

# Secondary Hemophagocytic Lymphohistiocytosis: Think of the Devil Lurking!

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**Keywords:** Adult, Critically ill, Hemophagocytic lymphohistiocytosis, Hemophagocytic syndrome, Infections, Macrophage activation syndrome. *Indian Journal of Critical Care Medicine* (2022); 10.5005/jp-journals-10071-24216

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening clinical syndrome of pathologic immune dysregulation and extreme inflammation. It is characterized by uncontrolled activation of lymphocytes with massive cytokine release (or “cytokine storm”). The subsequent tissue infiltration and resultant organ inflammation clinically manifest as a syndrome akin to sepsis with multiorgan failure. Primary HLH is a rare genetic disorder involving cytotoxic T cells and natural killer cells in the pediatric population. In contrast, secondary or acquired HLH is the more common form of HLH in adults, often triggered by infectious, autoimmune/inflammatory, or malignant disorders.<sup>1</sup>

Despite secondary HLH being increasingly recognized, there is scant published data available to describe the prevalence of HLH in intensive care unit (ICU) patients, especially from developing countries.<sup>2,3</sup> The article published in the current edition is an attempt to define the spectrum, etiology, and outcome of secondary HLH in critically ill patients from a tertiary care center in north India.<sup>4</sup> The researchers prospectively screened patients with fever and cytopenia involving two or more cell lineages<sup>4</sup> and were able to identify secondary HLH in 43.4% of patients, including infections as a trigger in 70%. The study confirms that tropical acute febrile illnesses (AFIs), tuberculosis, and kala-azar remain common causes of secondary HLH in our settings.<sup>5,6</sup> These observations are in contrast to the predominance of gram-negative pathogens as triggers of secondary HLH in studies from western ICUs.<sup>3</sup> Tropical AFIs like leptospirosis, enteric fever, malaria, dengue, scrub typhus (an acronym LEMDS is a helpful memory aid), and other unexplained/unidentified viral/bacterial infections frequently have overlapping clinical presentations.<sup>7,8</sup> The clinical manifestations like fever, cytopenia, and multiorgan dysfunction could be direct effect of the pathogen or a manifestation of dysregulated immune response.<sup>6–8</sup> Severe cases of tropical AFIs with persistent fever, organ failure, or cytopenia not improving with disease-specific therapy should be investigated for secondary HLH.<sup>5,6,9</sup>

The major limitation of the current study is the fact that many viral infections like Epstein–Barr virus, a frequent pathogen associated with infection-triggered HLH, was not specifically investigated.<sup>1,2</sup> The study was conducted before the coronavirus disease-2019 (COVID-19) pandemic, so it may have missed the COVID-19-associated HLH, which now has increasingly been reported.<sup>10</sup> The prevalence of aspergillosis and mucormycosis, the important fungi associated with secondary HLH in this report, has increasingly been reported during the COVID-19 era. Malignancies like lymphoma remain an important cause of secondary HLH;

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**How to cite this article:** Pannu AK, Bhalla A. Secondary Hemophagocytic Lymphohistiocytosis: Think of the Devil Lurking! *Indian J Crit Care Med* 2022;26(5):545–546.

**Source of support:** Nil

**Conflict of interest:** None

however, the diagnosis is challenging and often requires detailed hematological, radiological, and pathological examination and may be missed in a critically ill patient, if not specifically looked for.<sup>1,2</sup> Although an important autoimmune disease, systemic lupus erythematosus, was represented in this series, adult-onset Still’s disease, a common cause of macrophage activation syndrome, should also be kept in mind when thinking about systemic inflammation/autoimmunity.<sup>4,11</sup>

Diagnosis of secondary HLH is based on HLH-2004 criteria along with clinical suspicion.<sup>1</sup> Although hyperferritinemia is an important biomarker to raise suspicion; it remains less specific in adult patients than in pediatric patients.<sup>1,3</sup> An important point to remember is that no single clinical or laboratory parameter is sensitive or specific to unequivocally diagnose secondary HLH; however, soluble CD25 (also soluble interleukin-2 receptor), one of the diagnostic criteria in HLH-2004, is increasingly being reported to have significant diagnostic utility.<sup>1,5,12</sup> This parameter, however, was not evaluated in the index study. As the authors have rightly discussed that measurement of natural killer cell activity and soluble CD25 levels may not be readily available, the diagnosis may be missed or delayed in some. The H-Score (HLH-probability calculator) is a valuable tool and can be applied wherever a strong suspicion of secondary HLH is raised.<sup>1</sup> Genetic testing may be helpful in detecting potential predisposition to acquired HLH; however, it is not routinely recommended in adults.<sup>1</sup>

The underlying disease-specific management remains the mainstay treatment of secondary HLH in clinically stable patients; however, clinical deterioration or development of new organ failure necessitates adjunctive immunosuppressive/immunomodulatory therapy.<sup>1</sup> In the index study, patients were administered steroids, etoposide, cyclosporine, or intravenous

immunoglobulin (IVIg); yet, the mortality was significantly high (39.4%). The poor outcome in this study in secondary HLH may be due to the underlying disease or may have been modulated by immune suppression. The pathogenesis of different secondary HLH subtypes may vary, thus the immunosuppressive therapy (type, dose, or duration) needs to be individualized in a patient.<sup>1</sup> The authors also suggest that high-dose immunosuppression may aggravate underlying infections or may predispose a critically ill patient to secondary infections, resulting in morbidity and mortality. Sometimes, in a critically ill patient, secondary infections may be misdiagnosed as HLH relapse.<sup>1</sup> Some studies have demonstrated good outcomes with intravenous immunoglobulins (IV Igs) in critically ill adult patients.<sup>2</sup> Several small studies and case series have demonstrated that tropical AFI-related/triggered secondary HLH usually responds well to steroids or IVIg; however, more data are needed from controlled clinical studies.<sup>5,6</sup>

In conclusion, secondary HLH is more likely to be underdiagnosed in Indian ICUs due to overlapping clinical manifestations of fever and multiorgan dysfunction. Endemic infections are important triggers. Intensivists should be alert to the possibility of secondary HLH in patients with persistent organ dysfunction. Despite the heterogeneity, the current diagnosis and treatment of secondary HLH are heavily reliant on pediatric protocols for primary HLH. An alarming prevalence of nearly 40% in the index study incites us to develop improved strategies for prompt identification, to develop/look for better diagnostic biomarkers, and to have standardized treatment protocols for our critically ill patients in ICUs.

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