

Immune Mechanisms and Host Resistance in the Trauma Patient

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Sepsis is responsible for 75 percent of late deaths following major thermal injury or traumatic injury. Efforts to prevent and/or control sepsis should include an understanding of normal host resistance, proper resuscitation techniques, and nutritional support. Recent studies identifying T suppressor cell abnormalities in burn patients and macrophage defects in trauma patients are presented in this paper. Concluding remarks regarding future directions for research and therapy in this area are also made.

INTRODUCTION

As surgical skills have improved over the last several decades, surgeons have operated upon and cared for increasingly critically ill patients. Despite major advances in a number of areas, the problems of infection and sepsis continue to plague us. Although neurologic injury continues to account for approximately 50 percent of deaths following major trauma, sepsis has been identified as a cause of death in 75 percent of late non-neurologic deaths [1]. If a patient survives inhalation injury following a major burn, sepsis constitutes the most significant threat to life thereafter [2]. In these two high-risk groups, sepsis is associated with a 50 percent mortality, which is increased to 75 percent if multiple organ failure supervenes [3].

A number of factors must be considered when evaluating the risk of sepsis for the trauma patient. This article will attempt to highlight the following areas: normal host resistance, specific studies in trauma and burn patients, and future directions for therapy directed at preventing and/or treating sepsis. The area of host resistance and immunology has been rapidly changing with significant advances over the past few years. Because of the complexity of this area and the controversial nature of some of the data in the current literature, this review will attempt to aid the reader in developing a basic understanding of this field and a knowledge of what is currently accepted.

NORMAL HOST RESISTANCE

Host factors involved in defense against bacterial infection have classically been divided into nonspecific and specific factors. A brief outline of these factors is offered below.

Nonspecific Factors

Some of the nonspecific factors that are involved in host defense include phagocytosis, complement, age, mechanical barriers, nutrition, interferon, hormones, fibronectin

tin, and the coagulation-fibrinolytic system. Due to limitations of space, only phagocytosis will be discussed in detail.

Phagocytosis consists of a series of well-defined steps that occur in series as follows: (1) *chemotaxis*, or drawing of white cells into the area of bacterial infection; (2) *opsonization*, the process by which bacteria are made more susceptible to ingestion; (3) *ingestion* of the bacteria by neutrophils; and, finally, (4) *killing* of bacteria occurs in several fashions (oxygen-dependent and oxygen-independent mechanisms). The ability of a white cell to migrate toward a stimulus can be measured in several systems and has been shown to be abnormal in patients undergoing major surgery or following major trauma [4]. The entire process of phagocytosis is clearly a complex one and is well summarized in recent reviews by Cates [5] and by Johnston and Stroud [6].

Specific Immune Factors

The major components of the specific immune system are as follows: the bursa-equivalent (*B*) cells, which differentiate to plasma cells and are primarily responsible for the production of immunoglobulins or antibody; the thymus-derived (*T*) cells that are responsible for cell-mediated interactions between macrophages and B cells; and the population of accessory adherent cells consisting of wandering and fixed *macrophages* (MO), which have a diverse number of functions. All of these cells produce humoral components and have cellular interactions which are extremely complex. In-depth analysis is beyond the scope of this review, but an excellent recent summary by Paul et al. is available [7].

Premorbid Status

It is critical for the surgeon to evaluate carefully the various medical diseases that affect host resistance. There are a number of diseases that depress neutrophil function and therefore tend to inhibit phagocytosis (e.g., diabetes). Major trauma and burns have been shown to be associated with the increased risk of sepsis, and these conditions will be covered in more detail later. Other diseases putting patients at risk are malignancy, cirrhosis, renal transplantation, atherosclerotic cardiovascular disease, and malnutrition.

Although the term reticuloendothelial system has become relatively outmoded, the system of fixed and wandering monocyte macrophages (MO) are still critical in host defense. Obviously, previous splenectomy leads to abnormalities in this area, particularly in children [8], and recent studies have demonstrated a monocyte defect following splenectomy [9]. Patients with diseases such as lymphoma, sarcoidosis, sickle cell disease, various autoimmune diseases, and previous irradiation to the lymphoid system are all susceptible to phagocytic defects in the MO system and should be treated with special care when undergoing surgery or following trauma.

Surgical Risk Factors

In addition to the above premorbid factors, there are a number of negative factors involved in trauma patients that will decrease host resistance. Local wound factors that interfere with host resistance include necrotic tissue, inadequate wound perfusion or oxygenation, retained foreign body or suture material, and undrained hematoma or seroma. It follows that the surgeon must be gentle with tissue, maximize debridement of necrotic tissue, and optimize oxygenation and perfusion of surgical wounds.

Although the clinical suspicion that shock places patients at risk for sepsis has been held for some time, there are only a few studies that support this [10]. Steroids inhibit the inflammatory response of white cells and have been associated with increased mortality from sepsis in several settings. Dextran, stroma-free hemoglobin, fibrin debris, and transfusion reactions may also inhibit the function of fixed phagocytic cells.

A number of authors have looked at the interaction of host resistance and nutritional status [4]. Meakins and his group have shown that anergy occurs frequently in elective surgical patients and that this defect in delayed hypersensitivity can be either partially or completely restored by aggressive nutritional support pre-operatively [11]. Following major thermal injury or major trauma, caloric requirements may be as high as 5,000 kilocalories per day. Aggressive nutritional support with a combination of parenteral and enteral nutrition is critical to decrease the risk of sepsis and its associated mortality [12]. An excellent review of this entire field is available for those who wish to pursue this matter further [13].

STUDIES IN TRAUMA PATIENTS

Extensive studies have been performed over the last several years on the interrelationship of host defenses and trauma. A large body of data on host resistance surrounds patients following major thermal injury or major trauma, and therefore some comments will be made regarding these two entities.

Major Thermal Injury

It has been well documented in recent years that burn patients are among the most susceptible to sepsis and have the largest number of abnormalities in host resistance [14]. Obviously a major burn leads to disruption in the skin as a mechanical barrier, thereby destroying the low moisture and natural antimicrobials produced by the end-organs in the skin. If inhalation injury is present, mucous membranes in the respiratory tract are disrupted from a chemical tracheobronchitis, resulting in dysfunction of ciliary and alveolar macrophage with resultant pulmonary sepsis. In addition, there are problems in the phagocytic system with decreased cellular mobilization and intracellular killing of bacteria [15]. Delayed hypersensitivity is depressed, and more recently defects in specific immune function have been identified [16].

For those burn patients who do not die of inhalation injury, 75 percent of the late mortality is due to sepsis [1]. Previously we evaluated, following thermal injury, 24 patients with a mean age of 45, a mean burn size of 40 ± 13 percent, half of whom had inhalation injury. Twelve of these patients developed severe sepsis with a mortality of 66 percent, whereas the other group had no major septic episodes. When T cells from these patients were stimulated with phytohemagglutinin (PHA, a plant mitogen), the septic group had major depression of PHA response at five to seven days while the nonseptic patients had no depression or an elevation of the PHA response [17]. We hypothesized that one possible cause for this abnormality in the septic patients was a relative increase in T suppressor cell activity. To test this hypothesis, a mixed lymphocyte culture system was utilized in which the effect of burn patients' T cells and burn patients' cells depleted of T cells (by a sheep red blood cell rosette technique) were added to a normal highly responsive one-way mixed lymphocyte response (MLR). Whereas the burn patient T-cell populations were 75 percent suppressive at five to seven days post-burn (coinciding with the PHA nadir), the T-cell-depleted

populations had little or no suppression of the normal MLR at this time. This was putative evidence that there was an increase in T suppressor cell activity at five to seven days following thermal injury [18].

These abnormalities are interesting to immunologists, but it is difficult for clinicians to utilize them since the results take five to seven days to process. In a corollary observation, however, it was noted that red debris appeared on the Ficoll-Hypaque lymphocyte separation gradients in the layer where the mononuclear cells normally sediment. This observation was noted in all patients with sepsis, who had a 66 percent mortality, and in none of the patients who did not develop sepsis [19]. Utilizing this observation, it may eventually be possible to predict those burn patients at risk for life-threatening sepsis. More recently, using a murine burn model in our laboratory, we have been able to demonstrate the elaboration of a suppressor effector factor by T cells [20] and depressed production of interleukin-1 by MO [21]. These data suggest that there may be a macrophage defect that precedes the T-cell defect or perhaps even induces the T-cell defect. Further work in this area will need to be done, but a lot has been accomplished in the last few years and it is hoped that further advances in immunology will allow prevention of sepsis in this high-risk population.

Major Trauma

Studies of immunologic function and host resistance in major trauma patients have not progressed so rapidly as in major burn patients because of the heterogeneity of the trauma patient population. Nonetheless, several abnormalities have been identified, which suggest that further study is warranted in this area. Abnormalities in chemotaxis and neutrophil function have been associated with serum inhibitory substances that have recently been identified to be immunosuppressive polypeptides [22]. As previously mentioned, abnormalities of T-cell function arising in patients two weeks following splenectomy appear to be due to an inhibitory MO [9,23]. Miller et al. have also recently identified decreases in the production of plasminogen activator and increases in production of tissue thromboplastin factor in trauma patients [23]. Although trauma patients have depressed PHA responses compared to normals, splenectomy patients have much more profound depressions in PHA responses, occurring approximately fourteen to sixteen days post-operatively [9,23].

Further studies in this area were performed looking at the correlation of shock and sepsis following trauma. Twenty-one patients were studied following either major surgery or significant trauma by combining pleural macrophage from chest tube exudates with peripheral blood cells which had been filtered, removing the inhibitory macrophages. Seventeen of the patients had minimal or no sepsis and had antibody-forming cells in normal amounts ($164/10^6$ cells). In contrast, in patients with severe sepsis, 60 percent of whom died, the antibody-forming cell response was profoundly depressed ($9.2/10^6$ cells) [10].

In clinical studies of trauma patients we recently examined multiple demographic and clinical variables to try to develop predictors of outcome. In the final analysis only age, total injury severity score, the presence of shock on admission, and the length of time in shock were predictive of increased risk for mortality [24]. In order to try to identify trauma patients at risk, a study was recently designed to evaluate the proliferative response of T cells to PHA following surgical trauma and to correlate these results with post-operative infectious complications. Thirty-one patients were evaluated, of whom 19 had complete data. Of eight patients who developed post-

operative infections, two died, for a 25 percent mortality. The other eleven patients had no infections and no mortality. Age was similar in both groups (mean, 50.5 years) but average hospital stay was 31 days in the infected group and 12.5 days in the non-infected group. PHA responses in the infected population dropped to 25 percent of normal by day five to seven post trauma, whereas PHA responses were maintained at a normal level in the uninfected patient population. When adherent cells were depleted by adherence to plastic petri dishes, the PHA response in the infected group improved from 25 percent of normal to 80 percent of normal at day five to seven following trauma. The uninfected group, on the other hand, had a drop in the PHA response at day five to seven when adherent cells were depleted [25]. The explanation for these data is not completely clear, but one possible explanation is that there is a different balance between inhibitory and facilitory macrophages in the two patient populations. In this study the addition of indomethacin to unfractionated cells in culture with PHA led to increases in PHA responses in all groups, although this change was most dramatic in the infected patient population at five to seven days following trauma.

Although these data are preliminary, several conclusions can be drawn. PHA responses were depressed in some but not all patients after major injury, and patients with depressed responses were far more likely to develop septic complications. Depletion of adherent cells and/or addition of indomethacin to cell cultures improved PHA responses significantly *in vitro*, suggesting a possible role for an inhibitory macrophage in this setting [25]. The possibilities for future therapy in trauma patients based on these data are exciting, but it is premature to contemplate such studies at this point without further understanding of the complex immune abnormalities following trauma.

FUTURE DIRECTIONS

Numerous possibilities loom on the horizon for further research and possible therapeutic intervention in the critically ill trauma patient at risk for sepsis. Some modalities have already been tested in humans, whereas others have only been tested in animals or are conceptual possibilities. One very real therapeutic application of the above-mentioned data is the increasing trend to conserve the spleen whenever possible or to autotransplant splenic tissue in patients following splenic injury. There is good experimental support for this approach [26] and a small body of data is accumulating in humans. Following splenectomy in an animal model, glucan, a nonspecific immunostimulant, has been shown to have a protective effect [27]. Glucan has also had a protective effect in a model of *Staphylococcus aureus* bacteremia associated with enhancement in serum lysozyme activity [28].

Significant interest has been generated by efforts to utilize antisera to *E. coli* J5 as a vaccine. Enhanced opsonization and systemic clearance of bacteria resulted in improved survival in an animal model [29], and suggestive evidence has been presented utilizing this modality in humans [30]. Interest in improving opsonic function by utilization of cryoprecipitate to reverse deficiencies in opsonic α^2 -surface binding glycoprotein has been tested in trauma patients with some success [30]. The exact role of this therapy is undetermined as yet.

Perhaps the most important caveat that needs to be delivered regarding immunotherapy and the future study of host resistance is that the host resistance system is a very delicately balanced one. Efforts to stimulate the immune system may result in autoimmune abnormalities which might be just as deleterious to the critically ill

patient as the negative regulatory effects of immunosuppression. Although exciting advances have been made in this field in the last ten years, our knowledge is still incomplete, and therapeutic modulation of the immune system in humans must proceed with great caution.

SUMMARY

This article has attempted to highlight some of the factors that lead to alterations in host resistance in trauma patients. In caring for these patients a knowledge of normal host resistance, including the nonspecific and specific immune systems, is critical. Evaluation of the patient's premorbid status and specific injury is critical in identifying a group of patients at high risk. In burn patients, T suppressor cells have been clearly demonstrated in several systems, and recent works suggest that macrophage dysfunction early following burn injury may participate in the elaboration of suppressor T cells. It is clear that, following splenectomy, mitogen response to PHA and plasminogen activator synthesis is depressed at two weeks post-operatively, and data suggest that an inhibitory macrophage is involved in these abnormalities. In the trauma patient the data are less clear because of the heterogeneity of this patient population, but several recently described abnormalities have been outlined.

The trauma patient represents a significant challenge to the surgeon, not only in terms of early diagnosis and management but in terms of the prevention of late complications. It is suggested that aggressive resuscitation of shock, early support of ventilatory function, attention to detail in aseptic technique, and appropriate nutritional support may allow surgeons to decrease the mortality from sepsis following trauma. This high-risk group of patients will continue to provide clinicians with a challenge and research scientists with a number of interesting questions related to host resistance and immunity. It is hoped that in the future we will be better able to prevent sepsis in high-risk patients or treat it in those patients who do develop sepsis. Although this goal may never be reached entirely, the extensive number of exciting discoveries in this area over the last few years suggests that it is a realistic goal.

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