

# Characterizing sepsis: Another small piece of the puzzle

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Sepsis - infection associated with a dysregulated host inflammatory response leading to some degree of organ dysfunction<sup>[1]</sup> - is a common occurrence in critically ill-patients and is associated with considerable morbidity and mortality in this population. With no known specific curative therapy for sepsis, treatment essentially relies on eradication of the causative microorganism and support of individual organs. To optimize chances of survival, rapid diagnosis enabling such management to be started in a timely manner is essential.<sup>[2]</sup> Diagnosis of sepsis in critically ill-patients can, however, be difficult due to the variable and nonspecific signs and symptoms of sepsis in the critically ill-population.

Better characterization of the immune response and likely prognosis in individual patients may also help to improve outcomes and hence that interventions can be better targeted at the individual patient needs. With advances in molecular analysis and genomics testing, attention has been drawn to the potential role of gene expression profiling in identifying and characterizing patients with sepsis. It is well-known that patients vary in their individual immune response to infection and genetic diversity can influence the development of and outcomes from sepsis. A number of studies have now been published demonstrating that the carriage of one or more single nucleotide polymorphisms (SNP) of genes that encode for inflammatory mediators can influence risk of developing sepsis and/or outcome from sepsis.<sup>[3-5]</sup>

In this issue of the Indian Journal of Critical Care Medicine, Ramakrishna *et al.*<sup>[6]</sup> reported that the results of a study assessing the role of SNPs in the heat shock

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protein 70 gene (*HSP70*) on outcomes in medical intensive care unit (ICU) patients with sepsis. The *HSP70* family, comprising at least 14 members in humans,<sup>[7]</sup> is one of a large group of ubiquitous, evolutionarily conserved intracellular proteins first discovered in the early 1960s. Importantly, *HSP70* proteins also exist extracellularly, where they are involved in various aspects of intercellular signaling and in controlling immune and inflammatory reactions.<sup>[7]</sup> The *HSP70* family is now known to have multiple diverse functions including molecular chaperoning, apoptosis, innate immune signaling, and cytokine like stimulation of the production of pro- and anti-inflammatory mediators.<sup>[7]</sup> *HSP70* proteins are upregulated by temperature (hence the name), but also by other forms of stress, including sepsis, inflammation, exercise, hypoxia, etc., Increased expression of *HSP70* is found in various diseases characterized by inflammation, including sepsis, pancreatitis, auto-immune disease, and certain tumors. As reported by Ramakrishna *et al.*,<sup>[6]</sup> polymorphisms of *HSP70* have been reported in various groups of patients, including those with diabetes, sarcoidosis, inflammatory bowel disease, coronary artery disease as well as patients with sepsis, and the presence of such polymorphisms has been associated with worse outcomes.

In this study by Ramakrishna *et al.*,<sup>[6]</sup> 108 patients were studied, of whom 101 (94%) patients had at least one

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SNP; although, there was considerable variation in the frequency of the different alleles. The presence of one or more SNPs was associated with the development of hematological dysfunction and the need for mechanical ventilation. Interestingly, organ dysfunction occurred in just one of the seven patients without an SNP. Different polymorphisms were associated with different patterns of organ dysfunction and prolonged ICU length of stay. This study was not powered to detect differences in mortality. This study is limited by the relatively small number of patients for such an association study. The included patients also represent quite a specific population with one third presenting with viral H1N1 disease and one-fourth with scrub typhus; patients with malaria, leptospirosis, melioidosis and dengue fever also formed part of the population, limiting the generalizability of these results to other patients populations.

Nevertheless, despite these limitations, the observations made by Ramakrishna *et al.*<sup>[6]</sup> are interesting and potentially important. Although the clinical implications in terms of diagnosis, prognosis and therapeutics may not yet be obvious, the ability to better characterize patients with sepsis can only be beneficial as we struggle to provide more individualized patient care. The results of this study provide another

small piece of the seemingly increasingly complex puzzle of sepsis.

## References

1. Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: Time for change. *Lancet* 2013;381:774-5.
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.* Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165-228.
3. Kotsaki A, Raftogiannis M, Routsis C, Baziaka F, Kotanidou A, Antonopoulou A, *et al.* Genetic polymorphisms within tumor necrosis factor gene promoter region: A role for susceptibility to ventilator-associated pneumonia. *Cytokine* 2012;59:358-63.
4. Wurfel MM, Gordon AC, Holden TD, Radella F, Strout J, Kajikawa O, *et al.* Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. *Am J Respir Crit Care Med* 2008;178:710-20.
5. Li L, Nie W, Zhou H, Yuan W, Li W, Huang W. Association between plasminogen activator inhibitor-1-675 4G/5G polymorphism and sepsis: A meta-analysis. *PLoS One* 2013;8:e54883.
6. Ramakrishna K, Pugazhendhi S, Kabeerdoss J, Peter JV. Association between heat shock protein 70 gene polymorphisms and clinical outcomes in intensive care unit patients with sepsis. *Indian J Crit Care Med* 2014;205-211.
7. Henderson B, Pockley AG. Molecular chaperones and protein-folding catalysts as intercellular signaling regulators in immunity and inflammation. *J Leukoc Biol* 2010;88:445-62.

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