0148-6071/01/2504-0174$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 25, No. 4
Printed in U.S.A.

Original Communications

Most Infectious Complications in Parenterally Fed Trauma Patients Are Not Due to Elevated Blood Glucose Levels

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ABSTRACT. *Objective:* To determine the relationship between hyperglycemia and infectious complications in nutritional studies of trauma patients. *Methods:* Retrospective review of serum glucose values in two published randomized, prospective studies of patients receiving either enteral or parenteral feeding (trial 1) or isonitrogenous, isocaloric enteral diets (trial 2). Trial 2 also included patients prospectively followed who received little or no enteral feeding. *Results:* Patients randomized to enteral or parenteral feeding in trial 1 exhibited no significant differences in the highest recorded serum glucose (SG) until the fourth or fifth day after protocol entry. SG tended to be higher in infected than noninfected patients in the first 4 hospital days, but SG was far below values considered to increase the risk for infection (SG > 220 mg/dL). In trial 2, glucose levels tended to be slightly higher in infected than in noninfected patients within the first 5 days reaching statistical significance by day 5. Unfed control patients had similar SG values but significantly more major infectious complications. *Conclusions:* Patients developing infections had slightly higher SG levels than noninfected patients early in admission, but these SG values were far below levels considered a risk for infective complications. Significant hyperglycemia does not explain differences in infectious complications in critically ill trauma patients randomized to various routes and types of nutrition. (*Journal of Parenteral and Enteral Nutrition* **25:**174–179, 2001)

Laboratory and clinical studies demonstrate the advantages of enteral delivery of nutrients in reducing septic morbidity compared with parenteral feeding.[1–10] Proposed mechanisms for this increase in sepsis with total parenteral nutrition (TPN) include changes in gut permeability, bacterial translocation, and impaired mucosal immunity. Recently, hyperglycemia due to overfeeding leading to immunosuppression through polymorphonuclear leukocyte (PMN) dysfunction and glycosylation of immunoglobulins has been proposed as a potential cause of increased septic complications with parenteral nutrition.[11] The support of this argument is threefold. First, diabetic patients undergoing major cardiovascular or abdominal surgery, sustaining hyperglycemia (>220 mg/dL) on postoperative day 1, had an infection rate 2.7 times that observed in diabetic patients with serum glucose values <220 mg/dL.[11] Second, in the Veterans Affairs (VA) Cooperative Study of perioperative parenteral nutrition of general surgical patients, hyperglycemia (>300 g/dL) occurred in significantly more patients receiving parenteral nutrition in the perioperative period.[12] Third, in the meta-analysis of randomized trials comparing parenteral and enteral nutrition in critically ill surgical patients or critically injured patients, the mean glucose value was >200 mg/dL in the parenterally fed group on days 7 to 9 of the study compared with 132 mg/dL in the enteral-fed group during the same time frame.[13] As a result, speculation[11] evolved that differences in infectious outcome between enteral- and parenteral-fed patients are likely due to overfeeding and hyperglycemia with parenteral feeding.

To investigate the incidence of hyperglycemia in our two previously published studies[4,5] of trauma patients randomized to enteral, parenteral, or specialty enteral diets, we specifically examined the relationship between early hyperglycemia and septic morbidity and concluded that hyperglycemia fails to explain significant differences in infectious complication rates seen when route and type of nutrition are varied.

METHODS

A retrospective review was performed on the charts of 149 severely injured trauma patients requiring emergent celiotomy who had previously been entered into 1 of 2 trials comparing enteral *vs* parenteral feeding (trial 1: 98 patients)[4] or patients randomized to isonitrogenous, isocaloric diets (trial 2: 51 patients).[5] In the latter study, patients eligible for entry into the protocol but without enteral access were prospectively followed (but not randomized) for the development of infectious complications. Details regarding specific nutrient formulas, diet protocols, criteria for entry and diagnosis of infectious demographics, specific infectious complications, and measurements of nutritional status are extensively detailed in the index publications and are not reiterated in this paper. The present review evaluates all serum glucose values of each patient for the first 5 days of hospitalization to deter-

Received for publication, February 22, 2000.
Accepted for publication, February 16, 2001.
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mine the relationship between blood glucose values and the subsequent development of infection. The Institutional Review Board of The University of Tennessee Health Science Center approved the study design.

Trial 1

A total of 98 patients with an Abdominal Trauma Index (ATI) of 15 or greater were randomized to either enteral (ENT) or parenteral (TPN) diets within 24 hours of injury. Patients receiving the enteral diet received 11.6 ± 3.1 kcal/kg/d of glucose in the formula and sustained a significantly lower incidence in septic complications (ENT: 15.7% *vs* TPN: 40%, $p < .02$) after blunt and penetrating trauma. Parenterally fed patients received 14.1 ± 2.4 kcal/kg/d of glucose in the TPN formula. In addition to enteral *vs* parenteral comparisons, we divided trial 1 patients into 4 groups based on route of nutrition and infectious status: enteral noninfected (ENT-NON), enteral infected (ENT-INF), parenteral noninfected (TPN-NON), and parenteral infected (TPN-INF). Nine patients had no glucose levels recorded (2 patients died within 4 days of study entry), leaving 89 for this analysis (ENT, n = 46; TPN, n = 43).

Trial 2

Trauma patients admitted into this study required emergency laparotomy and had an ATI ≥ 25 or an Injury Severity Score (ISS) ≥ 20. Enteral access was obtained in 33 patients who were randomized to either the immune-enhancing diet (IED; n = 16) or an isocaloric, isonitrogenous diet (ISO; n = 17). Patients who met criteria for entry into the study by severity of injury (ISS or ATI), but who had no enteral access to start early enteral feedings, served as controls (n = 18) to evaluate outcome in patients receiving no specialized nutrition support. Patients given the immune-enhancing diet received 14.4 ± 1.3 kcal/kg/d of glucose in the enteral formula while the control diet patients received 14.3 ± 1.2 kcal/d. Sixteen of 18 patients in the unrandomized, but prospectively studied arm of the trial received no specialized nutrition support before the development of infectious complications; the amount of glucose in the IV fluids was unknown. Significantly fewer major infectious complications were noted in patients receiving the immune-enhancing diet (6%) compared with the other 2 groups (Isonitrogenous diet: 41% $p = .02$; nonrandomized, unfed control group: 58% $p < .002$). The highest incidence of major infectious complications occurred in the "unfed" patient population. Serum glucose levels were evaluable for all patients in this trial.

Statistical analysis

Significance for discrete (categorical) variables was determined with the χ^2 test of homogeneity or Fisher's exact test; all continuous variables were tested with either *t* tests or Mann–Whitney U tests. Before making each *t* test, we tested the assumption of equal or unequal variances with an F test and used the appropriate *t* test. Two-way analysis of variance was used to assess differences for infected and noninfected patients, for glucose per kilogram per day, and ISS and ATI scores. A repeated measures analysis of variance compared glucose values over time.

TABLE I
Maximum glucose values (mg/dL) during the first five days of hospitalization in patients receiving enteral (ENT) or TPN feedings

Diet	Day 1	Day 2	Day 3	Day 4	Day 5
ENT	159 ± 41	142 ± 24	141 ± 34	146 ± 42	145 ± 56
TPN	157 ± 32	154 ± 34	155 ± 31	164 ± 38*	179 ± 63†

*$p < .05$ *vs* ENT Day 4.
†$p < .02$ *vs* ENT Day 5.
ENT, enteral diet; TPN, parenteral diet.

RESULTS: TRIAL 1

Maximum blood glucose values over time in ENT and TPN patients

In this trial, TPN resulted in significantly more infectious complications than ENT feeding (17/43 [39.5%] TPN *vs* 8/46 [17.4%] ENT, $p < .02$). The maximum blood glucose values in mg/dL during the first 5 days of hospitalization is shown in Table I. There were no significant differences in blood glucoses between ENT and TPN patients until the fourth and fifth day of hospitalization when infections began to complicate postinjury recovery. Despite the significantly higher infectious rate and higher glucose levels with TPN, average maximum glucose values in either the TPN or ENT group were far below levels considered a risk factor for increased septic complications (>220 mg/dL).

Maximum blood glucose values in infected vs *noninfected patients regardless of route of feeding*

When route of nutrition is ignored and infected patients are compared with noninfected patients over the first 5 days of hospitalization, there were no significant differences in maximal (Fig. 1) or mean (Fig. 2) serum glucose values until the fifth day of hospitalization when infectious complications and the elicited stress response began to complicate postinjury recovery. Not until day 5 did infected patients have significantly higher maximum ($p = .007$) and mean ($p < .02$) serum glucose levels than noninfected patients. There were no significant differences between infected and noninfected patients in ATI (INF = 40.5 ± 5.9 *vs* NON = 42.6 ± 6.9, *ns*) or ISS (INF = 22.9 ± 2.8 *vs* NON = 29.7 ± 3.9, *ns*).

Influences of route of nutrition and infectious complications on maximum glucose values over time

When stratified by *both* route of nutrition and the presence or absence of infectious complications, mean maximum glucose levels in infected patients were higher than noninfected patients in both ENT and TPN groups during the first 4 hospital days, reaching statistical significance on day 2 (Table II). However, these values were well below levels considered at risk for

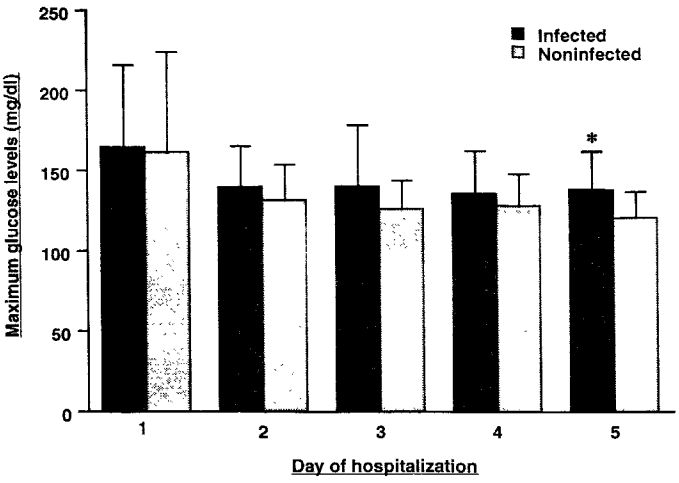

FIG. 1. Maximum glucose levels in m/dL over the first five days of hospitalization in infected and noninfected patients. There were no significant differences until the fifth day when infected patients had significantly higher blood sugars than noninfected patients.

deleterious effects on neutrophils and development of infection (ie, SG > 220 mg/dL).

Figure 3 demonstrates the outcome of patients with at least a *single* blood glucose level above or *all* blood glucose values below 220 mg/dL. Of the patients who developed an infection, 68% (17 of 25) never had a single blood glucose >220 mg/dL. Only 15 (17%; 5 ENT and 10 TPN) of the 89 patients entered into the studies experienced a glucose > 220 mg/dL at any time during the first 5 days of hospitalization, and 8 (2 ENT and 6 TPN) of these 15 became infected. Of the patients with all blood glucoses below 220 mg/dL, 17 of 74 (23%) became infected, accounting for two-thirds of all infections. Although the incidence of infection was significantly higher in the small group of patients that had blood glucose >220 mg/dL (8 of 15 hyperglycemic *vs* 17 of 74 nonhyperglycemic, $p < .03$), the majority of hyperglycemic episodes were sporadic, isolated

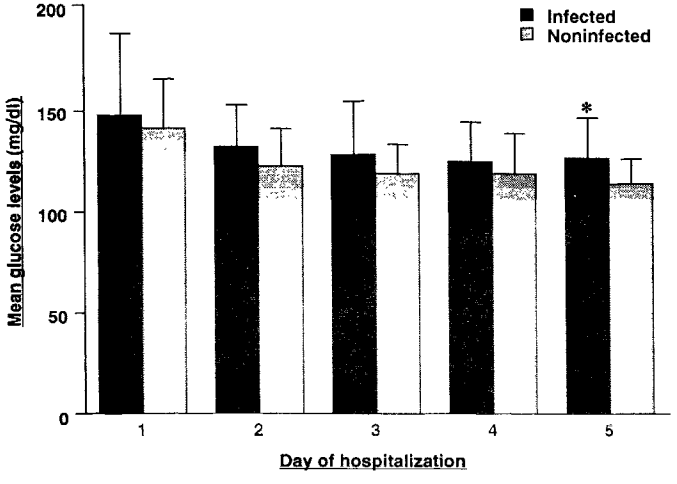

FIG. 2. Mean glucose level in infected *vs* noninfected patients over the first five days of hospitalization. There were no significant differences until the fifth hospital day as infectious complications developed.

TABLE II
Maximum glucose values (mg/dL) during the first four days of hospitalization

	n	Day 1	Day 2	Day 3	Day 4
ENT-NON	38	154 ± 33	140 ± 21[a]	136 ± 17[c,d]	141 ± 56[f]
ENT-INF	8	181 ± 60	154 ± 30	168 ± 68[c']	168 ± 74
TPN-NON	26	149 ± 32	140 ± 25[b]	146 ± 27[e]	158 ± 39
TPN-INF	17	168 ± 26	173 ± 37[a',b']	169 ± 31[d',e']	173 ± 36[f]

a *vs* a': $p < .0001$; b *vs* b': $p = .0002$; c *vs* c': $p < .01$; d *vs* d': $p = .003$; e *vs* e': $p < .02$; f *vs* f': $p < .007$.
ENT-NON, enteral noninfected; ENT-INF, enteral infected; TPN-NON, parenteral noninfected; TPN-INF, parenteral infected.

instances, and the majority of them occurred on the fourth or fifth hospital day as infectious complications were diagnosed and treated.

Cumulative incidence of hyperglycemic episodes over time

Table III stratifies patients with enteral or parenteral feeding by the presence or absence of hyperglycemia and the day on which hyperglycemia occurred. The stratification was carried out at 2 blood glucose levels: blood sugars >220 g/dL or blood glucose values ≥200 mg/dL. Of the 25 ENT or TPN patients who became infected, 20 (80%) never had a blood glucose >220 during the first 4 days of hospitalization, and 14 (56%) never had a blood glucose value above 200 mg/dL.

Only 2 of 46 (4.3%) of ENT and 3 of 43 (6.9%) TPN patients developed infectious complications preceded by a blood glucose >220 mg/dL at any time during the first 4 hospitalization days. Of the 6 infected TPN patients with a glucose value >220 by the fifth day, 4 had a single episode or day of hyperglycemia, and 3 of these episodes occurred on the fifth hospital day as infectious complications developed. The majority of infected or noninfected patients maintained blood sugars below 200 mg/dL in both ENT and TPN groups and were rapidly controlled when they became hyperglycemic.

If blood glucose plays any role in infectious complications of hyperglycemic trauma patients after injury, enteral feeding appeared protective. Three of 5 (60%) ENT patients with glucose values >220 mg/dL during the first 5 days of hospitalization developed no infectious complications *vs* 4 of 10 (40%) of TPN patients. Likewise, in patients with a glucose >200 mg/dL, 6 of 8 (75%) ENT patients *vs* 7 of 18 (38.9%) TPN patients remained free of infectious complications.

RESULTS: TRIAL 2

There were no differences in ATI or ISS between groups or between infected and noninfected patients. Despite significant differences in rates of infectious complications among the 3 groups, serum glucose levels were similar among them (Fig. 4). There were no significant differences in mean or maximum (Fig. 4) serum glucose values between infected and noninfected patients during the first 5 days of hospitalization. Although infected patients tended to have higher glucose levels than noninfected patients, this did not reach statistical significance, and the glucose values

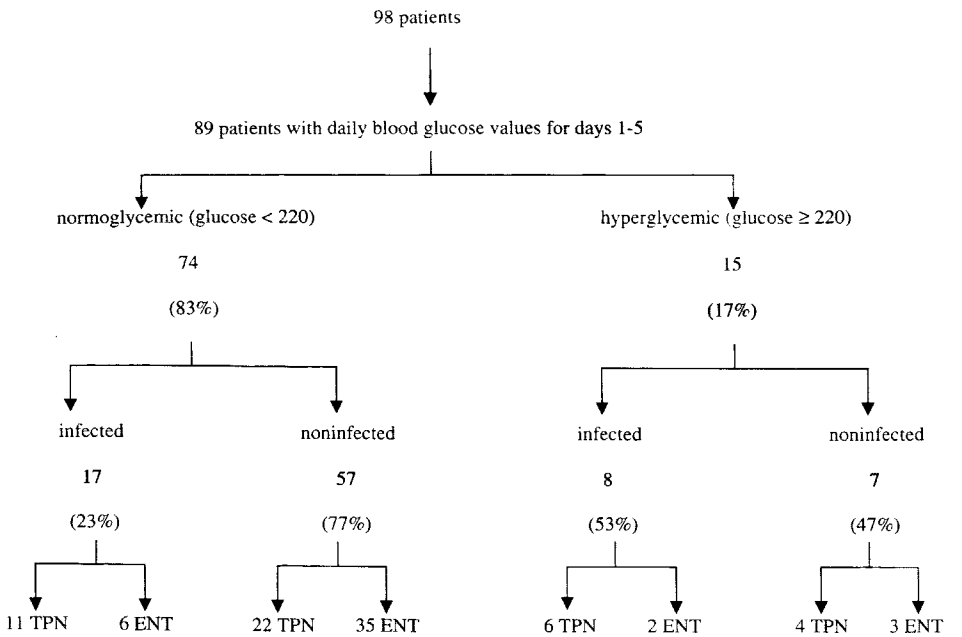

FIG. 3. The incidence of infected and noninfected patients in normal glycemic and hyperglycemic patients randomized to parenteral nutrition (TPN) or enteral (ENT) feeding.

were far below 220 mg/dL. Of the 27 patients who eventually became infected, only 5 patients (Table IV) had any SG levels above 220 mg/dL (1 immune-enhancing diet, 3 isonitrogenous, isocaloric control diets, and 1 unfed control patient). There was no association between infection and glucose values in this study.

DISCUSSION

The proposed mechanisms by which elevated serum glucose increase infectious complications is through impairment of PMN function and the glycosylation of immunoglobulins.[11] The level of hyperglycemia associated with increased risks of infection in diabetic patients has been reported to be >220 mg/dL, and although there is some conflicting evidence with regard to PMN function in diabetes,[13–17] investigators have noted improvement in granulocyte adherence,[18] chemotaxis,[19] and phagocytosis[20] with control of blood glucose below 220 mg/dL.

Clinically, Pomposelli and colleagues[10] confirmed the importance of glucose control in the first 2 postoperative days in diabetic patients. By avoiding glucose levels in this select group of patients above 220 mg/dL, the incidence of infectious complications was significantly reduced. Although hyperglycemia appears to affect outcome in a diabetic population, we do not agree that overfeeding and elevated postoperative glucose levels explain the clinical outcome differences in nutrition studies of trauma patients as suggested by these authors. In our analysis of glucose values obtained in 2 randomized, prospective studies of patients sustaining severe blunt and penetrating torso trauma, the average maximum serum glucose levels recorded over the first 5 days of hospitalization ranged from 120 mg/dL to 165 mg/dL in trauma patients randomized to enteral or parenteral feeding. These values are well below the 220 mg/dL considered necessary to interfere with granulocyte function. In addition, 70% of TPN patients and 75% of the enteral patients who became infected never had a blood glucose > 220 mg/dL, and the majority of infectious complications could not be explained by hyperglycemia even when the lower value of 200 mg/dL was chosen. An even stronger case can be made in the second study of very severely injured patients where

TABLE III
Cumulative incidence of infectious complications over the first five days of hospitalization

Through Hospital Day	Patients with Blood Glucose ≥220*				Patients with Blood Glucose ≥200*			
	Enteral		TPN		Enteral		TPN	
	Noninfected (n = 36)	Infected (n = 8)	Noninfected (n = 26)	Infected (n = 17)	Noninfected	Infected	Noninfected	Infected
1	2	2	1	0	5	2	2	3
2	2	2	2	1	5	2	3	6
3	2	2	2	1	5	2	4	6
4	3	2	3	3	6	2	6	7
5	3	2	4	6	6	2	7	11

*Once patients are listed on a particular day, they remain in the cumulative total even if the episode was an isolated, single event.
TPN, parenteral diet.

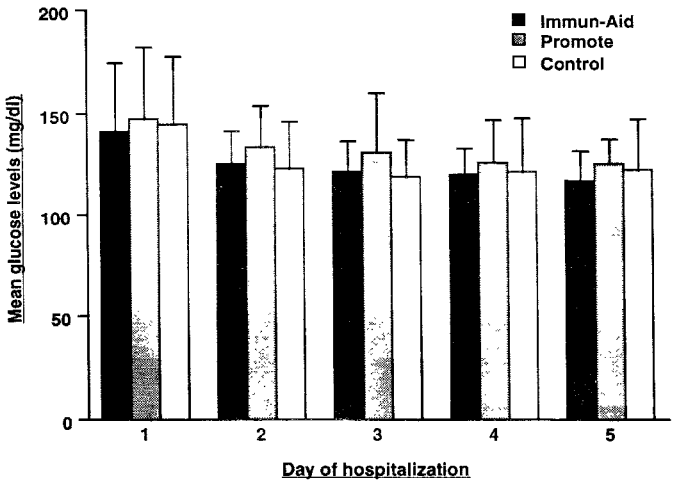

FIG. 4. Mean glucose values for patients randomized to an immune-enhancing diet, an isonitrogenous, isocaloric control diet, or an unfed patient population. There were no significant differences in blood glucose values between any of the groups during the first five days of hospitalization.

major septic episodes were influenced by diet but almost no patients developed hyperglycemic episodes. Therefore, unless one implicates totally different mechanisms for the development of infectious complications in these 2 studies, hyperglycemia plays a relatively unimportant part in the development of abscess and pneumonia after severe trauma. We conclude that route and type of nutrition appear to be the most important determinant of infectious complications in these studies rather than level of serum glucose.

These results seem to be at odds with Pomposelli's interpretation of published data from the VA cooperative study[11] and the meta-analysis of enterally and parenterally fed trauma and general surgical patients.[3] In the VA cooperative study, however, although glucose levels were significantly higher in parenterally fed patients, it is unknown when the hyperglycemia occurred during the clinical course and whether it occurred before, during, or after the onset of infectious or noninfectious complications which themselves aggravate hyperglycemia through release of cytokines, cortisol, and catecholamines. Similarly, within the meta-analysis, blood sugars were significantly higher in parenterally fed patients at baseline (160 mg/dL) or at the midpoint of the study (days 4 to 6) when glucose levels approximated 178 mg/dL. However, the severe hyperglycemia (>200 mg/dL) associated with increased infectious rates in parenteral patients did not occur until the end of the study (on days 7 to 9) in a time frame characterized by the presence of septic complications in a severely injured trauma population.

We interpret our results to mean that hyperglycemia appears to be a *response to* septic morbidity rather than the *cause of* septic morbidity. The majority of infectious complications were diagnosed between the fourth and eighth hospital day. It is impossible, however, to determine exactly how long infectious complications manifested themselves metabolically before their diagnosis. For example, although diagnosis of an intra-abdominal abscess may be made by CAT scan on the sixth hospital day, that infectious complication certainly had been present before the diagnosis, inducing the metabolic changes of stress. Similarly, there is almost certainly an active infective process occurring within pulmonary parenchyma before more obvious manifestation of pulmonary infiltrates and purulent sputum, which readily leads to the diagnosis of pneumonia and the institution of therapy. It seems logical, but unprovable, that the hyperglycemia noted in infected patients in the first few days after injury was a metabolic response to the developing infection; thus, it is no surprise that patients who ultimately become infected are more hyperglycemic early in their hospital stay. Despite this, most remain far below the 220 mg/dL, which has been associated with neutrophil dysfunction. Unfortunately, the increase in hyperglycemia in patients who develop infections is not helpful as a diagnostic tool because a 15 mg/dL difference in glucose between infected and noninfected groups (shown on Table I) is too subtle to be clinically relevant and probably too low to impair immune defenses.

This is not to say that hyperglycemia may not play some role; patients with glucose values >220 mg/dL had a significantly higher rate of infectious complications (55%) than patients whose blood sugars were below 220 mg/dL (23%), and thereby, hyperglycemia may aggravate the infectious complications. But this effect probably is relatively minor as shown in the second trial where severely injured trauma patients with an ATI > 25 or an ISS > 20 had a range of major septic infectious complications from 6% to 58% depending upon nutrition therapy, but average blood sugars remained almost identical between groups. In fact, very few patients in this study had significant hyperglycemia at any time, and patients who received little, if any, nutrition support had the highest rate of major septic complications and could not possibly have been overfed. Taken *in toto*, the increase in infectious complications in any group within the 2 studies cannot be explained by hyperglycemia.

A number of mechanisms have been proposed for the increased infectious complications associated with parenteral feedings. Histologic changes occur within the gastrointestinal tract in association with increases in mucosal permeability and increases in bacterial translocation in animal models.[21–25] Although atrophy does occur within the duodenal mucosa of humans with parenteral nutrition,[22] the extent of the histologic changes are not nearly as dramatic as data noted in experiments with rats, which have a proximal small bowel that reduces its mucosal mass by 40% to 50%

TABLE IV
IED vs ISO vs No Feeding

	IED (n = 16)	ISO (n = 17)	No Feeding (n = 19)
Major infections	1 (6%)	7 (41%)	11 (58%)
Number of patients with glucose >220 mg/dL	1	3	1

IED, immune enhancing diet; ISO, isonitrogenous, isocaloric control diet.

when not enterally fed.[23] Increases in permeability do occur after trauma but have returned to normal by day 7, and increases in permeability do not appear to be associated with increases in infectious complications.[24,25] The more likely cause is secondary to atrophy of the gut-associated lymphoid tissue (GALT) associated with parenteral nutrition associated with decreased levels of intestinal and respiratory IgA and loss of established antiviral and antibacterial defenses.[7–9,26–28] Although it has not yet been tested in the clinical population, maintenance of mucosal immunity provides a cogent explanation for differences in the rates of intra-abdominal abscesses and pneumonia in parenterally fed patients.

CONCLUSIONS

Higher rates of infectious complications with parenteral nutrition have been demonstrated in many clinical studies. These findings have been reported by experimental work demonstrating both histologic and immunologic changes associated with parenteral nutrition. Although mild but significant increases in serum glucose may be markers of subsequent infections in critically injured patients, uncontrolled glucose levels do not explain the increased rates of infection associated with parenteral nutrition, at least in trauma and surgical patients.

ACKNOWLEDGMENTS

The authors thank Kazuhiko Fukatsu, MD, for his assistance in preparing the illustrations and Doris Parsons for secretarial support.

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