsis: after hospital discharge			
Oral nutrition	Should provide high-protein oral nutrition supplements to all pts 2–3 × d for 3 mo to 1 y after discharge Protein goal: 1.2–2.0 g/kg/d kcal goal: may be 4000–5000 kcal/d based on Minnesota Starvation Study	• Oral intake exceedingly poor in ICU pts • Recent large RCT, large database observational data, and meta-analysis: reduced mortality, complications, LOS, and hospital costs • Minnesota Starvation Study: >4000 kcal/d required for recovery • Potential for post-ICU hypermetabolism and catabolism to persist for months to years after ICU discharge	4,7,9,42–47
Vitamin D	• Measure vitamin D level at ICU admit in ALL pts • Vitamin D <20: receive 100,000 units of vitamin D_2 or D_3 for 5 d in first week and then 1–2× weekly (monitoring levels) for ICU stay and likely in post-hospital period	• Many vitamin D–deficient pts worldwide; vitamin D essential to immune function and muscle restoration and function • Data in ICU: significant relationship between vitamin D deficiency and adverse ICU outcomes • Recent large RCT in ICU: mortality benefit to repletion	58–63

Abbreviations: EN, enteral nutrition; GLN, glutamine; IL-6, interleukin 6; IV, intravenous; K, potassium; LBM, lean body mass; LOS, length of stay; Mg, magnesium; NRS, nutrition risk score; PN, parenteral nutrition; PO_4, phosphate; pts, patients; RCT, randomized controlled trial; TPN, total parenteral nutrition; w/o, without.

supplemental and full TPN support versus EN in the ICU setting demonstrated no increase in infection risk with TPN.[29–31] This finding is likely due to improvements in glucose control, central line infection control measures, and, potentially, improved (non–pure soy–based) balanced lipid formulations that reduce infection compared with pure soy lipid.[32,33] In support of early TPN use, the new SCCM/ASPEN guidelines indicate that for any patient at high nutrition risk (NRS 2002 ≤5 or NUTRIC score [without IL-6 score] ≤5) or found to be severely malnourished when EN is not feasible, *exclusive PN should be initiated as soon as possible following ICU admission*.[24]

Chronic and Recovery Phase of Sepsis: Significantly Increased Protein and Calorie Needs

Chronic phase: postresuscitation increase in nutrition delivery

As successful resuscitation of the acute phase of sepsis occurs and patients stabilize, an increasing amount of protein (1.2–2.0 g/kg/d) and calories (25–30 kcal/kg/d) needs to be delivered to reduce further loss of LBM, allow for early mobilization, and encourage functional recovery (see Fig. 1, Table 1B). The concept of adequate protein and calorie delivery improving QoL is well described in a recent study of ICU patients mechanically ventilated for greater than 8 days.[5] After adjustment for covariates, patients receiving inadequate nutrition over the first ICU week (<50% of predicted calorie/protein need) had an increased mortality compared with those patients receiving adequate nutrition delivery (>80% of calorie/protein needs). These data also demonstrate that for every 25% increase in calorie/protein delivery in the first ICU week, there was an improvement in 3-month post-ICU physical QoL scores (as measured by the 36-Item Short Form Health Survey [SF-36] score), with medical ICU patients showing significant improvements in both 3- and 6-month SF-36 scores.[5]

Recovery phase: continued increase in nutrition delivery needs: role of the Minnesota Starvation Study in intensive care unit recovery

As patients improve and enter the recovery phase, caloric intake likely needs to increase further, with implementation of aggressive rehabilitation and exercise interventions. The landmark Minnesota Starvation Study performed at the end of World War II[7,34] (a study all medical students and hospital practitioners should be taught or read for themselves) provides essential data on the nutritional needs required to recover from the fundamental severe LBM loss observed after sepsis. This seminal study demonstrates that a healthy 70-kg human, following significant weight loss, requires *an average of 5000 kcal/d for 6 months to 2 years to fully regain lost muscle mass and weight*.[7] As many ICU patients have similar marked weight/LBM loss, in addition to prolonged hypermetabolism and catabolism (which Minnesota subjects did not have as they were healthy volunteers), we must recognize that significant calorie/protein delivery will be required to restore this lost LBM and improve QoL. During the recovery phase of critical illness, the body experiences a massive increase in metabolic needs, with TEE increasing as much as approximately 1.7-fold greater than REE.[20] In the second week following sepsis, this increases to a TEE of approximately 3250 kcal/d or 47 kcal/kg/d, virtually identical to the World Health Organization's requirements for normal, healthy humans. In younger trauma patients (mean age: 34 years), Uehara and colleagues described an even greater increase in caloric need in the second week after injury to an *average of approximately 4120 kcal/d or 59 kcal/kg/d*. This amount is nearly identical to the 4000 kcal/d that Ancel Keys demonstrated was needed to recover from starvation in the young Minnesota subjects (Table 2).

Table 2
Summary of caloric needs of critically ill and healthy individuals in the context of the Minnesota Starvation Study and actual current intensive care unit calories

	Mean REE (kcal/d)	TEE (kcal/d)	TEE/Weight (kcal/kg/d)
Uehara et al[20] ICU study			
Patients with sepsis (mean age: 67 y)			
Week 1	~1854	1927 ± 370	25 ± 5
Week 2	—	3257 ± 370	47 ± 6
Trauma patients (mean age: 34 y)			
Week 1	~2122	2380 ± 422	31 ± 6
Week 2	—	4123 ± 518	59 ± 7
WHO Calorie Requirements Healthy Subjects[a]			
Men	—	~3000	44 (Range: 35–53)
Women	—	~2500	36 (Range: 29–44)
Minnesota Starvation Study calorie delivery	— energy	Delivered (kcal/d)	Delivered energy/ weight (kcal/kg/d)
Baseline period	—	3200	~50
Starvation period	—	~1800	23–30
Recovery period delivery (for recovery to occur)	—	~4000	~60

Actual average kcal/d: 1034 kcal/d.
Delivered in critically ill patients.
Over first 12 days of ICU stay.[15]

Abbreviations: REE, resting energy expenditure; TEE, total energy expenditure; WHO, World Health Organization.

[a] Data for healthy 7-kg person with intermediate physical activity (1.75 physical activity level factor) (Reference: Human energy requirements Report of a Joint FAO/WHO/UNU Expert Consultation - http://www.fao.org/docrep/007/y5686e/y5686e00.htm#Content. Accessed September 12, 2017).

Current Practice of Nutrition in Sepsis and Intensive Care Units Worldwide: Do We Already Hypocalorically Feed Our Patients Beyond the Acute Phase?

Extensive data for current international nutrition delivery in critical care are available from the International Nutrition Survey conducted regularly by the Canadian Critical Care Nutrition Group (www.criticalcarenutrition.com). These data reveal that *average calories delivered in ICU over the first 12 days is 1034 kcals and 47 g of protein* (see Table 2).[6] This period is far longer than the first 1 to 4 days of the acute phase whereby hypocaloric feeding (with moderated adequate protein) may make physiologic sense. More troubling is the fact that this total is far lower than the 1800 kcal/d calories and approximately 0.8 g/kg/d protein that led to severe starvation in the Minnesota Starvation Study. Thus, drawing comparison in nutrition delivery between ICUs worldwide and the landmark Starvation Study

Minnesota Starvation Study (Starvation Period)
1800 kcal/d
0.75 to 0.8 g/kg protein
ICU patients worldwide for first 12 days in ICU
1034 kcal/d
0.6 g/kg protein

These data confirm that ICU patients worldwide average far less energy and protein than healthy subjects in the legendary Minnesota Starvation Study. This study would likely never be repeated today because of the ethics of inducing potentially life-threatening starvation in healthy volunteers. We know that starvation in humans leads to slowing of metabolic rate and reduced protein catabolism over time. Unfortunately, after the first ICU week, critical illness leads to significant hypermetabolism and severe ongoing protein losses. Moreover, 30% to 50% of ICU patients are malnourished at hospital admission[35] (unlike the well-nourished men in Key's Minnesota Starvation study), thus, greatly increasing the risk of ongoing in-hospital starvation. We must critically examine and measure actual practice in our individual ICUs, as most already underfeed calories and protein well beyond the acute phase. Methods to improve EN, including prokinetic agents[36] and postpyloric feeding, have not been successful in addressing this global ICU iatrogenic malnutrition. New guidelines calling for the abandonment of checking gastric residual volumes (GRVs),[37] or changing GRV cutoffs to greater than 500 mL before feeding is stopped, may show promise to help improve EN delivery.[24] In a recent RCT, postpyloric feeding did not reliably prevent aspiration or increase EN delivery[38] so gastric feeding should be the primary route to deliver EN. Finally, could iatrogenic malnutrition in the ICU likely explain in part the increasing number of ICU survivors who ultimately become victims of PICS, never to walk again or return to a meaningful QoL after ICU discharge?[3,13,39,40]

These data demand that we ask whether our septic patients have been unable to recover their QoL after ICU for months to years because of our lack of understanding of their fundamental metabolic needs in different phases of their illness, especially following ICU and hospital discharge.

Intensive Care Unit/Hospital Discharge Nutrition Delivery to Optimize Recovery

Can patients discharged from critical care following sepsis consume adequate calories and protein to enable optimal recovery (see Fig. 2, Table 1C)? In the week following endotracheal extubation, an observational study demonstrated an average spontaneous calorie intake of 700 kcal/d; the entire population studied consumed less than 50% of calorie/protein needs for 7 days.[4] This study also emphasizes the importance of closely observing food intake in postoperative patients. In patients who have lost significant weight following surgery or illness, a considerable period of significantly increased calorie and protein delivery is required for recovery.[41] To address this, a large body of data demonstrates that oral nutrition supplements (ONS) must become a fundamental part of our post-ICU and hospital discharge care. A meta-analysis in a range of hospitalized patients demonstrates that ONS reduces mortality, reduces hospital complications, reduce hospital readmissions, shortens length of stay, and reduces hospital costs.[42–45] A large hospital database analysis of ONS use in 724,000 patients matched with controls not receiving ONS showed a 21% reduction in hospital LOS; for every $1 spent on ONS, $52.63 was saved in hospital costs.[46] Finally, a recent large RCT of 652 patients in 78 centers studied the effect of high-protein ONS (HP-ONS) with b-hydroxy-b-methyl butyrate (HP-HMB) versus placebo in elderly, malnourished (Subjective Global Assessment class B or C) hospitalized adults. HP-HMB reduced 90-day mortality by approximately 50% relative to placebo (4.8% vs 9.7%; relative risk 0.49, 95% confidence interval [CI]: 0.27–0.90; *P* 5 .018). The number needed to treat to prevent 1 death was 20.3 (95% CI: 10.9, 121.4).[47] As it is well known that ICU patients recovering from sepsis will not consume sufficient calories and protein to recover optimally, the use of HP-ONS will be essential. It is strongly recommended for all patients once oral intake is resumed for at least 3 months (and up to 1 year) following ICU discharge.

Correction of Vitamin/Micronutrient Deficiencies and Specific Nutrient Delivery

In addition to protein and calorie needs, a new and growing body of literature is identifying nutrients that should and should not be administered in the early acute phase of sepsis (see Table 1). These nutrients are discussed specifically later.

Micronutrients and electrolytes

Recent literature demonstrates a meaningful number of patients may be deficient in trace elements at ICU admissions or become deficient during their stay.[48] Refeeding syndrome is a real and present danger to malnourished ICU patients. This syndrome must be monitored via evaluation of electrolytes (phosphate, potassium, magnesium) and repletion when needed.[49,50] Casaer and van den Berghe[48] advocate for continuous infusion of trace elements: *"Routine administration of intravenous micronutrients and vitamins plus electrolyte replacement is justified during the acute phase of critical illness until full enteral intake is reached."*[48]

Thiamine

Thiamine is an essential vitamin for aerobic nutrient metabolism, playing a vital role in the Krebs' cycle and the pentose-phosphate shuttle.[51] New data indicate that thiamine deficiency occurs in up to 35% of patients with septic shock.[52] A recent double-blind RCT showed that administration of 200 mg thiamine to patients with septic shock did not improve lactate levels or other outcomes overall.[52] However, in thiamine-deficient patients, there was a statistically significant decrease in mortality over time, and a reduction in lactate at 24 hours, in those receiving thiamine (P 5 .047). These data have been supplemented by a recent retrospective before- after clinical study, showing significantly reduced mortality in patients with septic shock receiving thiamine, vitamin C, and low-dose steroids.[53] Hospital mortality was 8.5% (4 of 47) in the treatment group compared with 40.4% (19 of 47) in the earlier control group (P<.001). These trial data do, however, require confirmatory larger RCTs. As thiamine measurement is costly and not routinely performed, and thiamine itself is quite inexpensive and carries almost no risk, a recommendation for all patients with septic shock to receive 200 mg thiamine twice daily for 7 days after ICU admission seems reasonable to improve outcomes, though with the caveat that additional data are needed.

Vitamin C and antioxidants

As mentioned earlier, a potential benefit of vitamin C with thiamine and low-dose steroids has recently been described.[53] The doses of vitamin C used in this Marik trial are high, yet seemed to be safe and can be considered for use. Some concern for oxalate nephropathy should be considered, especially in patients with significant renal dysfunction, although the Marik group[53] has denied any incidence of this in their short-term vitamin C use. This practice has been seemingly safe in short-term use in the burn setting.[54] Consistent use of vitamin C at this level, as is often done in burn patients to reduce fluid leak and fluid requirements,[54] may challenge some ICU pharmacies to keep up with demand as this practice will be new to many centers. Routine use of selenium and other antioxidants has shown promise in meta-analysis[55]; however, recent large RCTs have not shown benefit.[56,57]

Vitamin D

A rapidly growing body of data demonstrates a significant proportion of the population of the United States and other industrialized nations is vitamin D deficient.[58] Data in ICU and surgical patients show that vitamin D deficiency has a significant association with postoperative complications and adverse ICU outcomes.[59–61] A key recent RCT found

that ICU patients with vitamin D levels less than 12 ng/mL experienced a significant improvement in hospital survival with aggressive supplementation of vitamin D_3 given orally or via the nasogastric tube at a single dose of 540, 000 IU followed by monthly maintenance doses of 90,000 IU for 5 months.[62] This dose will be difficult for many centers to administer if concentrated vitamin D solutions are not available. A recent double-blinded pilot RCT of 50,000 IU vitamin D_3 or 100,000 IU vitamin D_3 daily for 5 consecutive days enterally (total vitamin D_3 dose 5 250,000 IU or 500,000 IU, respectively) reported a significant decrease in hospital length of stay in the 50,000 IU D_3 per day (25 **T** 14 days) and 100,000 IU D_3 per day (18 **T** 11 days) groups compared with the placebo group (36 **T** 19 days; *P* 5 .03).[63] Vitamin D levels are, thus, recommended to be checked at ICU admission and once weekly thereafter in all patients with septic shock. For patients found to be deficient (<30 ng/mL), a repletion dose of 100,000 units of vitamin D_2 or D_3 for 5 days in the first week and 1 to 2 times per week thereafter (monitoring levels) for the duration of the ICU stay is reasonable. Larger trials on the role of vitamin D supplementation in sepsis and critical illness are currently underway.

Glutamine

Glutamine (GLN) is the most abundant nonessential free amino acid.[64] Low GLN levels have been associated with poor outcomes.[65] Thus, GLN has been labeled a conditionally essential amino acid during prolonged critical illness, leading to the hypothesis that GLN supplementation would improve outcomes.[64] However, signals showing a risk of harm have come from 2 large-scale multicenter trials evaluating mortality using a combination of high-dose intravenous/enteral GLN (the REDOXS (REducing Deaths due to OXidative Stress) study)[56] or a high-dose enteral mixture of different nutrients including GLN (the METAPLUS trial).[66] These new trials were both targeted to investigate GLN (and other nutrients) as primary pharmaconutrients and not as supplementation to PN. These data suggest that patients in the early phase of sepsis, on vasopressors, or in renal failure (especially without dialysis) should not get supplemental GLN. Two recent meta-analyses[67,68] have confirmed that traditional PN supplementation with intravenous GLN is safe, reduces mortality and LOS, and improves outcome. Based on 9 level 1 and 19 level 2 studies, the investigators concluded, *"When PN is prescribed to ICU patients, parenteral GLN supplementation should be considered."*[67] Patients in need of PN and those with burns, trauma, or malignancies may continue to benefit from supplemental GLN, administered either intravenously less than 0.35 g/kg/d or enterally less than 0.5 g/kg/d.[69,70] TPN routinely contains only 19 amino acids, so GLN must be supplemented, and not given pharmacologically, in a stable form to provide complete nutrition.

Lipids

Current use of pure soy lipid as part of PN should likely be abandoned, as it is immunosuppressive and proinflammatory.[71,72] This point is particularly true given the now worldwide availability of balanced lipid solutions containing various combinations of fish and/or olive oil. There are also data supporting a benefit of using fish oil containing balanced lipid formulations versus soy lipid alone in patients requiring TPN in the ICU or postoperative setting. These data include a recent meta-analysis of 23 RCTs, including 1502 surgical and ICU patients, which demonstrated that fish oil–containing lipids reduced length of stay and infectious complications versus traditional soy-only lipids.[32] A more recent meta-analysis of 10 RCTs demonstrated that fish oil–based intravenous lipids significantly reduced infections in critical illness.[33] It is, thus, recommended that when TPN is used, a modern, balanced lipid that reduces soy lipid content should be given.

SUMMARY

In conclusion, to optimize nutrition delivery, we need to consider basic metabolism and our historical understanding of data for recovery from severe LBM loss (starvation) to use targeted nutritional care in sepsis. If we are to optimize patient outcomes and start creating survivors and not victims following sepsis and intensive care, we must continue to evolve our delivery of personalized nutritional needs, which almost assuredly change over the course of illness. The presence of nutritional risk and metabolic reserve as defined by the NUTRIC score and CT scan- or ultrasound-guided LBM assessment should guide how we feed our patients, with high risk (NUTRIC ≤5 or patients with sarcopenia) getting aggressive early calorie and protein delivery via early EN and/or PN. Furthermore, we must all read and revel in the defining achievement that is the Minnesota Starvation Study[7] and learn from its landmark lessons. Most important among these is that even healthy subjects require significant calories (typically >4000 kcal/d) to recover from massive weight and LBM loss such as occurs following sepsis. How many of our care protocols, or our patients, acknowledge or achieve this well-described goal? Is it possible this lack of understanding of caloric and protein needs during recovery and, thus, suboptimal provision has led to the extremely poor long-term outcomes and QoL that follows ICU care? Only time and further research will tell for sure. This increase in calorie delivery should be targeted to when patients are recovering. Use of emerging metabolic cart technology[73] and, perhaps, even bedside C13 breath testing to target overfeeding/underfeeding and substrate delivery[74,75] will help guide this in the future. Finally, we must learn to target and incorporate nutritional therapies, such as vitamin D, probiotics, and anabolic/anticatabolic agents, to optimize our patients' chances of survival and to thrive against all evolutionary odds. We have long known Mother Nature does not want our ICU patients to win this war and become *survivors and not victims*. But to begin winning this war on long-term ICU outcomes and give our patients back the lives they came to us to restore, we must ensure we are giving the right nutrition, to the right patient, at the right time.

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