Dying with or Because of Invasive Fungal Infection? The Role of Immunity Exhaustion on Patient Outcome

Andrea Cortegiani, Vincenzo Russotto, Santi Maurizio Raineri, Cesare Gregoretti, Antonino Giarratano

Department of Biopathology and Medical Biotechnologies (DIBIMED), Section of Anesthesia, Analgesia, Intensive Care and Emergency, Policlinico P. Giaccone, University of Palermo, Italy

De Rosa et al. considered clinical scores, biomarkers and their combination as useful aids for an early antifungal treatment and advocated the adoption of de-escalation therapy in an antifungal stewardship approach as a possible key for a better management of these patients. Authors considered the high burden of invasive fungal infections in terms of patient outcomes and costs and focused on current strategies for their optimization.

The fact that many non-neutropenic, critically ill patients with invasive fungal infection die despite being treated with effective antifungal agents may provide interesting insights on additional, patient-related conditions that may play a role for final outcome.

The role of immunity in septic patients has been studied for many years. Nowadays, we have evidence on the role of impaired immunological response in not-formally considered immunosuppressed patients (e.g. non-transplant recipients, non-neutropenic patients), namely decreased cytokines production, increased number of T regulatory cells and of pro-apoptotic signal (programmed cell death 1receptor, PD-1 and ligand, PD-L1) (1-3). Moreover, it should be also considered that nosocomial sepsis is commonly caused by weakly virulent pathogens (*Acinetobacter spp., Pseudomonas spp., Stenotrophomonas spp., and Candida spp*.) and septic patients show a high incidence (25–35%) of reactivation of viruses (cytomegalovirus, herpes simplex virus) which are hold in abeyance by an effective immunological response. Recently, Spec et al. (4) (from Hotchkiss' group) published an observational study investigating the immunophenotype of non-neutropenic patients with candidemia compared to critically ill, non-septic controls. Both CD4 and CD8 T cells of patients with candidemia expressed markers of cell exhaustion (PD1 and PD-L1) and a down regulation of positive co-stimulatory molecules (4). These preliminary data may represent the missing brick contributing to explain the paradox between the reduction of the incidence of invasive fungal infections and the lack of survival benefit after untargeted antifungals administration (5, 6). We may speculate that the impaired immune response may have a causative role on the lack of benefit of highly effective antifungals or it may rather represent a marker of severe underlying disease. If confirmed, the identification of immunologic exhaustion as a hallmark of patients with a higher risk of invasive fungal infections may be considered for better selection of patients in future trials of antifungal treatments. Moreover, it may open the door to a novel therapeutic approach to fungal sepsis based on immunomodulatory therapies. To date, research efforts on

Address for Correspondence:
Andrea Cortegiani
E-mail: cortegiania@gmail.com

Turk J Anaesthesiol Reanim 2016; 44: 285-6
DOI: 10.5152/TJAR.2016.0013

Available online at www.jtaics.org

antifungal sepsis focused on strategies for early administration of antifungals given the reported high attributable morbidity and mortality of invasive fungal infections. This has led to development of clinical scores, identification of fungal biomarkers and untargeted approaches for invasive fungal infection prevention (7, 8). Evidence from randomized trials did not demonstrate, to date, an advantage of untargeted administration of antifungals in non-neutropenic critically ill patients (9, 10). In this sense, antifungal drug administration has been included among the growing list of "the less is better" interventions in ICU. Despite this lack of evidence, up to 8% of ICU patients without proven Candida spp. infection receive an antifungal drug and a significant proportion of patients who received an antifungal will not develop a fungal infection (11). This has led to antifungal exposure with increased risk of emergence of resistance, drug-related adverse events and costs (12). Furthermore, the issue of immunological impairment should perhaps be clinically evaluated by epidemiological and microbiological perspectives for Enteropathogenetic syndromes and for the possibilities of invasive infections included in the acronym "CCC": Candida, Carbapanemases-producing bacteria (such as Klebsiella pneumoniae) and C. difficile colitis (13-15).

After 30 years of research, there are still some unsolved questions about antifungal treatment in non neutropenic critically ill patients remains:

1) Should we go on with early administration of antifungals to critically ill patients despite the evidence not supporting their use to improve survival?

2) How to better select patients who may the most from antifungal administration?

3) Will immunomodulatory therapies be a feasible, valuable option for patients with fungal sepsis or at risk of developing it?

To date, international guidelines and a stewardship approach are the only available answers.

References

1. Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defence against Candida fungal infections. Nat Rev Immunol 2015; 15: 630-42. [CrossRef]
2. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. Nat Rev Immunol 2006; 6: 813-22. [CrossRef]
3. Muenzer JT, Davis CG, Chang K, Schmidt RE, Dunne WM, Coopersmith CM, et al. Characterization and modulation of the immunosuppressive phase of sepsis. Infect Immun 2010; 78: 1582-92. [CrossRef]
4. Spec A, Shindo Y, Burnham CA, Wilson S, Ablordeppey EA, Beiter ER, et al. T cells from patients with Candida sepsis display a suppressive immunophenotype. Critical Care 2015; 20: 1-9. [CrossRef]
5. Cortegiani A, Russotto V, Raineri SM, Giarratano A. The paradox of the evidence about invasive fungal infection prevention. Critical Care 2016; 20: 114. [CrossRef]
6. Russotto V, Cortegiani A, Raineri SM, Giarratano A. From bedside to bench: the missing brick for patients with fungal sepsis. Critical Care 2016; 20: 191. [CrossRef]
7. Cortegiani A, Russotto V, Raineri SM, Giarratano A. Antifungal prophylaxis: update on an old strategy. Eur J Clin Microbiol Infect Dis 2016; 35: 1719-20. [CrossRef]
8. Cortegiani A, Russotto V, Raineri SM, Giarratano A. Is it time to combine untargeted antifungal strategies to reach the goal of 'early' effective treatment? Critical Care 2016; 20: 241. [CrossRef]
9. Cortegiani A, Russotto V, Maggiore A, Attanasio M, Naro AR, Raineri SM, et al. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. Cochrane Database Syst Rev 2016: CD004920. [CrossRef]
10. Cortegiani A, Russotto V, Raineri SM, Gregoretti G, Giarratano A. Should we continue to use prediction tools to identify patients at risk of Candida spp. infection? If yes, why? Critical Care 2016; 20: 351. [CrossRef]
11. Azoulay E, Dupont H, Tabah A, Lortholary O, Stahl JP, Francais A, et al. Systemic antifungal therapy in critically ill patients without invasive fungal infection. Critical Care Med 2012; 40: 813-22. [CrossRef]
12. Alexander BD, Johnson MD, Pfeiffer CD, Jiménez-Ortigosa C, Catania J, Booker R, et al. Increasing echinocandin resistance in Candida glabrata: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis 2013; 56: 1724-32. [CrossRef]
13. De Rosa FG, Corcione S, Raviolo S, Montrucchio C, Aldieri C, Pagani N, et al. Candidemia, and infections by Clostridium difficile and carbapenemase-producing Enterobacteriaceae: new enteropathogenetic opportunistic syndromes? Infez Med 2015; 23: 105-16.
14. De Rosa FG, Corcione S, Cavallo R, Di Perri G, Bassetti M. Critical issues for Klebsiella pneumoniae KPC-carbapenemase producing K. pneumoniae infections: a critical agenda. Future Microbiol 2015; 10: 283-94. [CrossRef]
15. De Rosa FG, Corcione S, Pagani N, Di Perri G. From ESKAPE to ESCAPE, From KPC to CCC. Clin Infect Dis 2015; 60: 1289-90.[CrossRef]