predictors; this has not been made systematically previously to the best of our knowledge. Furthermore, we applied a predefined American Clinical Neurophysiology Society nomenclature–based EEG scoring and tested it for both poor and good outcome outside a strict randomized controlled trial environment. In fact, in the study first describing it (3), the specificity for highly malignant patterns was 100%: false positive predictions of poor outcome were thus not found in that analysis.

In the discussion, we also already clearly acknowledged that reactivity has an imperfect interrater reliability (2), and we completely agree that this item needs to be broadly validated. By recommending nipple pinching, which has been meanwhile independently found to be the most sensitive stimulus by other groups (4), we feel we added practical valuable information. We routinely integrated background evaluation (and occurrence of epileptiform transients) in the assessments, and believe in any case that convergent findings from two centers with heterogeneous approaches support generalizability of our results. We also already acknowledged that recordings took place at heterogeneous timings (for instance, that was clearly the case for the routine EEGs: 17.9 ± 6.2 hr after CA); our intent was rather to point out that in resource-limited settings, a spot EEG during targeted temperature management and sedation, and the follow-up recording afterwards, contain valuable prognostic information, as already pointed out previously (5).

We agree with that heterogeneous recovery speed of brain function might influence results of the EEG assessment after targeted temperature management. Observations performed for the vast majority earlier than 24 hours following CA offer robust prediction to both outcome directions; this is valuable in clinical practice. Finally, given the (low) false positivity of EEG for poor outcome prediction, we cannot but reiterate the need for multimodal assessments in this setting (6).

Drs. Rossetti and Rabinstein contributed equally. The authors have disclosed that they do not have any potential conflicts of interest.

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REFERENCES

1. Hofmeijer J, Ruijter BJ, Tjepkema-Cloostermans MC, et al: Early Electroencephalography Dynamics After Cardiac Arrest. *Crit Care Med* 2017; 45:e1093
2. Rossetti AO, Tovar Quiroga DF, Juan E, et al: Electroencephalography predicts poor and good outcomes after cardiac arrest: A two-center study. *Crit Care Med* 2017; 45:e674–e682
3. Westhall E, Rossetti AO, van Rootselaar AF, et al; TTM-trial investigators: Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. *Neurology* 2016; 86:1482–1490
4. Fantaneanu TA, Tolchin B, Alvarez V, et al: Effect of stimulus type and temperature on EEG reactivity in cardiac arrest. *Clin Neurophysiol* 2016; 127:3412–3417
5. Alvarez V, Sierra-Marcos A, Oddo M, et al: Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. *Crit Care* 2013; 17:R190
6. Rossetti AO, Rabinstein AA, Oddo M: Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurol* 2016; 15:597–609

DOI: 10.1097/CCM.0000000000002542

Interpreting Immune Mediator Dysbalance in Sepsis

To the Editor:

With great interest, we read the study published in a recent issue of *Critical Care Medicine* by Frencken et al (1). The study (1) assessed whether the balance of proinflammatory and anti-inflammatory cytokines would be associated with early or late mortality in critically ill patients with sepsis. Frencken et al (1) chose interleukin (IL)-6 and IL-10 as a marker for proinflammation and anti-inflammation, respectively. Blood samples were obtained in 708 patients at admission, days 2 and 4, and at ICU discharge. Data were analyzed in respect to 4-day, 28-day, and 1-year mortality. Frencken et al (1) found that both IL-6 and IL-10 levels were independently associated with mortality, whereas the IL-6/IL-10 ratio was related to an increased risk for secondary infections but not to mortality. Frencken et al (1) conclude from their findings that the balance of respective inflammatory mediators is not associated with mortality in patients with sepsis (1).

The new data underline previous findings that plasma concentrations of single cytokines, such as IL-6 and IL-10, are indeed associated with mortality in septic patients (2). However, the "balance" of the sepsis-induced host's immune response can most likely not be reflected by analyzing a ratio of two pleiotropic cytokines. This might be true for several reasons including the fact that cytokines 1) may both have "proinflammatory" and "anti-inflammatory" effector functions (e.g., IL-6); 2) originate not only from activated immune cells (e.g., IL-6 release by epithelial or endothelial cells following tissue trauma); 3) may be antagonized by circulating regulatory molecules (e.g., soluble gp130 for IL-6, IL-1 receptor antagonist for IL-1β); 4) clearance rates may differ markedly making it difficult to compare plasma concentrations and local effector function; and 5) may be influenced by levels of other pleiotropic cytokines (e.g., tumor necrosis factor-α, IL-12). Importantly, systemic cytokine levels do thus not reflect the balance of the immune system or immune cell function and do not represent a specific type or phase of the hosts' immune response. Even when repeatedly measured, systemic cytokine levels do therefore not adequately portray the dynamic changes that are well-known to occur in sepsis and do not seem to reflect "immune balance" (3–5). Thus, assessment of an "immune balance" may require investigation of indices of cellular (and humoral) immune function.

source: https://doi.org/10.7892/boris.105630 | downloaded: 12.10.2024

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Immune "function" may best be assessed by direct analysis of cellular function (e.g., ex vivo cytokine production) or assessment of antigen-presenting capability. In this context, standardized assessment of monocyte human leukocyte antigen-DR (HLA-DR) on circulating myeloid antigen-presenting cells may be of particular interest as the expression of HLA-DR can be considered the "net result" of effector function of pleiotropic proinflammatory and anti-inflammatory mediators and was described to best reflect injury-associated immunosuppression, in particular in critically ill patients with sepsis (3–5).

The excellent new data provided by Frencken et al (1) allow for important new insights into the dynamics of cytokine mediators in sepsis and respective clinical usage, but caution seems advised in respect to drawing of conclusions on the status or dynamics of the host's immune response via exclusive analysis of circulating mediators.

The authors have disclosed that they do not have any potential conflicts of interest.

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REFERENCES

1. Frencken JF, van Vught LA, Peelen LM, et al; MARS Consortium: An Unbalanced Inflammatory Cytokine Response Is Not Associated With Mortality Following Sepsis: A Prospective Cohort Study. *Crit Care Med* 2017; 45:e493–e499
2. Boomer JS, To K, Chang KC, et al: Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011; 306:2594–2605
3. Monneret G, Venet F, Pachot A, et al: Monitoring immune dysfunctions in the septic patient: A new skin for the old ceremony. *Mol Med* 2008; 14:64–78
4. Hotchkiss RS, Monneret G, Payen D: Immunosuppression in sepsis: A novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis* 2013; 13:260–268
5. Schefold JC: Measurement of monocytic HLA-DR (mHLA-DR) expression in patients with severe sepsis and septic shock: Assessment of immune organ failure. *Intensive Care Med* 2010; 36:1810–1812

DOI: 10.1097/CCM.0000000000002547

The authors reply:

We thank Pfortmueller et al (1) for their interest in our study (2) and for their thoughtful remarks regarding the complexities of the host response in sepsis. How to assess whether a patient exhibits a hyper- or hypoinflammatory response to infection has been the subject of considerable debate yet is considered essential in the quest for new sepsis treatments (3). Because no single biomarker has emerged as an indisputable measure of immune function (including human leukocyte antigen-DR expression on circulating myeloid antigen presenting cells) (4), various approaches to characterizing the balance of the host response have been advocated, such as transcriptomic assessments (5), but also the balance of circulating inflammatory mediators (4, 6). Therefore, we measured a wide range of circulating mediators, several of which are well known to have either predominantly proinflammatory (interleukin [IL]-6, IL-8, and IL-1β) or anti-inflammatory (IL-10 and IL-13) action and studied the effects of mediator imbalance on mortality at different time points after sepsis onset. Subsequently, we did not look at a simple ratio of these markers (because this would ignore the "magnitude" of the overall response) but rather performed extensive interaction analyses to explicitly model inflammatory mediator balance. As put forward by Pfortmueller et al (1), this approach arguably does not provide a fully comprehensive assessment of immune response. In this respect, a better understanding of the interdependence between the multitude of circulating inflammatory proteins and various other tests of immunity is urgently needed. As it is unlikely that one irrefutable test of immune function will arise in the near future, combining multiple existing biomarkers through structural equation modeling or latent class analysis could become an exciting new avenue for future research (7).

The authors have disclosed that they do not have any potential conflicts of interest.

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REFERENCES

1. Pfortmueller CA, Meisel C, Schefold JC: Interpreting Immune Mediator Dysbalance in Sepsis. *Crit Care Med* 2017; 45:e1094–e1095
2. Frencken JF, van Vught LA, Peelen LM, et al; MARS Consortium: An unbalanced inflammatory cytokine response is not associated with mortality following sepsis: A prospective cohort study. *Crit Care Med* 2017; 45:e493–e499
3. Boomer JS, Green JM, Hotchkiss RS: The changing immune system in sepsis: Is individualized immuno-modulatory therapy the answer? *Virulence* 2014; 5:45–56
4. Leentjens J, Kox M, van der Hoeven JG, et al: Immunotherapy for the adjunctive treatment of sepsis: From immunosuppression to immunostimulation. Time for a paradigm change? *Am J Respir Crit Care Med* 2013; 187:1287–1293
5. van Vught LA, Klein Klouwenberg PM, Spitoni C, et al; MARS Consortium: Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. *JAMA* 2016; 315:1469–1479
6. Hotchkiss RS, Monneret G, Payen D: Sepsis-induced immunosuppression: From cellular dysfunctions to immunotherapy. *Nat Rev Immunol* 2013; 13:862–874
7. Prescott HC, Calfee CS, Thompson BT, et al: Toward smarter lumping and smarter splitting: Rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. *Am J Respir Crit Care Med* 2016; 194:147–155

DOI: 10.1097/CCM.0000000000002582

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