

Evaluation of Immune Organ Dysfunction in Critical Illness

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ABSTRACT

In critically ill patients, organ dysfunction is usually assessed, monitored, and processed. Growing evidence shows that there are serious rashes caused by the disease. The immune system can be observed in most ICU patients, and persistence of an anti-inflammatory phenotype (as in sepsis-associated immunosuppression) as well as “hyper inflammatory” is associated with increased morbidity and mortality. Contrary to popular belief, changes in functional immunity are not appropriate. Creative protein, procalcitonin, or numerical analysis of the number of white blood cells (sub). Cytokines are also unsuitable for the following reasons: short half-life and pleiotropic, non-proprietary origin in immune cells; Ability to be antagonized by circulating inactivating molecules. Therefore, in addition to the quantification of leukocytes and the use of routine biomarkers, direct evaluation. The function of immune cells is obviously necessary to characterize the state of the immune system. This may include, for example, determining ex vivo release of cellular cytokines, phagocytosis. Activity and/or ability to present antigens. As a result, standardized flow cytometry Assessment of major histocompatibility complex II human leukocyte antigens (Related to D) (HLADR) was of particular interest. Monocyte HLADR (mHLADR) It modulates the interaction between innate immunity and acquired immunity and can play the following roles: “Global” Biomarkers of Trauma-Related Immunosuppression and Its Reduction manifestations may have adverse clinical outcomes (e.g., secondary infection risk, mortality). Recent data related to injuries Immunosuppression can be reversed, opening up new therapeutic possibilities in affected patients. Here we discuss its potential scientific and clinical value. Functional immunity assessment and focus on monocytes/macrophages and an overview of the current state of knowledge and potential prospects for those affected critically ill cases.

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Review

The immune machine is an critical organ in better lifestyles forms, and its disorder or “failure” can be lifestyles-threatening. In humans, the immune machine is ubiquitously dispensed inside all organs and includes humoral and cell additives prepared in particularly complicated dynamic social community architecture-like structures [1]. Key functions of the immune machine include harm manage in inflammation/contamination and tumor recognition/surveillance [1]. Despite its paramount importance, however, the immune machine or “immune organ” is usually unnoticed on extensive care units (ICU) today [2-7]. This might also additionally at the least in part be because of the truth that its purposeful popularity can not be safely assessed through use of recurring biomarkers including C-reactive protein, procalcitonin, or numerical distribution of leukocyte (sub)-sets. Nevertheless, numerical evaluation of leukocyte (sub-) populations might also additionally offer essential extra information, e.g., whilst appreciably deranged [8-10]. The traditional preliminary immune machine reaction to crucial infection includes systemic and neighborhood launch of inflammatory mediators and cytokines and activation of specific immune and different cells. This might also additionally cause awesome phenotype modifications in immune cells [4,6,11,12]. The conventional expertise became that out of control launch of proinflammatory mediators (e.g.,

interleukin (IL)-1, tumor necrosis factor (TNF)- α) might decide unfavourable scientific consequences in sufferers with septic shock [4,11]. Consequently, anti inflammatory including anti-TNF- α or anti-lipopolysaccharide (LPS) techniques have been then examined in large-scale scientific trials. However, respective trial effects lower back terrible or indicated expanded intervention-associated mortality. This highlighted that an anti inflammatory technique might now no longer offer fashionable benefits for large populations of sufferers with sepsis/septic shock [2-5,7,12]. Thereafter, immune popularity characterization in large affected person cohorts the usage of novel biomarkers allowed for a extra profound expertise. When searching at an individuals’ immune reaction, a excessive inter-character variance and particularly dynamic modifications may be observed over time [4]. It is now well known that many critically ill patients show evidence of coexistence of inflammatory and counterregulatory anti-inflammatory responses in the early stages of serious illness [13,14]. Early pro-late anti-inflammatory phenotype [2,4,7,11,12]. “Clean Effect” (i.e., resulting phenotype) this profound anti-inflammatory action is termed “sepsis (or trauma)-associated immunosuppression (SAI/IAI)” and involves reduced release, phagocytosis, and expression of proinflammatory mediators. Cell surface receptors involved in antigen presentation activity (eg major histocompatibility complex (MHC) class II) [4,7,11,12]. This may be due to increased immunological resistance, increased immune cell death, and genomic alterations. Expression profile [6,11]. Interestingly, the latest data shows that Circulating immune cells and corresponding anti-inflammatory phenotypes only For

example, it can be found in the spleen or tissues of the lungs and other solid organs [11]. From a clinical point of view, it is important to distinguish between episodic and persistent disease. Immunosuppression. Evidence shows that patients who do not recover from immunosuppression-related damage (or sepsis) are at an increased risk (secondary). Infected or non-viable [4,6,11, 15]. This includes postoperative conditions [16], trauma [17], burns [18], pancreatitis [19, 20], parenchymal organ transplantation [21], liver damage [22] or kidney damage [23], stroke [24]. Myocardial infarction/ heart failure and cardiac arrest [25-28], sepsis [15]. Recent technological advances now allow better recognition/monitoring of SAI/VCI, opening up new possibilities. How to recognize, monitor and treat this functional immunity “organ failure” [7].

Immunological markers of serious illness to identify patients at risk for SAI/IAI and related complications. It seems important to briefly summarize the main immune responses to injury (Figure 3). The first reaction to an injury or infection is usually local activation. Fluid factors (eg, complement factors) followed by antigen-presenting cells (APC) Located in the native adaptive interface (ie, monocytes/macrophages or dendritic cells) [6,29]. When activated, APC releases cytokines (eg, TNF α , IL1, IL6). More APCs and other mediators that attract and activate neutrophils Phagocytosis and adaptive immune cell stimulation after migration to inflow area lymph Nodes (eg, antigen-loaded dendritic cells) [6, 29]. APC was induced after phagocytosis Antigen presentation occurs through upregulation of class II transactivators (CIITA) and relocalization of MHC class II molecules from intracellular storage [29, 30]. Altitude Antigen loading Surface expression of human leukocyte antigen (D-related) (HLADR; a) MHC class II key molecule induced in monocytes/macrophages and dendritic cells) T cell receptors (TCRs) and co-stimulatory molecules (eg) CD86CD28 and CD40CD40L) (Fig. 3). Over time, “anti-regulatory” responses may occur It occurs in monocytes/macrophages and dendritic cells and increases the production of anti-inflammatory cytokines (such as IL10) [31,32]. As a result, monocytes and dendrites Cell inactivation with reduced expression of both HLADR and co-stimulation Figure 3 Activation of important immune cells by infection. Numerous bacterial infections cause sepsis important antigen presenting cells (APCs) (ie, monocytes/macrophages, dendritic cells). Activated APCs primarily express inflammatory cytokines and present antigens It binds to major histocompatibility complex (MHC) class II complexes (such as HLADR). Antigen binding HLADR Triggers the binding of T cell receptors (TCRs) to co-stimulatory molecules (such as CD 40CD40L). Adaptive immune system a reaction is initiated that leads to the elimination of the infection. At z. B. Overwhelming infection inactivation of monocytes, such as sepsis-related immunosuppression (SAI). SAI is characterized by shifts towards an anti-inflammatory phenotype with predominant expression of IL10 and decreased HLADR It results in impaired expression, infection clearance and increased mortality. In IAI this is deactivated Phenotype can be observed immediately after injury. Poor phagocytosis, molecules as an indicator of antigen presentation, Decreased induction of adaptive immune response. Another expansion Myeloid-derived suppressor (MDSC), an immature population of bone marrow cells The immunosuppressive function first described in cancer has also been demonstrated in patients With sepsis [33, 34]. Very recently, MDSC had been proven related to extended immunosuppression, specifically with dwindled T mobileular features and improvement of nosocomial infections in sufferers with sepsis [35,36]. In addition, seriously unwell sufferers generally display marked apoptosis-precipitated lymphopenia and impaired lymphocyte characteristic which make a contribution to sepsis- and injury-

related immunosuppression as recently reviewed elsewhere [37].

Key cytokines: serum degrees of IL-6, IL-10, and TNF- α

Serum cytokine degrees are automatically assessed in a few establishments for in advance recognition, estimation of prognosis, and (intra-individual) follow-up of seriously unwell sufferers. However, it have to be mentioned that they do now no longer replicate immune mobileular capability as cytokines are broadly speaking pleiotropic, derived from special cells consisting of non-immune cells, might also additionally be counteracted via way of means of herbal inhibitors (e.g., gp130 for IL-6), and feature variable clearance rates [4,6,11,12]. In the following, we speak 3 cytokines with pathophysiologic and/or diagnostic relevance in crucial illness: IL-6 is a powerful pleiotropic cytokine with particularly pro-inflammatory effector characteristic. IL-6 is expressed via way of means of monocytes/macrophages, endothelial lineage cells, and fibroblasts and augments immune responses through induction of T mobileular activation, B mobileular proliferation and differentiation, and stimulates acute segment protein release (e.g. C-reactive protein). Systemic IL-6 is detected swiftly with top serum degrees determined after approximately 2 h after an inflammatory insult. IL-6 is normally assessed through automatic enzyme-linked immunosorbent assay (ELISA) in specialised laboratories or through point-of-care tests (blood, liquor). Owing to its speedy induction and quick half-life, serial IL-6 evaluation might also additionally offer well timed tracking of an inflammatory burden when, e.g., in comparison to serial C-reactive protein measurements. Although expanded IL-6 degrees imply damaging medical results in adults with sepsis/septic shock, implementing of IL-6 dimension in habitual diagnostic paintings up became now no longer proven to enhance patientcentered medical results. Nevertheless, IL-6 became proven beneficial for sepsis diagnostics in neonatal/pediatric seriously unwell sufferers.

IL10 is considered to be the most prominent and exemplary anti-inflammatory cytokine. Like IL6, IL10 is predominantly expressed by monocytes/macrophages and has a short circuit. It can be determined by half-life and ELISA. IL10 has been evaluated in several studies and is functionally associated with a “classical” biphasic response model for severe injuries of In contrast to IL6, increased IL10 expression induces antigen resistance and enhances SAI. Increased susceptibility to infection, IL10 blockade reversed endotoxin resistance in some preclinical studies, and some reports show predictive values for IL10 Mortality and/or (secondary) infections. TNF α is an important pro-inflammatory cytokine produced primarily by monocytes/Macrophages of early sepsis. It automatically stimulates effector function and promotes the initiation of adaptive immune responses. Some studies show that TNF α is elevated Levels are associated with increased mortality. Compared to other whole body Inflammation marker, TNF α , does not seem to be very characteristic regarding outcome prediction.

Functional marker

TNF α release in Exvivo Exvivo LPS-induced TNF α production in whole blood (eg, after 4 hours of stimulation) Allows quantification of monocyte and dendritic cell production/release TNF α . Reduced TNF α release in Exvivo is an important feature of immunosuppression. Severely ill patients [4,12]. Nevertheless, ex vivo TNF α release may not be a suitable diagnostic marker for cell-mediated immune function, as it requires sample handling and standardized protocols for specific stimulus conditions. Uncommon today. There is an accepted standardized protocol for assessing TNF α release in Exvivo, which hinders multicenter collaboration. Recently, the measurement of intracellular TNF α

in monocyte cells from whole blood by flow cytometry has been tested with promising results in the following points: Improved test feasibility.

Functional marker

Phagocytosis assay Phagocytosis involves recognition and swallowing of pathogens, followed by elimination of pathogens. A large number of predominantly innate immune cells are involved in phagocytosis (eg Neutrophils, monocytes/macrophages, dendritic cells). Decreased phagocytic capacity is associated with increased susceptibility to (secondary) infection in the rodent model. In humans, on the other hand, the direct effects of serious illness on phagocytosis are not fully understood. Phagocytosis of neutrophils Sepsis, while other neutrophil functions, including the production of chemotaxis and/or oxidative bursts, can be impaired in parallel. In general, phagocytosis assays are heterogeneous and vary in specificity. The standardized experimental protocol is missing. As a result, there is greater variation within and between labs. Therefore, phagocytosis assays may be used in a limited manner to assess immune function both in clinical routines and in multiple centers. A clinical trial that tests immunological interventions.

Functional marker

mHLADR expression HLADR is an MHC class II molecule and is mainly expressed in monocytes / Macrophages, dendritic cells and B cells [29]. The surface expression is indispensable for antigen presentation [29]. Although increased HLADR expression reflects activation Analysis of immune cells showing a phenotype in which reduced expression is accompanied by downregulation of antigen-presenting capacity and a shift from pro-inflammatory cytokine production to anti-inflammatory cytokine production [4,12]. Surface expression of HLADR in monocytes/macrophages Essential for the initiation of the adaptive immune response [11,29]. This signal can be switched in parallel and/or co-stimulatory molecules (eg CD40 CD40 Ligand binding) (Figure. 3). Considering the importance of monocyte HLADR (mHLADR) Expression associated with the induction of adaptive immune responses, Dendritic cells with monocytes and T cells were colloquially called “immunological synapses.” Therefore, it was proposed to use an assessment of mHLADR expression. “Global” functional markers of immune function [4,5,7,12]. Certainly meaning Expression of mHLADR was first described in patients who underwent organ transplantation about 30 years ago, but patients with low expression of HLADR were Withdrawal from iatrogenic immunosuppression without graft rejection [50].

Flow cytometric evaluation of mHLADR expression

Expression of monocyte HLADR occurs via fluorescence activated cell sorting (FACS) From EDTA samples. FACS is a simultaneous enumeration Assessment of multiple surface and intracellular antigens in a particular subset of immune cells after staining with a fluorescent dye-labeled antibody (Fig. 4). In 2005, the Quantibrite™ HLADR assay was established as the first standardized method for assessing flow cytometry mHLADR with low interlaboratory variability. Variation (CV) 15%, Skills Test CV & It; 4%), which allows comparison of datasets collected in multicenter collaborative studies. Previous method of reporting HLADR percentages Positive cells (% HLADR) or mean fluorescence intensity (MFI) lacked internationally recognized analytical standards and prevented comparison of results between centers. In contrast, in the Quantibrite™ HLADR assay, with calibration beads A specially formulated antibody-fluorescent dye conjugate that allows the measurement of bound HLADR antibody (mAb/cell) per cell, regardless of the combination of flow cytometers and device settings used in various laboratories. Despite recent advances

in standardization, flow cytometry still requires a specialized laboratory Instrument and personnel, standardized analytical protocols, and timely handling of samples (For mHLADR, up to 4-6 hours in a standard EDTA tube at room temperature). Delaying sample testing can induce monocyte activation and artificially increase mHLADR expression. EDTA anticoagulant treatment Whole blood storage on ice or in the refrigerator, or use a tube containing a cell preservative such as CytoChex® BCT improves the analytical stability of mHLADR (and Meisel et al., Unpublished data). However, CytoChex® BCT tubes are expensive and not widely available. Mottled & Fixed samples can be stored for at least 52 hours prior to analysis. Therefore, the evaluation of mHLADR as a biomarker of immune function is usually usually near the hospital laboratory [7]. In addition, blood samples are usually processed during normal laboratory business hours rather than 24 hours a day. Recently automated spreadsheets Cytometers have been studied as a potential point of care tool for bedside mHLADR assessment. This can be an important step in improving the availability of immune surveillance. A tool for intensive care physicians. Furthermore, quantification of HLADR expression, etc. Markers for innate and adaptive immunity (dys) regulation by real-time or digital PCR Helps overcome some of the above limitations of flow cytometry mHLADR Analysis of SAI/IAI patients and their improved identification. However The usefulness of these assays needs further investigation.

Threshold level

Using a previous non-standardized mHLADR scoring method with positive rates for monocytes, most investigators (including our group) set a cutoff of 30%. HLADR-positive monocytes for trauma-related severe immunosuppression (previously referred to as “immune paralysis”). A recent comparison of traditional methods Perform standardized mHLADR quantification (provided as mAb/cell) We found that a cutoff value of (previously) 30% HLADR-positive monocytes corresponds to approximately 5000 mAb/cell and 45% mHLADR corresponds to approximately 8000 mAb/cell. That A range of 30-45% HLADR-positive monocytes is referred to as “border immunosuppression”. So, using a threshold of 8000 mAb/cell, SAI/IAI was used in subsequent interventional clinical trials. Most importantly, you are not alone. Reduced mHLADR values should be considered clinically important, but rather Persistence of low mHLADR levels indicative of recovery failure [4,7,12,15]

Expression of monocyte HLADR in certain diseases Sepsis/septic shock

Sepsis is the most commonly evaluated clinical manifestation of mHLADR. Decreased mHLADR expression at admission, days 1-3 [15] and days 6-8, were significantly associated with increased mortality. Some studies show Differences related to the results of mHLADR expression are displayed only on days at 3-4 (or later), mHLADR returns to normal in survivors but not in non-survivors [15]. Two other studies have shown dynamic changes (or recovery) Inclined) mHLADR expression from 3 to 7 days after injury Mortality rate [15]. In one of these studies, though not important, Predicted, delta values for individual mHLADR values at time points 0, 3, and 7 during measurement days 0-3, 0-7 and 3-7, mortality was highly predicted. These results have been confirmed in both adult and pediatric patients. 1 Description of better predictions of relative changes in mHLADR expression Absolute values are due to the potential for large interpersonal variation in monocyte HLADR levels. Monocyte HLADR expression on days 3-5 and 6-8 is also independent Predicts the onset of secondary infections. Recovery of mHLADR may also reflect the normalization of important metabolic pathways in

sepsis, but to a greater extent. We need clinical data.

Major surgical procedure

Several research assessed whether or not decreased mHLA-DR expression predicts destructive final results following most important surgical procedures. Culprits for put up-surgical immune suppression can be surgical trauma, associated intraoperative hypotension, and expanded perioperative launch of corticosteroids or catecholamines. Moreover, anesthetic pills together with fentanyl can also additionally make a contribution to harm-related immunosuppression (IAI). In sufferers with cardiovascular surgical procedure, use of extracorporeal circuits is typically related to a massive pro-inflammatory response [16]. Cardiopulmonary bypass can be observed with the aid of using IAI pondered with the aid of using impaired monocytic ex vivo LPS-caused cytokine launch and reduced mHLA-DR [16]. The nadir of mHLA-DR changed into typically determined on postoperative days 1–three, however faded mHLA-DR expression changed into proven to persist as much as postoperative day 10 in a enormous wide variety of sufferers. In large research investigating the predictive strength of mHLA-DR on final results in pediatric and grownup sufferers put up-cardiac surgical procedure, decreased mHLA-DR expression on postoperative day three changed into related to expanded period of ICU stay/mechanical air flow and improvement of postoperative sepsis after adjustment for bypass time, pass clamp time, complexity of surgical procedure, and a pediatric mortality risk score. In adults, mHLA-DR expression on postoperative days 1–five changed into substantially exceptional among sufferers who later evolved sepsis vs. with an simple course and changed into a issue with a excessive discriminatory strength to discover sufferers with contamination put up cardiac surgical procedure [16]. In sufferers with ruptured stomach aortic aneurysms, mHLA-DR expression after surgical procedure changed into substantially related to mortality although this changed into now no longer associated with expanded postoperative contamination rates.

Multiple Trauma

Diminished mHLA-DR expression changed into determined in lots of sufferers with a couple of trauma [17]. In a potential observational trial in one hundred and five critically injured sufferers (harm severity score, ISS>25), upward thrust in mHLA-DR till days three–four following trauma, and now no longer at any in advance day, changed into related to non-improvement of extreme contamination/sepsis after adjusting for confounders [17]. The dynamic impact of mHLA-DR healing changed into additionally proven in sufferers with a couple of trauma and ISS>9. Further research document an affiliation among mHLA-DR expression and prevalence of put up-trauma sepsis as early as day 2. Monocytic HLA-DR expression changed into additionally related to expanded intrapulmonary shunting after extreme trauma that is related to expanded occurrence of pulmonary sepsis and improvement of acute respiration misery syndrome (ARDS).

Central nervous system (CNS) damage

Infection is a common complication in patients following acute central nervous system injury. Especially, Pneumonia is associated with worse neurological outcomes and remains the leading cause of death. Experimental studies have shown that suppression of cellular and humeral immune function due to CNS injury contributes to a high frequency of infection [24]. Several clinical studies have demonstrated reduced mHLADR expression. Cerebral ischemia, subarachnoid hemorrhage, spinal cord injury, or Neurosurgery. It is important to note that in patients with CNS lesions and subsequent infectious complications, mHLADR levels were lower than those with an already uncomplicated clinical course well before onset

on day 1 after stroke. Infection, indicating that cessation of host responses contributes to an increased risk of infection following CNS injury. More recently, we have identified stroke-induced immunosuppression in a large, prospective, multicenter study. Expression of mHLADR), such as dysphagia and There is a higher risk of aspiration.

Burn Injury

Only few facts are to be had in burn sufferers. One look at in sufferers with extreme burn injury (> 30% of frame surface) shows that days 2–three mHLA-DR expression is appreciably related to multiplied mortality [18]. Patients who later evolved sepsis had appreciably decrease mHLA-DR expression withinside the resulting days [18].

Pancreatitis

Reduced mHLA-DR expression is related to multiplied sickness severity in sufferers with extreme pancreatitis [19,20]. Suppression of mHLA-DR or reduced mHLA-DR is related to improvement of sepsis [19,20]. After day three, failure to get better in mHLA-DR expression turned into related to reduced survival [19].

Transplantation

The software of mHLA-DR evaluation in sufferers post (e.g., renal) transplantation turned into investigated greater than 25 years ago. Increased mHLA-DR expression turned into discovered to be related to an multiplied fee of transplant rejection [21] and might serve to reveal iatrogenic immunosuppression. Failure to get better to ordinary mHLA-DR ranges after transplantation is related to multiplied quotes of past due post-transplant pneumonia in pediatric populations. In adults after liver transplantation, reduced mHLA-DR expression ranges are related to pneumonia and cytomegaly virus (CMV) reactivation.

Cardiopulmonary arrest

Monocytic HLA-DR expression predicts final results in sufferers after cardiac arrest (CA). In fifty five sufferers after out-of-health facility CA from non-shockable rhythm, mHLA-DR ranges have been appreciably reduced whilst in comparison to wholesome controls. In this look at, non-survivors confirmed one of a kind mHLA-DR dynamics among days zero to one and 1 to three whilst in comparison to survivors. Whereas the slope among days zero and 1 turned into steeper in non-survivors, mHLA-DR expression persisted to lower from days 1 to three in non-survivors (multiplied after day 1 in survivors) [25].

Other clinical symptoms including

Acute kidney injury and acute liver failure Predicted value of mHLADR for outcomes in patients with acute kidney injury (AKI) was investigated in study [23]. Despite decreased expression of mHLADR in AKI Contrast with patients whose predicted values were not identified in the study Mortality rate [23]. Few studies have examined mHLADR expression in acute or acute patients Decompensated chronic liver disease [22]. A corresponding study found a significant association between mHLADR expression and admission mortality. Changes in predicted values when dynamic changes over time are studied. The power of mHLADR to predict mortality was similar or Lower than the EndStage Liver Disease Model (MELD) score [22].

Injury-related immunosuppression

Reversal with therapeutic intervention Given the potential of mHLADR for immune surveillance, some interventions Biomarker-controlled treatment strategies have been tested in clinical studies. Corresponding approaches included in vitro

removal of inhibitors by selective immunoadsorption, immune stimulation with interferon gamma (IFN γ) [32] or stimulation. Granulocyte macrophage colony stimulating factor (GM-CSF) was used. Potential another approach is interleukin 7 (IL7) or one anti-PD ligand molecule (anti-PD ligand). PDL1).

Interferon gamma (IFN γ)

Stimulation of ubiquitously expressed IFN γ receptors leads to activation numerous pro-inflammatory signaling pathways. In epoch-making research, Doecke et al. IFN γ immune stimulation has been shown to restore mHLADR expression in patients with sepsis-related immunosuppression (SAI) [32]. Can improve the elimination of infections Received by 30% of adult patients with invasive fungal sepsis and mHLADR due to the use of IFN γ in a randomized, double-blind clinical trial of trauma. Inhaled IFN γ Treatment with IFN γ has been shown to reverse and increase SAI Decrease in TNF α , IL10, increase in mHLADR level, SAI phenotype. It is unclear whether administration of IFN γ to IAI will reduce the mortality rate of affected patients, and a larger study is needed. Importantly, no major side effects of IFN γ -induced immune stimulation were observed [32].

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

Randomized, double-blind, placebo-controlled trial in 38 patients after treatment for sepsis, we were able to show a reversal of persistent SAI Subcutaneous GM-CSF. In addition to removing SAI (defined by mHLADR) Expression > 15,000 mAb / cell) Improvements in related patient-centric endpoints were observed, including reduced duration of mechanical ventilation. Discovery, insight, discovery. It is supported by other groups that GM-CSF reverses SAI. Whether clinical endpoints such as secondary infection rate are affected by therapeutic use GM-CSF is currently under study (NCT02361528). However, small studies have shown to be promising. The result of reduced infection rates or shortened duration of infection in critically ill patients with immunodeficiency treated with GM-CSF. In another randomized controlled trial in patients with sepsis and severe respiratory dysfunction, oxygenation in patients receiving GM-CSF was significantly improved. We have recently been able to demonstrate this in newborns Decreased mHLADR expression may reflect very early immunological immaturity Meta-analyses on neonates and GM-CSF therapy showed increased survival When treated with very low preterm infants (<2000 g) and infants with neutropenia GM-CSF. Importantly, no clinical trials reported related side effects GM-CSF treatment.

Conclusion

Serious illnesses can often induce persistent injury-related immunosuppression. It adversely affects the associated patient-centric endpoint but, Organ dysfunction detection, monitoring, and aftercare are the main tasks of intensive care physicians, but "immune organ" dysfunction is now largely overlooked. Because the numerical distribution of white blood cell (sub) counts, for example, B. cannot be evaluated properly. B. Cytokines, procalcitonin or acute phase proteins. Importantly, a quantitative assessment of a given cell population itself does not indicate its functional state. Today, the flow cytometric assessment of mHLADR expression can serve as one. A standardized "global" biomarker for assessing immune function. Decreased sustainability Expression of mHLADR reflects certain associated immunological phenotypes. With adverse clinical outcomes. However, mHLADR assessments currently require specialized laboratories that are not available at all facilities. Continue With proof of immunological efficacy, biomarker-driven immunological interventions for injury-related immunosuppression are performed in well-characterized

populations using relevant patient-centric clinical outcomes. Should be (Example: mortality rate). We assume that in the future of intensive care medicine, there is a great need for personalized medicine that takes into account individual immune function. Improves outcomes for affected patients.

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