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Antibiotics and the Postburn Hypermetabolic Response

J. PAUL WAYMACK, M.D., Sc.D.

Severe burn injury has been documented to significantly increase resting metabolic energy expenditure. The increase in metabolic rate appears to be possibly correlated with the degree of burn wound colonization and infection with bacteria. Prevention of such colonization and infection through the use of topical antimicrobial agents appears to decrease the metabolic alterations resulting from burn injury. These findings indicate that appropriate use of topical antibacterial agents may decrease the metabolic demands seen in burned patients. Burn-induced translocation of intestinal bacteria has also been hypothesized to contribute to the postburn hypermetabolic response. Attempts at preventing this entity in a burned guinea pig model through the use of selective decontamination of the digestive tract by the administration of enteral antibiotics have failed to demonstrate any measurable effect.

Major thermal injuries result in marked alterations in metabolic and hemodynamic function in burn victims (22); the changes are among the most profound seen with

any disease process. They include chronic increases in resting metabolic energy expenditure, body temperature, respiratory rate, and cardiac rate, which can be further exaggerated by the presence of superimposed infections. This paper reviews the etiology of these alterations with special reference to the contribution of bacteria to the

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metabolic changes. It also reviews the effect antibacterial agents can have in altering these changes.

EFFECT OF BURN INJURY ON METABOLISM

Burn injury results in multiple metabolic and physiologic alterations. One of the more prominent is the hypermetabolic response which has been demonstrated to increase rapidly following resuscitation, and peak in the second postburn week (2). Patients with massive burn injuries can achieve metabolic rates of 200% of normal during this period (22), making achieving positive nitrogen balance difficult due to the excessive requirements for calories and nitrogen.

EFFECT OF INFECTION ON METABOLISM

Infections can markedly alter physiologic function in both burned and nonburned patients (6). The changes include an increased rate of resting metabolic energy expenditure, plus alterations in protein, carbohydrate, and fat metabolism (12), alterations that appear due primarily to the release of various mediators by the host's leukocytes in response to exposure to microorganisms. The two cytokines which have been most frequently reported to alter metabolism are interleukin-1 (IL-1) and tumor necrosis factor (TNF). Both are produced primarily by monocytes and macrophages as part of their response to exposure to foreign antigens. Each exerts immunostimulatory effects as well as altering multiple components of the host's metabolism.

IL-1 causes muscle protein breakdown with resulting release of free amino acids into the systemic circulation for use by the liver (11). The amino acids are extracted by the liver and utilized for acute phase protein synthesis and gluconeogenesis (10). IL-1 also raises the patient's baseline metabolic rate, induces fever, and stimulates wound healing (13).

TNF can also alter the metabolic response to trauma and wound healing (19). TNF at lower concentrations increases resting metabolic rate and induces fever. Low levels of TNF elevate serum glucose levels through the stimulation of gluconeogenesis and glycogenolysis. Exposure to higher concentrations of TNF are toxic and can result in hypoglycemia, hypothermia, and eventual metabolic exhaustion (16).

EFFECT OF BURN WOUND INFECTION AND COLONIZATION ON METABOLISM

It has been demonstrated in animal models that colonization and infection of burn wound can alter metabolism within days after the burn wound becomes contaminated (20). Studies using rat models have documented alterations in the levels of albumin, transferrin, and complement factor 3 during the initial week following contamination of the burn wound with *Pseudomonas aeruginosa*, and noted that these changes precede measurable changes in resting metabolic energy expenditure.

In patients with extensive burn wounds it is well established that there is a gradual increase in burn wound colonization (18); this occurs despite the use of topical antimicrobial agents such as mafenide acetate and silver sulfadiazine. Such agents merely delay the onset of and decrease the level of bacterial colonization. With the use of such agents, significant colonization of the burn wound does not usually occur until 1 to 2 weeks following the burn injury.

Colonization of the burn wound with bacteria may in part be responsible for the hypermetabolic response seen in burned patients. Support for this hypothesis comes from the work of Aulick and his colleagues. In one study they subjected rats to a 30% total-body-surface area scald burn and infected half the animals with nonvirulent *Pseudomonas aeruginosa* strain (3). At days 3-4 and 7-8 following burn injury the rate of oxygen consumption in both the seeded and unseeded burned rats was elevated compared to preburn consumption. More important, the rate was significantly greater in the seeded group compared to the unseeded group at both time sequences (Table I). This difference was no longer apparent at 14-15 days after burn injury; however, at that time cultures revealed that the degree of bacterial colonization of the burn wounds was equal in the seeded and unseeded groups. Aulick et al. also noted that seeding increased core temperature at days 3-4 and 7-8 following burn injury compared to unseeded rats (Table I). As with the rate of oxygen consumption, this difference was no longer apparent at days 14-15 after the burn.

If the bacteria which colonize the burn wound are responsible for the hypermetabolic response, then prevention or delay of the response should be possible through the use of topical antibacterial agents. This was reported to be the case in another study by Aulick et al. (4). They subjected rats to the same burn injury and infected one third with *Staphylococcus epidermis*, one third with either a virulent or nonvirulent *P. aeruginosa*, and left one third of the wounds unseeded. The burn wounds were then treated with either topical silver sulfadiazine, topical mafenide acetate, or were given no treatment. Two weeks after burn injury metabolic rates were measured, blood and spleens were cultured, plus the wounds were examined histologically. Burn injury resulted in an increase in the rate of oxygen consumption

TABLE I
Metabolic parameters in burned rats seeded with *P. aeruginosa* and unseeded

Postburn Day	Unseeded Burn	Seeded Burn	p
Oxygen Consumption (ml/hr/kg)			
3-4	0.88 ± 0.02	1.07 ± 0.02	<0.001
7-8	0.94 ± 0.02	1.11 ± 0.02	<0.01
Colonic Temperature (°C)			
3-4	37.0 ± 0.1	37.4 ± 0.1	<0.01
7-8	37.0 ± 0.1	37.4 ± 0.1	<0.01

from 0.81 ± 0.01 ml/hr/gm immediately before burn injury, to 0.99 ± 0.02 ml/hr/gm in nonbacteremic rats at 2 weeks following burn injury. The animals found to be bacteremic, as evidenced by positive blood or spleen cultures plus histologic documentation of burn wound invasion, were also found to have a significant increase in the rate of oxygen consumption of from 0.83 ± 0.01 ml/hr/gm to 1.20 ± 0.01 ml/hr/gm. The oxygen consumption increase in the bacteremic rats was significantly greater than in the nonbacteremic rats ($p < 0.001$). The bacteremic rats were noted to have a significant increase in the core body temperature of from $36.8 \pm 0.1^\circ\text{C}$ to $37.7 \pm 0.1^\circ\text{C}$ ($p < 0.01$), whereas the nonbacteremic rats did not exhibit a significant change in temperature ($37.1 \pm 0.1^\circ\text{C}$ to $37.3 \pm 0.1^\circ\text{C}$). Finally, the increase in the rate of oxygen consumption seen in burned rats seeded with both virulent and nonvirulent strains of *P. aeruginosa* was noted to be preventable by treatment with mafenide acetate cream. The mafenide acetate was noted to decrease concurrently the bacterial content of the seeded wounds to the levels seen in wounds of unseeded rats.

The burn wound colonization effect on metabolism does not appear to be mediated through endotoxin. It has been reported that a constant infusion of *P. aeruginosa* lipopolysaccharide endotoxin (LPS) into the subcutaneous tissue of burn wounds in a rat model failed to alter resting metabolic rate (5). It was further noted that when burned rats had wounds seeded with nonvirulent *P. aeruginosa* and were allowed to become hypermetabolic, there were no measurable levels of endotoxin in the serum of any of the rats. The increased metabolic rate demonstrated in burned rats colonized and infected with *P. aeruginosa* thus appears due to release of substances other than or in addition to LPS.

The development of infections in burned patients has also been demonstrated to alter the liver's response to burn injury. Wilmore et al. documented an increased rate of hepatic alanine uptake and glucose production in burned patients compared to nonburned controls (23). When burned patients with an infection were compared to noninfected burned patients, the liver's uptake of alanine and production of glucose became greater than in burned patients without evidence of infections. This increased rate of gluconeogenesis by the liver in response to burn injury and infection ultimately decreased in severely septic patients who had developed multiple organ system failure.

EFFECT OF GUT TRANSLOCATION ON METABOLISM

Another physiologic alteration which may result from major burn injury is the translocation of bacteria and/or endotoxin from inside the gut lumen, through the mucosa, and into the submucosa (7, 9, 15). Once there, the bacteria and/or endotoxin can be transported by either lymphatic channels or mesenteric veins to the systemic

circulation. Upon entering the portal or systemic circulation such products can markedly alter host metabolism.

Although questioned by Wood (24), it has been reported by Mochizuki et al. that administration of enteral feedings in the immediate postburn period blunts the postburn hypermetabolic response and prevents atrophy of the mucosal tissue (17). These two facts may be related in that protection of the mucosa has been hypothesized to prevent or decrease gut translocation of bacteria, and endotoxin. Arita et al. have previously demonstrated in a guinea pig model that infusion of endotoxin into the portal vein results in a significant increase in the animal's basal metabolic rate (1). Infusion of the same endotoxin at a 25-fold greater dosage into the peritoneal cavity failed to result in any measurable hypermetabolic response. These findings led the investigators to hypothesize that it is necessary for the endotoxin to pass through the liver in order for it to be processed by the Kupffer cells. Such cells have the capacity to alter metabolic rate by increasing the rate of synthesis and release of such metabolically active compounds as IL-1 and TNF. These findings suggest that translocation may occur in burned patients and contribute to the postburn hypermetabolic response.

EFFECT OF ENTERAL ANTIBIOTICS ON METABOLISM

It has been hypothesized that prevention of translocation and its sequelae may be possible through the use of selective gut decontamination by enteral antibiotics. If prevention were possible it might be expected to decrease the incidence of infectious complications and to decrease the hypermetabolic response. There have been several reports that administration of enteral antibiotics decreases the incidence of bacterial infections in critically ill patients (8, 14). In one of these studies the decrease was most pronounced in trauma patients (8). These clinical studies did not evaluate the effect of enteral antibiotics on metabolic rate in the patients.

There is one report of an attempt to blunt the postburn hypermetabolic response in a burned guinea pig model by preventing gut translocation through the use of enteral antibiotics. In that study guinea pigs were administered various antibiotics and endotoxin binding agents beginning 24 hours before the infliction of a 30% total-body-surface area full-thickness burn (21). The antibiotic regimens included polymyxin B sulfate 50 mg/kg/day, trimethoprim 4 mg/kg/day, and Sulfamethoxazole 20 mg/kg/day in one group, neomycin 50 mg/kg/day, and clindamycin 15 mg/kg/day in a second group, and neomycin 50 mg/kg/day, clindamycin 15 mg/kg/day, polymyxin B sulfate 10 mg/kg/day, sodium deoxycholate 20 mg/kg/day, and Kaopectate 0.5 ml/kg/day in a third group. A control burn group was administered saline. None of these antibiotic regimens were found to alter the animals' resting metabolic energy expenditure at any

time point during a 2-week study period. The enteral antibiotic regimens also did not alter the animals' liver, jejunal mucosa, ileal mucosa, or carcass weight compared to the saline-treated group measured after 2 weeks of treatment. The splenic weight in the control group was significantly greater than each of the three antibiotic treatment groups (0.80 ± 0.08 gm versus 0.50 ± 0.06 gm, 0.39 ± 0.02 gm, and 0.42 ± 0.05 ; $p < 0.01$ ANOVA). Whether this increased weight represented superior nutrition or immunostimulation from chronic exposure to increased numbers of translocated bacteria and their products was not addressed. The possibility exists that the failure of the enteral antibiotics to alter the metabolic parameters assayed was due to an inability of these agents to adequately sterilize the gut. It also might be the result of antibiotic-related destruction of significant numbers of the intestinal bacteria with resulting liberation of large amounts of endotoxin, which subsequently translocated. However, the multiplicity of antibiotic/endotoxin binding agent regimens makes it more likely that obtaining alterations in metabolic rates in burned patients through the use of enteral agents is not possible.

CONCLUSIONS

Prevention of burn wound colonization by the use of antibacterial agents appears to decrease the magnitude of the postburn hypermetabolic response. Attempts at preventing the hypermetabolic response through the administration of enteral antibiotics has not demonstrated efficacy to date.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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DISCUSSION OF SECTION ON NUTRITION AND METABOLISM

DR. WOLFE: I have really more of a comment than a question. It is in response to some points that Doctor Curreri made with regard to the resting energy expenditure measurements and to share some data which are in press and not yet published. But we have had the opportunity to measure total energy expenditure in burned patients using the double-labeled water method, which integrates energy expenditure over several days and overcomes the problems Doctor Curreri referred to with regard to spot measurements, and related dose measurements to spot measurements of resting energy expenditure measured by indirect calorimetry and also then attempted to relate the total energy expenditure to available equations.

I think the important point is that, in fact, by far the closest correlation was between the total energy expenditure and the resting energy expenditure. It was about 1.3 times the resting energy expenditure. In relating the total energy expenditure to any of the various equations we weren't able to find any significant correlation in those approaches. So that, in fact, I do think, and these are severely burned patients, that there is merit in measuring the resting energy expenditure and that the relationship between resting energy expenditure and total energy expenditure is quite close. Those data will be published in *The American Journal of Physiology* in the next few months.

DR. HEIMBACH: Our clinical experience would confirm that. We have had several patients in whom it has been quite interesting that using the formula, which is what we always use to start out providing nutrition, and we could see how elevated oxygen consumptions can, in fact, be correlated with the amount we are feeding patients. This becomes important in a

patient who has been on a ventilator, who has difficulty in weaning from the ventilator.

If they make so much CO₂ in terms of converting their calories to fat, it is very difficult to wean them from the ventilator. Also, as you decrease the amount of calories that they get, you can just watch a stepwise decrease in their oxygen consumption and often get them off the ventilator. So, I would agree that it is a useful adjunct if not a substitute for the formula.

DR. CURRERI: I would just respond to that. I hope that I didn't give the impression that I think that that is an invalid way of looking at things. I think my concern is, number one, the expense of it and what you get back for that much expense, because it is an expensive procedure. The equipment is not all that expensive because it lasts for quite a period of time, but the technical excellence that is necessary to do it reliably is. I think the second thing that concerns me about it is the fact that people, I believe, hook onto a number that they think is now telling them something that is very interesting, when in fact it might not, depending on the conditions and the environment in which they are taking these measurements.

Now, I have no problem with Bob Wolfe doing it, because he knows how to do indirect calorimetry and he knows what other things have to be controlled to get reliable results. But, I am concerned about it in the community hospital where these carts are being used in ways such that I would guess that the range of measurements at any single time might vary very considerably because of lack of controls.

DR. BLACKBURN: This looks like the end of the nutritional support, and I wonder if we have—one data base that wasn't put on board would be again Wes Alexander's published in the *Journal of Trauma* last year, clinical feeding paradigms of modular feedings between a formula with 30% fat as vegetable oil as opposed to his own formula that virtually eliminates the vegetable oil, drops the per cent of calories as fat and replaces it with fish oil. That also was in the lead article in *JPEN* this month that showed a striking difference in human mortality in burns as well as the major sepsis rate. So I think those two papers should certainly be part of this symposium. It leads me then to ask perhaps, Bill and David and others, what you think is the optimal composition of the enteral component or the total feeding so as to avoid starvation as well as overfeeding in the composition?

DR. HEIMBACH: Let me pass that on to the panelist, Dr. Curreri.

DR. CURRERI: Well, it is a difficult question to answer from a number of aspects. I guess the real question is how necessary is it to get to that ideal diet. But, I think that Wes Alexander has at least convinced me that there is real benefit to the Omega-3 oil saturated fatty acids as he has shown in guinea pigs and now just recently in a small clinical series. As I said at the very end, I think that probably (I think Bob Wolfe said this also) that the amount of fat we give is probably far too high in that we really don't require fat except as a caloric source and for essential fatty acids.

But I think that there might be some real metabolic benefits to the use of Omega-3 fats. For that reason, I think that that needs to be looked at with some degree of promise. I am not aware of any data that have shown benefit to specific protein compositions. I think that some data are beginning to accumulate that the source of carbohydrates may make some difference. But I think it is too early to speculate on that.

DR. HEIMBACH: Paul, what do you do at the world famous burn unit in San Antonio?

DR. WAYMACK: We use the medium-weight triglycerides rather than the Omega-3. I would like to make one comment on the Omega-3. The Omega-3 obviously prevents the synthesis of PGE₂, which is a critical regulator of metabolic and immu-

nologic function. I think the exact importance of this metabolite is still being delineated. It is certainly down regulatory on the immune system. Whether this is good or bad depends on the situation.

I think that there are some other models that Alexander and his colleagues have utilized which have shown that in certain endotoxin situations, a diet such as that increases mortality in their animal models, which I think goes along with some recent data indicating that PGE improves survival in endotoxin shock. So I think we are still a long way away from having the final answer as far as what is the ideal fat composition in burn diets.

DR. HEIMBACH: One of the things that impresses me, from reviewing the literature in preparation for this session today, is that there appears to be a very big species difference between rats and guinea pigs and people and primates and canines and so on, and that comes as no great surprise since our diets are ordinarily very different for the needs that we have. I think that we have to be careful about intercalating what is good for a guinea pig as being what is good for a burned patient. We should keep in mind, I think, that there are reasons that things like glutamine are not supplied in commercial preparations. I think it turns yellow or it smells bad or something after a little while.

For the vast majority of burned patients, it probably doesn't make all that much difference. There are probably only a very few who are teetering on the tightrope of life in whom altering their diet makes a very big difference. But, that doesn't, for a moment, underemphasize the need for finding out what is going on.

DR. F. CALDWELL: I would like to make a comment about the diet. First of all, you know rats do best on cafeteria food. If you want to just measure any parameter, so they may be more like us than you think. That is our approach to feeding. First of all, we establish what the known requirements are for an individual patient using conventional indirect calorimetry and then use hospital food plus supplemented nocturnal enteral feedings to reach that goal.

We have usually reached that by the middle of the second week except in the patients who become septic. Then, feeding is a real problem. We are just getting into the arginine and glutamine area. We are trying their impact on people who have a predicted fatality outcome of 90 plus percent just to see if in this group, we can do something.

DR. HEIMBACH: It is obvious that your rats have never eaten in our cafeteria. Yes, sir.

DR. LONG: Calvin Long, Baptist Medical Center in Birmingham. I have two comments, certainly concerning what Bob said about the factors related to activity. I published in the mid-'70s, not as eloquent in terms of using double-labeled water but simply making some measurements in hospitalized patients with activity diaries, and came up with about 20% of the resting energy expenditure for activity of patients in bed, and for those who were not confined to bed approximately 30%. So it is gratifying to see these confirmations these days based on my early publications which really were not as sophisticated, as I have said.

The second point is that looking at the composition of the fuel mixtures that we should provide patients, I have recently submitted and it has been accepted by the *Journal of Trauma* the use of isotopic-labeled glucose to suggest that the contribution of the diet from carbohydrates should be approximately 60% of calories. Based on nitrogen losses in the urine of patients, we can approximate that the protein intake, on a calorie equivalent basis, should be about 20%. So that leaves about 20% for fat. I think this seems to agree with what Bill has just suggested and I think that the data might be more appropriate with further studies. But, I would suggest these ratios at the present time.

DR. HEIMBACH: Would the panelists agree with them?

DR. WILMORE: David, as close friends as we are, I can't let your comment go by that nutrition in sort of a general sense probably is okay for everybody. I would point out two things. One thing, the glutamine data that I presented simply by adding 40 cents of glutamine took 6 days off the hospitalization of this patient group. That is at \$3000 a day. That may not mean anything to a rich burn surgeon from Seattle but to a poor little researcher from New England, that is pretty good. Second, the

paper that has already been mentioned, where the Omega-3s were added to a diet, showed a reduction in length of stay in the hospital.

What we are seeing is a transition from diet as a food and as a nutrient, to diet affecting physiologic and pharmacologic functions. I think while your comment may be appropriate for the 1980s, this is 1990 and we are looking ahead. I think diet in the future as we can manipulate things will have great impact on that outcome.



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