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Immune Functional Testing in Clinics: Feasibility and Prediction of Deleterious Outcomes*

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Nosocomial infections (NIs) remain a serious and frequent complication of (ICUs) hospitalization and represent an important economic burden by significantly increasing hospitalization cost (1). Predicting which patients are at increased risk for developing NI is most likely one of the major challenges in the forthcoming evolution of ICU patients’ care (2).

Although plainly obvious, the necessity of a robust immune response to battle against germs has been largely under recognized over years in the assessment of risk factors for NI. Meanwhile, increasing evidences indicate that a delayed immune failure occurs after any systemic inflammatory response syndrome. This is illustrated in ICU patients by infections normally solely pathogenic in an immunocompromised host (3–5).

Importantly, this immune suppression has been shown to be induced after a variety of severe injuries leading patients to the ICU: sepsis, trauma, burn, pancreatitis, surgery, and stroke (6). It is thus of major interest to delineate the mechanisms sustaining this immunosuppression in ICU patients. To this purpose, in this issue of Critical Care Medicine (7), Deknuydt et al present an elegant work on the orchestration of immune response in patients with brain injury (BI). These patients present with similar features of immunosuppression and are characterized by high rates of NI (8). Here, the authors investigated BI patient’s immune response within the model of granuloma formation in response to Bacillus Calmette–Guerin. This very interesting model provides in vitro a nice reflection of the coordination of both innate and adaptive immune cells to mount a protective response against a pathogen (9).

The most important result of this study is the observation that BI patients developed a significantly lower number of granulomatous structures and that this decrease was even more pronounced in patients who were to develop NI. Another interesting aspect was to show that, in BI patients, granulomatous structures were characterized by poorly differentiated multinucleated cells (indicating a low level of maturity) and by low numbers of natural killers and γδ T cells. These parameters tended to be exemplified in patients with delayed infections. With that said and as duly acknowledged by the authors, the understanding of intimate mechanisms responsible for such results would deserve further investigations (e.g., role of regulatory T cells, decreased monocyte human leukocyte antigen-DR expression). Despite these limitations, this study provides the first observation of a global defect of immune functions in BI patients as illustrated by impaired granuloma formation in response to Bacillus Calmette–Guerin.

Beyond these results, the work of Deknuydt et al (7) underlines the interest of functional testing to evaluate the immune response in ICU patients. Indeed, as there is no clinical sign for immune failure, prevention of NI by identification of patients at risk may rely on the use biomarkers. Of them, functional testing remains the gold standard because it directly measures ex vivo the capacity of a cell population to respond to an immune challenge. Here, although the low number of patients precludes any definitive conclusions, these preliminary results tend to indicate that functional testing may be indicative/predictive of deleterious outcomes in clinic. Similarly, two hallmarks of ICU-acquired immunosuppression are usually reported: the decreased monocyte capacity to release proinflammatory cytokines in response to endotoxin challenge and the lowered lymphocyte proliferation. Overall, these protocols provided excellent insights regarding pathophysiology but remain barely usable on a routine clinical monitoring basis (long incubation time, lengthy cell purification procedures, low standardization, etc.). Thus, one major challenge in the forthcoming years is to abolish the gap between comprehensive and compelling studies like that from Deknuydt et al (7) and functional testing usable on routine daily practice.

One solution could be the development of surrogate markers of leukocyte functionality. The best example is the decreased expression of the major histocompatibility complex class II molecule human leukocyte antigen-DR on circulating monocytes. This decreased expression has been observed to correlate with monocyte functional response (tumor necrosis factor production after stimulation and antigen presentation capacity) and to be predictive of deleterious outcomes (mortality, nosocomial
infections) in various clinical contexts (6). In contrast, no such marker is available regarding lymphocyte functionality. To date, the best available test for assessment of lymphocyte functional response remains the measure of proliferation in response to specific antigens (tuberculin, tetanus toxin) or nonspecific stimulations (phytohemagglutinin, anti-CD3, anti-CD28 antibodies) with all the limitations inherent to such measurement (tritiated thymidine uptake, several day-incubation time).

As lymphocyte alterations are associated with increased mortality/NI rates and as recent works suggest that impaired lymphocytes can be rejuvenated after stress/injury (10, 11), novel therapeutic strategies reversing ICU-acquired immunosuppression in ICU patients are proposed (12). Knowing the pivotal role of lymphocytes (mainly CD4+ T cells) in orchestrating immune responses, one may expect that, by restoring their function, one can generate a global positive effect on the overall immune response, both mediated by lymphocytes and innate immune cells. In such indications, therapies like recombinant human interleukin-7 or anti-PD1 antibodies, already used in other clinical contexts, could represent interesting candidates. However, before such treatments can be administered to patients, robust and rapidly available markers measuring lymphocyte functions in the clinic on a routine basis are urgently needed. These tests will enable the clinicians not only to identify the patients that will benefit from such therapy but also to follow response to treatment.

REFERENCES


Obesity Paradoxes—Further Research Is Needed!*

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Obesity makes nearly every aspect of care of critical ill patients more difficult. In general, a relative risk of death is 1.19 for those with a body mass index (BMI) from 30–35 and increases to 2 for those with a BMI >40 (1). The clinical impression is that BMI is a very important predictor of outcome for ICU patients. However, recent published outcome studies have paradoxically demonstrated a survival benefit for obese patients in the ICU (2, 3). This discrepancy leads us to ask, Why? As the prevalence of obesity continues to rise among the ICU population, it is important for medical teams to understand the underlying mechanisms and the relationship between obesity and critical illness, thereby improving the care of critically ill patients.

In this issue of Critical Care Medicine, Marques and Langouche (4) challenge the “obesity paradox” and provide a detailed summary of the differences in adipose tissue between healthy subjects and critically ill patients, focusing on morphology, gene expressions of leptine, adiponectin, and cytokines and key components in glucose and lipid metabolism pathways. The evidence strongly suggests that during critical illness, the adipose tissue is a metabolically active organ. The functions of adipose tissue Marques and Langouche (4) elaborate initially seem to be quite obvious: new and small fat cells are created in the adipose tissue for increasing insulin sensitivity, more glucose and triglycerides are stored in adipose tissue as a nutrition and energy reservoir to protect against hypercatabolism, and changes in gene expression on all measured parameters in the fat tissue favor the alteration of inflammatory responses for a better outcome. It seems that adipose tissue acts as a buffer for a possible adaptive and protective role in optimizing changes of

*See also p. 317.

Key Words: adipose tissue; critical illness; obesity

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