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USE OF PROBIOTICS IN BURN PATIENTS TO IMPROVE NUTRITIONAL STATUS AND CLINICAL OUTCOMES: A HYPOTHESIS

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ABSTRACT: ***Mounting evidence correlate low serum albumin level to higher mortality, morbidity and poor outcome in a range of medical situations including burns. Serum albumin might be corrected via administration of human albumin solution (HAS) or, nutritionally, through promotion of hepatic albumin synthesis and /or suppressing acute phase response (APR). While results of a meta-analysis concluded that a trend toward reduced morbidity could be discerned in trials of burns, and hypoalbuminemia, a Cochrane Database Systematic Reviews suggested albumin administration might increase the risk of death. In this paper, I hypothesize that when serum albumin is being kept continuously normal by providing adequate nutrition/and or probiotics, problems with rapid systemic changes are better avoided than when albumin is rapidly "administered" or "normalized" with HAS. Probiotics have shown no harm in ICU patients (except for an increased bacterial translocation and enterocyte damage in postburn acute pancreatitis), and their use has shown numerous beneficial effects in the critically ill. At present there are no clinical trials investigating the effect of a probiotic on the nutritional status of burn patients and their clinical outcomes. Large clinical trials of the efficacy of probiotics in improving nutritional status and clinical outcomes in burn are warranted.***

KEYWORDS: Albumin; Burns; Clinical outcome; Nutrition; Probiotics; Quality of life

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INTRODUCTION

Burn patients are at increased risk of hypermetabolism, hypercatabolism (Borsheim *et al.* 2010; Williams *et al.* 2009) and malnutrition (Demling, 2005). Increasing evidence suggest that malnutrition itself is a predictor of poor outcome in burn patients (Bongers and Griffiths, 2006; Wasiak *et al.* 2006; Windsor *et al.* 1998a). Serum albumin level is considered as one of the most predictive parameters of malnutrition in a range of diseases (Mijac *et al.* 2010; Grzegorzewska, 2009; Harris *et al.* 2008; Kamimura *et al.* 2005; Charlton *et al.* 2005; Ignacio de *et al.* 2005). However, it has been argued that use of albumin has of no benefit for patients' outcome (e.g., mortality or morbidity), and there are disputes on albumin administration to critically ill patients, including burn patients (Cooper *et al.* 2006; Liberati *et al.* 2006; Pulimood and Park, 2000).

Low serum albumin has been correlated to higher mortality, morbidity and poor treatment outcome in a range of medical situations (bdel-Wahab *et al.* 2010; Boyle *et al.* 2006a; Cheung *et al.* 2009; Davenport *et al.* 2010; Dziedzic *et al.* 2004; Famakin *et al.* 2010; Fung *et al.* 2002; Gariballa *et al.* 1998b; Gariballa *et al.* 1998a; Ghany *et al.* 2010; Haraguchi *et al.* 2009; Huang *et al.* 2010; Ikeda *et al.* 2010; Kalantar-Zadeh *et al.* 2003; Kawamura *et al.* 2009; Kopple *et al.* 2008; Koseoglu *et al.* 2009; Pacella *et al.* 2009; Pasqualetti *et al.* 1992; Pollock *et al.* 1989; Rady *et al.* 1997a; Rady *et al.* 1997b; Reisman *et al.* 1997; Rozzini *et al.* 2005; Segall *et al.* 2009; Tung *et al.* 2007; Wiedermann *et al.* 2010; Yang *et al.* 2009) including burns (Table 1) (Al *et al.* 2009; Kim *et al.* 2003; Kumar, 2010; Moorthy *et al.* 2000; Murtaza *et al.* 2009). Initially depressed serum albumin level is associated with increased mortality in the majority of burn patients (Al *et al.* 2009; Kim *et al.* 2003). In the study of Kim et al, the initial serum albumin level < 2.5 g/dl was also associated with a risk of death that was 2.7 times as high as

that for the initial serum albumin level e" 2.5 g/dL in multivariate analysis (Kim *et al.* 2003). Also, incidence of complications such as acute renal failure (Kim *et al.* 2003) and diarrhea (Hwang *et al.* 1994) were significantly higher in patients with initially depressed albumin levels.

Among its multiple physiologic roles, it plays an essential part in the generation of colloid-oncotic pressure (Mendez *et al.* 2005). The influence of burn damage on albumin biosynthesis and breakdown rates has not been as extensively studied as that on inflammatory mediators. Immediately after injury,

Table 1. Mortality, morbidity and outcome prediction value in relation to low serum albumin* in selected medical situations

Medical Situation	Mortality	Morbidity	Prediction of outcome
Acute stroke	+ (Famakin et al. 2010)	+ (Gariballa et al. 1998b; Gariballa et al. 1998a)	+ (Dziedzic et al. 2004; Gariballa et al. 1998b; Gariballa et al. 1998a)
Lung cancer with postobstructive pneumonia	+ (Haraguchi et al. 2009)	+ (Haraguchi et al. 2009)	+ (Haraguchi et al. 2009)
Gastrointestinal bleeding	+ (Koseoglu et al. 2009)	+ (Koseoglu et al. 2009)	+ (Tung et al. 2007)
Hemodialysis	+ (Kalantar-Zadeh et al. 2003; Kopple et al. 2008; Segall et al. 2009; Yang et al. 2009)	+ (Kopple et al. 2008; Segall et al. 2009)	+ (Kalantar-Zadeh et al. 2003)
Chronic hepatitis C and advanced fibrosis	+ (Blake et al. 1993)	+ (Ghany et al. 2010)	+ (Ghany et al. 2010)
Ruptured abdominal aortic aneurysm	+ (Davenport et al. 2010)	+ (Davenport et al. 2010)	+ (Davenport et al. 2010)
Hepatocellular carcinoma	+ (Ikeda et al. 2010)	+ (bdel-Wahab et al. 2010; Cheung et al. 2009)	+ (Ikeda et al. 2010; Pacella et al. 2009)
Child class A cirrhosis	+ (Pasqualetti et al. 1992; Reisman et al. 1997)	+ (Pasqualetti et al. 1992; Reisman et al. 1997)	+ (Kawamura et al. 2009)
End stage renal disease	+ (Fung et al. 2002)	+ (Pollock et al. 1989)	+ (Blake et al. 1993)
Acute kidney injury	+ (Wiedermann et al. 2010)	+ (Boyle et al. 2006)	+ (Boyle et al. 2006)
Elderly ambulant patients	+ (Rozzini et al. 2005)	+ (Huang et al. 2010)	+ (Rozzini et al. 2005)
Cardiovascular surgery	+ (Rady et al. 1997a; Rady et al. 1997b)	+ (Rady et al. 1997a; Rady et al. 1997b)	+ (Rady et al. 1997a; Rady et al. 1997b)
Burns	+ (Al et al. 2009; Kim et al. 2003; Kumar, 2010; Murtaza et al. 2009)	+ (Al et al. 2009; Kim et al. 2003)	+ (Kim et al. 2003; Kumar, 2010)

*As serum albumin which is not influenced by administered human albumin solution.

Inconsistencies in beneficial effects of albumin in burn patients might be wholly or partially related to whether serum albumin is corrected using HAS or via promotion of hepatic albumin synthesis and /or suppressing acute phase response (APR). I have intentionally limited the scope of this review on benefits of the use of the supplement probiotics that might directly and /or indirectly enhance albumin synthesis, lessen APR and transcapillary leak, and subsequently improve outcome prognosis. A brief overview of causes of hypoalbuminemia, albumin kinetics, and results of meta-analyses on HAS administration are presented and then evidences of hypothetical benefits of probiotics in burn patients to improve medical outcomes and nutritional measures are shown.

CAUSES OF HYPOLABUMINEMIA IN BURNS

Albumin is the predominant product of hepatic protein synthesis and one of the more abundant plasma proteins. plasma albumin level rapidly decreases and remains significantly depressed even at 60 days post-burn (Bonate, 1990). The half-life of serum albumin in well patients who are stable is known to be approximately 17 days. However, when a patient is suffering with an acute illness such as sepsis, trauma, burns, or after an extensive operative procedure, the serum albumin level decreases (Spiess *et al.* 1996).

ALBUMIN KINETICS IN BURNS

Human studies

It would be desirable to know whether this fall in serum albumin is due to increased catabolism, decreased synthesis, or a combination of both factors.

Spiess *et al* (Spiess *et al.* 1996) investigated the kinetics of albumin catabolism under these circumstances to clarify the issue. The serum albumin remained below 3.0 g/dL in each critically ill, hypoalbuminemic patients receiving total

parenteral nutrition (TPN) and did not change statistically throughout the study. The radioiodinated albumin half-life ranged from 5.52 to 11.76 days (mean 9.10 days; compared with published normal of approximately 17 days). The equilibration time was 3 to 7 days. The average albumin catabolized for this group was similar to previously reported normal subjects, 0.18 g/kg/d. These data argue for both a synthetic and catabolic defect that explains the hypoalbuminemia in this patient group (Spiess *et al.* 1996).

Li *et al* (Li *et al.* 2003) explored the mechanism of hypoalbuminemia in patients with severe sepsis. I(125)-labeled albumin was administered intravenously to 10 health volunteers and 10 patients with severe sepsis. Blood samples were taken at 0, 1, 2, 4, 8, 12, 24 hours and 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 18, 22, 25 days for the measurement of the dose of gamma-radiation and the curve of concentration and time. The half-life time in septic group was obviously shorter than that in control group (8.2 ± 1.4 vs. 12.5 ± 1.7, $P < 0.01$). The transportation rate in the septic group was higher than that in the control group [(4.4 ± 1.9) x 10(-2)/h vs. (2.4 ± 0.6) x 10(-2)/h, $P < 0.05$]. There was no significant difference in apparent volume of distribution between the two groups. They concluded that in patients with severe sepsis, the distribution rate of albumin from vessel to tissue was obviously increased and the decomposition rate of albumin was markedly improved.

Animal studies

In one animal study, Sprague-Dawley rats received either a 30% flame burn (n = 12) or a sham burn (n = 12) and were allowed to recover for 11 days. Burned animals showed slower weight gains and a 25% to 30% higher resting energy expenditures compared with controls. On postburn day 11, synthesis of secreted hepatic proteins was measured by incorporation of leucine during a 2-hour isolated liver perfusion. Synthesis of total secreted proteins, the seromucoid fraction, and complement component C3 was significantly increased in burned animals, whereas synthesis of albumin was unaltered. In spite of unchanged albumin synthesis, plasma albumin concentrations were 50% lower in burned animals than in control animals throughout the postburn period. These findings suggest that decreased albumin synthesis is not the mechanism responsible for persistent hypoalbuminemia that follows burn injury (Hiyama *et al.* 1991).

Briefly, hypoalbuminemia in burns may result from transcapillary leak, large volume body fluid losses, dilution due to fluid resuscitation (Pulimood and Park, 2000) and altered compartmentation (Brown *et al.* 1976). It was previously believed that albumin synthesis is decreased in burns (Moshage *et al.* 1987). However, results of recent human studies (Martini *et al.* 2010) and animal models of burns (Brown *et al.* 1976; Hiyama *et al.* 1991) show that albumin synthesis actually is enhanced. These later findings suggest that there is increased degradation of albumin or its transcapillary leakage. If this is the case, albumin substitution using HAS might not effectively correct the hypoalbuminemia, unless underlying causes are removed.

HAS AND BURNS

HAS is used in a range of medical and surgical problems. Approved indications are the emergency treatment of shock and other conditions where restoration of blood volume is urgent, burns, hypoalbuminemia, and hypoproteinaemia. Although HAS is more expensive than other colloids and crystalloids (Alderson *et al.* 2004) and the use of this relatively expensive therapy accounts for up to 30% of the total pharmacy budget in certain hospitals (Mendez *et al.* 2005), it is recommended for correcting hypovolemia instead of using less expensive nonprotein alternatives (Haynes *et al.* 2003; Sedrakyan *et al.* 2003).

In major burn wounds of more than 15% TBSA mediator-associated reactions lead to capillary leak resulting in a critical condition (Joneidi-Jafari *et al.* 2009). This global systemic capillary leak can be attributed, at least in part, to inflammatory mediators produced as a result of cellular injury (Klein *et al.* 2009). Furthermore, although the majority of burn centers use the crystalloid-based Parkland formula to guide fluid therapy, patients actually receive far more fluid than the formula predicts.

Hazards and risk of HSA

Early, aggressive treatment of burn shock has been the mainstay of burns resuscitation, but recently there have been growing concerns that burn-injured patients are being over fluid-resuscitated with excessive quantities of crystalloid, often with indistinct and inappropriate endpoint targets. With rapid administration of albumin there is up to a fourfold increase in volume retention, which can result in fluid overload, especially pulmonary edema. Maintenance of the plasma oncotic pressure by albumin blunts the natriuretic response to sodium loading. Infusion of albumin also results in water and sodium retention (Pulimood and Park, 2000). Du *et al* (Du *et al.* 1991) found that early use of plasma leads to improved cardiac parameters, decreased volume requirements, and lower weight gain, compared with pure crystalloid resuscitation. Also, O'Mara *et al*. demonstrated decreased fluid requirements and lower intraabdominal pressures with use of plasma in the first 48- h following large TBSA (>50%) burns (O'Mara *et al.* 2005). Resuscitation with large volumes of crystalloid has numerous adverse consequences, including worsening of burn edema, conversion of superficial into deep burns, and compartment syndromes. For a review on modern trends in fluid therapy for burns, see Tricklebank (Tricklebank, 2009).

Results of different studies on HAS in burns

In a meta-analysis of cohort studies and controlled trials in acute illness, each 1 mg/dL decline in serum albumin concentration was shown to increase the odds of mortality by 137%, morbidity by 89%, prolonged intensive care unit (ICU)

and hospital stay by 28% and 71%, and increase resource utilization by 66% (Vincent *et al.* 2004). For each 2.5 mg/dL decrement in serum albumin concentration the odds of death have been reported to increase by 24–56% (Yap *et al.* 2002), but correcting hypoalbuminemia has no impact on outcome in the critically ill. The association predicts overall and cause-specific mortality. The serum albumin concentration, therefore, appears to be a sensitive predictor of preclinical disease and disease severity. The protective effect of higher levels of serum albumin persists after adjustment for other known risk factors, pre-existing illness, and the exclusion of early mortality (Feldman *et al.* 2000). However, the impact of albumin infusion on survival has been the subject of several studies.

A 1998 meta-analysis of 24 randomized trials suggested that HSA might increase mortality (Anonymous, 1998). However, that result could not be confirmed in a 2001 meta-analysis that included all 24 trials from the 1998 meta-analysis plus an additional 18 trials (Wilkes and Navickis, 2001). Recently, the blinded randomized Saline versus Albumin Fluid Evaluation trial involving nearly 7,000 hypovolemic patients demonstrated no difference in mortality between the albumin and saline groups (Finfer *et al.* 2004). A Cochrane Database Systematic Reviews suggested that there is no evidence that albumin administration reduces the risk of death in critically ill patients with hypovolaemia, burns or hypoalbuminemia, and a strong suggestion that it may increase the risk of death (Alderson *et al.* 2004).

Interestingly, another simultaneous meta-analysis that was carried out by Vincent *et al* (Vincent *et al.* 2004) on seventy-one randomized, controlled trials (including surgery or trauma, burns, hypoalbuminemia, high-risk neonates, ascites, and other patients) concluded that a trend toward reduced morbidity could be discerned in trials of burns, and hypoalbuminemia (Vincent *et al.* 2004). Although there appeared to be differences in the effects of albumin depending on clinical indication and type of complication, these differences may have been at least partly due to contrasting control group albumin dose. Thus, when albumin was compared with a control group regimen completely devoid of albumin, morbidity was significantly reduced in the albumin group across most comparisons of clinical indications and complication types. Also, in the subset of included trials applying more rigorous standards for diagnosing and reporting complications, the beneficial effect of albumin in that meta-analysis was stronger (Regtien *et al.* 2005; Vincent *et al.* 2004).

A NOVEL APPROACH TO CORRECT HYPOALBIMINEMIA

A question is, apart from methodological bias (or biases), why results of statistical comparisons on the beneficial effects of normal serum albumin levels on mortality, as well as its effects on morbidity and other complications, do not act the same as when *i*) serum albumin is "normalized" using rapid human albumin administration with that of *ii*) when serum albumin is already within normal range (or close to normal range) in burn patients who received (or are receiving) adequate nutrition? This suggests the hypothesis that there might be a difference between "normal" serum level and "normalized" serum level. In other words, serum albumin may be best (or most) beneficial when it is continuously kept within normal levels or close to normal levels; and that "normalization" of the serum levels using rapid human albumin administration may not totally imitate its normal functions. Synthesized albumins play its multiple physiologic roles as it is released to the circulation, while administered human albumin lacks such an attribute or albumin synthesized in the body is correlated with another physiological process that is the actual process that aids burn victims. Another possibility is that serum albumin provides its protective effect during the burn.

Herein, I present a review to propose novel mechanisms for probiotics albumin enhancing effect in burn patients, as well as other available theoretical potential benefits, and scientific evidences in the critically ill to justify running clinical trials of probiotics supplementation in burn patients. A probiotic can be defined as a preparation of, or a product containing, viable, defined micro-organisms in sufficient numbers, which alter the microbiota by implantation or colonization in a compartment of the host and by that exert beneficial health effects in this host (Schrezenmeir and de, 2001; Sanders, 2008). Probiotic preparations and products most commonly contain strains of lactobacilli, bifidobacteria or saccharomyces, or mixtures of these strains. Probiotics should fulfill strict criteria before consideration for use in patients receiving enteral tube feeding, including safety, viability during processing and storage, gastrointestinal survival and function (Tuomola *et al.* 2001; Rijkers *et al.* 2010; Pineiro and Stanton, 2007; Silley, 2006).

PROBIOTICS AND SAFETY

Safety is an essential characteristic for probiotic use in patients receiving enteral tube feeding and, although rare, a number of case reports of infection or sepsis following probiotic use have been reported (Munoz *et al.* 2005). Those individuals at particular risk of probiotic sepsis include immunocompromised patients, premature infants, patients with a central venous catheter and those in whom the probiotic is delivered via jejunostomy (Boyle *et al.* 2006b). See Whelan for a review (Whelan, 2007).

Gaps exist in our knowledge regarding mechanisms of action of different probiotics, most effective strains—single or multiple, cost effectiveness, risk-benefit potential, optimum dose, frequency and duration of treatment etc. More information is needed on safety profile of probiotics in immunocompromised state of the critically ill in view of rare reports of fungemia and sepsis and a trend toward possible increase in nosocomial infection (Singhi and Baranwal, 2008).

However, the clinical safety of *Lactobacillus casei* Shirota (107 colony-forming units/d) was demonstrated in twenty-

eight pediatric patients in the ICU who received enteral tube feeding, none of whom developed positive lactobacillus growth in any of the bodily fluids (e.g. blood, urine, endotracheal aspirates) or surface swabs (e.g. skin, central catheter tips) analyzed (Srinivasan *et al.* 2006).

Also, single-center studies have shown that probiotics containing anaerobic bacteria may reduce the rate of necrotizing enterocolitis, the severity of necrotizing enterocolitis, and/or bacterial sepsis (Bin-Nun *et al.* 2005; Dani *et al.* 2002; Lin *et al.* 2005). Probiotcs decreased significantly the risk for sepsis by bloodstream infections and the occurrence of ventilator-associated pneumonia (VAP) in patients with multiple injuries (Giamarellos-Bourboulis *et al.* 2009). A combination of probiotic strains (a mixture of 6 *lactobacillus*, *lactococcus*, or *bifidobacteriae* probiotic bacteria) reduced bacterial translocation in acute pancreatitis, but was associated with increased bacterial translocation and enterocyte damage in patients with organ failure (Besselink *et al.* 2009). Pancreatitis is a frequent complication after large burn injuries. About 40% of burn patients developed hyperamylasemia or hyperlipasemia well after the admission period (23 ± 3 days), and all enzyme abnormalities were temporally associated with emerging infections (Ryan *et al.* 1995).

Thus, the use of probiotic supplementation in this group of patients would be limited. The safety and efficacy of probiotics in burn patients warrant well-designed clinical trials.

EFFECTS ON NUTRITIONAL STATUS

Effect on serum albumin

In the only published double-blinded feeding trial which determined effect of fermented milk containing Lactobacillus johnsonii La1 (LC1) on albumin in the elderly, twenty-four completely enterally fed elderly in-patients aged over 70 years were randomly assigned into two groups. All subjects were administered 3768 kJ (900 kcal)/d of total enteral nutrition through tube feeding for 12 weeks. Subjects in the LC1 group were administered 373 kJ (89 kcal)/d of LC1 fermented milk after feeding of 3395 kJ (811 kcal)/d of enteral nutrition for 12 weeks. In the control group, 373 kJ/d of the same amount of enteral nutrition as was replaced from the fermented milk. In the LC1 group, the percentage of days with infections during the run-in observation period was 15.4 (SD 17.3) %, which significantly decreased to 5.7 (SD 8.1) % during the intervention period ($P = 0.018$), and the reduction was larger than that of the control group ($P = 0.047$). Blood hemoglobin increased ($P < 0.05$), and there was a tendency towards an increase in serum albumin and a decrease in tumor necrosis factor-alpha (TNF-α) in the LC1 group. Also, there was a trend towards an increase in blood phagocytic activity (a natural immunity marker) in the subjects whose initial level was low in the LC1 group. There were no changes in those parameters in the control group. This study suggested that administration of fermented milk containing the probiotic L. johnsonii La1 may contribute to suppressing infections by improving nutritional and immunological status in the elderly (Fukushima *et al.* 2007).

Effect on albumin biosynthesis

In piglets probiotics have been shown to induce/enhance albumin biosynthesis within 14 days. Harding *et al* (Harding *et al.* 2008) determined whether maintaining adequate nutrition compared with administering probiotics affected protein synthesis, colon histopathology, and oxidative stress in macronutrient-restricted piglet model of colitis. Piglets (n = 8/group) receiving dextran sulfate to induce colitis were randomized to 3 treatment groups: macronutrient restricted (MR); macronutrient restricted with VSL #3 probiotics (MRP), or well nourished (WNC). An additional 8 piglets served as healthy references for comparative purposes given the unique nature of the experimental model. Compared with MR piglets, both WNC and MRP piglets had higher protein synthesis rates in liver and plasma protein pools. However, only adequate nutrition increased protein synthesis in the colon and decreased colitis severity. Whereas probiotics did not stimulate gastrointestinal protein synthesis or reduce colitis severity, a signaling mechanism between the gut and liver seemed to be responsible for the probiotic-induced increase in liver protein and plasma protein synthesis (Harding *et al.* 2008).

Effect on prognostic inflammatory and nutritional index (PINI)

In the only published randomized double blind, controlled trial, Lu *et al* (Lu *et al.* 2004), investigated the influence of early enteral nutrition with synbiotics on the plasma endotoxin level, the nutritional state, the inflammatory response and the incidence of infectious complications in severely burned patients. Forty severely burned patients were randomly divided into A and B groups with 20 in each group. The patients in group A received early enteral nutrition with synbiotics that included four kinds of lactic acid bacteria and four kinds of fibers, while those in group B received early enteral nutrition with synbiotics including only four kinds of fibers. The patients with 80% to 280% coefficient unit burned surface were further divided into A1 (n = 10) and B1 (n = 11) groups. The plasma endotoxin level in group A (37.9 ± 5.4) ng/L was significantly lower than that in group B (59.1 ± 7.9) ng/L ($P < 0.05$) on 10th postburn day. The abnormal rate of plasma endotoxin in group A (36.7%) was significantly lower than that (49.2%) in group B ($P < 0.05$). Blood culture was positive in 3 patients in group A, and 5 in group B. There was no obvious difference in the incidence of infectious complication between the two groups. There was no obvious difference in plasma IL-1 level between A1 and B1 groups at different time points. The plasma IL-6 level in A1 group in 10th and 14th postburn day was significantly lower than that in B1 group ($P < 0.05$). The PINI in A1 group on the 10th postburn day was significantly lower than that in B1 group (Lu *et al.* 2004). This suggests that early enteral nutrition with synbiotics was helpful in decreasing inflammatory stress response and possibly enhancing albumin levels, and that such determinations should be replicated further in other randomized clinical trials.

It is noteworthy that PINI has been previously correlated to outcome prognosis in a range of situations such pressure ulcer (Reynolds *et al.* 2006), head and neck squamous cell carcinoma (Tartour *et al.* 1997), hospitalized elderly patients (Bonnefoy *et al.* 1998), and critically ill patients with acute respiratory failure (Schlossmacher *et al.* 2002).

Effect on weight gain

A recent systematic review of eleven randomized controlled trials on probiotic Lactobacillus species supplementation in full-term neonates showed that infants who receive a supplement had slightly better weight gain than did controls (weighted mean difference, 1.07 g; 95% confidence interval, 0.14-1.99; 4 trials) (Rao *et al.* 2009).

PROBIOTICS AND MEDICAL OUTCOMES

Probiotic supplements have been shown to shorten the length of stay in trauma patients (Falcao, I and de Aguilar-Nascimento, 2004; Kotzampassi *et al.* 2006). Length of stay in burn patients reported in the literature ranges from 22 to184 days (mean: 75.7 days; body surface burn of 51.1 ± 27 % , range 20-90%) (Bargues *et al.* 2009), from 1 to 114 days (The median and mean hospital stays were 16 and 22.8 days, respectively; The mean TBSA burned was 9.4 ± 15.3% in adults and 19.8 ± 18.6% in children) (Kut *et al.* 2006), and from 1 to 86 days (mean: 12 days; the median TBSA burned was 14%, range 1-100%) (Soares de Macedo and Santos, 2006).

Remembering the study by Fukushima *et al* (Fukushima *et al.* 2007) (significant increase in hemoglobin, serum albumin and significant decrease in TNF-α at 12 weeks of administration of fermented milk containing the probiotic L. johnsonii La1 through enteral nutrition), it seems that burn patients who will be staying more than 2 weeks would probably be the group which would be most benefited from probiotic supplementation.

BENEFICIAL EFFECTS OF PROBIOTICS IN BURN PATIENTS

Possibly probiotics may benefit burn patients in different hypothetical pathways: their direct/indirect effect on *i*) albumin biosynthesis, *ii*) transcapillary leak, *iii*) suppression of inflammation/immunomodulation, *iv*) prevention of bacterial translocation, *v*) weight gain promotion, and *iv*) possibly other pathways.

In vitro (in cultured colonocytes) (Panigrahi *et al.* 2007) and animal studies (Brunt *et al.* 2008; Harding *et al.* 2008) have shown that probiotics directly enhance protein synthesis possibly through induction of genes involved in regulation of transcription and protein biosynthesis (Jeschke *et al.* 2004b).

Severe burn induces the hepatic APR (Jeschke *et al.* 2004a; Wu *et al.* 2004). Despite adequate nutritional support, a severe thermal injury induced the proinflammatory APR for a prolonged period. Thus, the liver with the hepatic APR plays a more important role during catabolism after burn than previously believed (Matsumoto *et al.* 2007). Data from human (Jiang *et al.* 2010) and animal (Braga *et al.* 1998; Emmanuel *et al.* 2007; Gianotti *et al.* 1999) trials confirmed that probiotics significantly suppressed APR, lessened the anorexic effects of Lipopolysaccharide-induced APR resulting in a trend toward body weight gain (Wischmeyer *et al.* 2001).

It is well-known that injury promotes the synthesis of acute phase proteins through the release of proinflammatory cytokines such as TNF-α, and IL-6. This may be associated with a quick impairment of the nitrogen balance, loss of lean body mass, and catabolism (Braga *et al.* 1998; Emmanuel *et al.* 2007). The postburn drop in prealbumin, retinol binding protein, albumin, and transferrin levels confirms that burns impair the synthesis of constitutive proteins and induces a sharp production of proinflammatory cytokines (Braga *et al.* 1998; Peng *et al.* 2005; Wischmeyer *et al.* 2001). Albumin synthesis is suppressed when there is inflammation (Kaysen *et al.* 2004).

Different probiotics have been shown to significantly suppress plasma levels of pro-inflammatory cytokines (TNF-α, 1L-1β, IL-6 and IFN-γ) and to enhance anti-inflammatory cytokines (IL-10 and TGF-β) (Nishitani *et al.* 2009; Selvam *et al.* 2009; Twetman *et al.* 2009). Increased albumin synthesis following probiotic supplementation plasma may be partly related to changes in cytokine profiles, which stimulate the acute phase response. Probiotic treatment decreased circulating levels of TNF- α and IL-6 while concurrently increasing circulating levels of IL-10 (Llopis *et al.* 2009; Loguercio *et al.* 2005; McCarthy *et al.* 2003). Through their effects on peroxisome proliferators activated receptors, butyric and propionic acids, which are formed as a result of fermentation of fiber by probiotic bacteria, may reduce the expression of adhesion molecules and exert anti-inflammatory action both in the gastrointestinal tract as well as systemically (Di *et al.* 2005). The mechanisms of action might involve direct immunomodulatory effect (Giamarellos-Bourboulis *et al.* 2009; Naruszewicz and Kozlowska-Wojciechowska, 2005), prevention of bacterial translocation (Besselink *et al.* 2009; Giamarellos-Bourboulis *et al.* 2009), or more likely a combination of both.

The profound hypermetabolic response to burn injury is associated with insulin resistance and hyperglycemia, significantly contributing to the incidence of morbidity and mortality in this patient population. These responses are present in all trauma, surgical, or critically ill patients, but the severity, length, and magnitude is unique for burn patients (Gauglitz *et al.* 2008). Probiotics have been shown to significantly improve insulin sensitivity and glucose tolerance (Laitinen *et al.* 2009; Yadav *et al.* 2007; Yadav *et al.* 2008), which consequently improves the systemic inflammatory reaction to severe trauma in burn patients (Jeschke *et al.* 2004b).

Probiotic may also acts as a shuttle liberating effective enzymes, proteins and trophic factors during their intestinal transit that improve host immune defenses, digestion, and absorption of nutrients. For example, Saccharomyces boulardii,

which is a non-pathogenic biotherapeutic agent, widely prescribed in a lyophilized form in many countries over the world, secretes during its intestinal transit polyamines, mainly spermine and spermidine that regulate gene expression and protein synthesis (Buts and De, 2006).

To date the mechanism of these immunomodulatory effects is not well understood. To unravel the immunomodulatory signaling mechanism, Kim *et al* (Kim *et al.* 2006) investigated the effects of two strains of *Lactobacillus rhamnosus* (a human commensal with known immunomodulatory properties), L. rhamnosus GG and GR-1, in modulating production of TNF-α in human monocytic cell line THP-1 and mouse macrophages. Live L. rhamnosus GG and GR-1 or their spent culture supernatant induced minuscule amounts of TNF production but large quantities of granulocyte-colony stimulating factor (G-CSF) in macrophages compared with those induced by pathogenic Escherichia coli GR-12 and *Enterococcus faecalis*. They demonstrated that G-CSF secreted from L. rhamnosus GG- and GR-1-exposed macrophages suppressed TNF-α production induced by E. coli- or lipopolysaccharide-activated macrophages through a paracrine route. The suppression of TNF-α production by G-CSF was mediated through activation of STAT3 and subsequent inhibition of c-Jun-N-terminal kinases (JNKs). The inhibition of JNK activation required STAT3α-mediated de novo protein synthesis. Their finding demonstrated a novel role of G-CSF in L. rhamnosus-triggered anti-inflammatory effects and its mechanism in the suppression of TNF-α production in macrophages (Kim *et al.* 2006).

FEEDING IN BURN PATIENTS

Whenever gastrointestinal function permits it, enteral nutrition was superior to parenteral nutrition early after burns (Chen *et al.* 2007). In patients with major trauma and burns, total enteral nutrition significantly decreased the APR and incidence of septic complications when compared with TPN. Poor outcome in acute pancreatitis was associated with a high incidence of systemic inflammatory response syndrome and sepsis (Windsor *et al.* 1998b).

I suggest that burned patients supplemented with probiotcs would require less albumin substitution to maintain normal levels compared with patients who are not supplemented with probiotics. Implications of probiotcs supplementation may cover burn patients who are on oral and /or enteral feedings. Some hepatic acute phase and constitutive proteins remain abnormal even 2 years after injury (Thomas *et al.* 2004). Thus, patients who had been receiving TPN might be benefited from probiotcs "after" weaning from TPN and during convalescence form a thermal injury.

CONCLUSION

Different affect of serum albumin synthesized by the body from administered albumin, which may be different in functions, on mortality and morbidity may partly explain this discrepancy. Either that or it is not the albumin itself that is having an effect, but something else, the synthesis of which by the body is also changed by the probiotics.

It might be concluded that when serum albumin is being kept continuously normal by providing adequate nutrition/ and or probiotics, problems with rapid systemic changes that include cardiovascular, hematological, renal, pulmonary, and immunological effects (Alderson *et al.* 2004) are better avoided than when albumin is rapidly "administered" or "normalized" with human albumin solution.

It would be difficult to administer HAS totally tailored to suit the individual patient and timed to mirror the dynamic pathophysiological processes underlying burn shock. However, enhanced albumin synthesis in severely burned patients during the flow phase (Martini *et al.* 2010), and significant improvement in the distribution rate of albumin from vessel to tissue, and decomposition rate of albumin in patients with severe sepsis (Li *et al.* 2003), suggest that endogenously timely synthesized albumin may function better than administered human albumin solution in terms of tailoring to suit the individual patient and mitigating or maybe "damping down" dynamic pathophysiological processes.

To the best of my knowledge, probiotics have shown no harm in ICU patients (except for a postburn acute pancreatitis in some cases of severely burned patients), and their use has shown beneficial effects in terms of lower incidence of diarrhea (Whelan, 2007; Madsen, 2008), lower VAP (Siempos *et al.* 2010), enhanced immune function (Madsen, 2008), delayed respiratory tract colonization/infection by *Pseudomonas aeruginosa* (Forestier *et al.* 2008), and fewer infectious episodes (Koretz, 2009).

At present there are no clinical trials investigating the effect of a probiotic on the nutritional status of burn patients and their clinical outcomes. Large clinical trials of the efficacy of probiotics in improving nutritional status and clinical outcomes in burn patients are warranted. Available evidence on beneficial effects of probiotics on albumin synthesis, prevention of bacterial dislocation, immunomodulation, and weight promoting effects seem to justify running clinical trials of probiotics supplementation in burn patients.

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