



Hemophagocytic Lymphohistiocytosis and Other Culture Negative Sepsis-Like Syndromes in the ICU

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Case Presentation

A 57 year old man with history of idiopathic panniculitis on long-term steroid treatment presented to the hospital with a 1 month history of dyspnea, malaise, nausea and vomiting. He was hypotensive and tachycardic with an acute kidney injury. Prior to this presentation, he had been hospitalized for 2 weeks at a nearby hospital with similar symptoms and had been found to have multifocal ground glass opacities on CT of the chest. His condition after admission improved with fluid resuscitation, stress-dose steroids, and treatment for presumed sepsis. Infectious and rheumatologic workups were negative. He was noted to have bilateral pulmonary infiltrates (Fig. 79.1a, b). One week after discharge, however, he presented again with systemic inflammatory response syndrome (SIRS). A bronchoscopy revealed only acute and chronic organizing pneumonia, with no evidence of infection. A bone marrow biopsy was performed, which demonstrated a hypercellular marrow. Pulse dose steroids were initiated for organizing pneumonia and he improved significantly over the next week with continuation of empiric antimicrobials and tapering of steroids. After 1 week of this regimen, however, he again decompensated with hypoxia and hypotension. Worsening infiltrates were noted on his chest radiograph (Fig. 79.1c). Ferritin was elevated at 7652 ng/mL, and sIL-2R was elevated at 3432 U/mL. Triglycerides were normal and fibrinogen was elevated. Given his unremarkable bone marrow biopsy 7 days before and elevated fibrinogen, the possibility of hemophagocytic lymphohistiocytosis (HLH) was dismissed as his hyperferritinemia and elevated sIL-2R were attributed to history of blood transfusion and occult infection. He continued to improve with empiric antimicrobials and steroids, and was

discharged from the hospital 5 days after admission to the ICU to complete a course of levofloxacin on 40 mg of prednisone daily.

He presented to the hospital for the third time 2 days after discharge with hypotension and hypoxia requiring endotracheal intubation and vasopressors, and antibiotics and steroids were restarted. He was admitted to the ICU and his pulmonary status rapidly improved. After 3 days, however, he again decompensated with hypotension and an elevated lactate. He received intravenous fluids and intravenous steroids. Given the unclear association between changes in his antimicrobial regimen, steroid dosing, and clinical condition, his steroid dose was decreased from 40 mg prednisone daily by 10 mg each day. A repeat bone marrow biopsy was performed, which showed rare hemophagocytic macrophages but no evidence of malignancy. The next day, in the setting of reducing his steroid dose, he again had an episode of hypoxia and hypotension. Ferritin was measured at that time and was 9148 ng/mL, increased from 4074 ng/mL the day before (Fig. 79.2). sIL-2R was measured and was elevated at 3494 U/mL. A diagnosis of HLH was made, and he was started on chemotherapy with etoposide and high dose dexamethasone. Eight weeks had elapsed since his initial presentation.

The patient was initiated on etoposide and dexamethasone without cyclosporine per the HLH-94 protocol. He rapidly improved and was moved to the hematology/oncology ward. His course was complicated by recurrent fevers and rising ferritin with the addition of filgrastim to his regimen after 3 weeks of therapy. This was discontinued and he improved uniformly from then on. After 1 month he was transferred to the physical medicine service for rehabilitation, and was subsequently discharged to home. He continued to do well 2 months after his diagnosis, and was preparing for allogeneic bone marrow transplant at that time.

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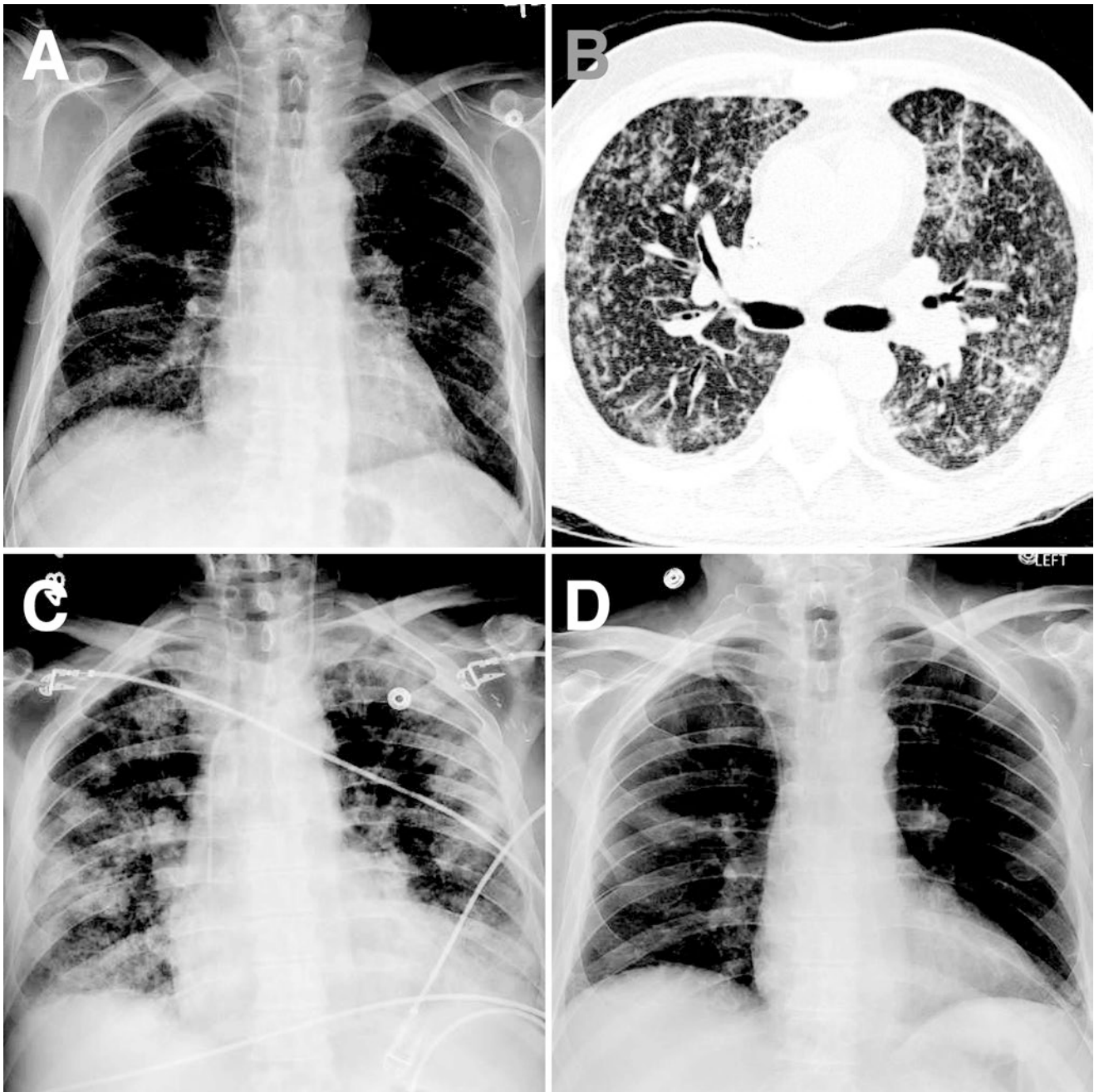


Fig. 79.1 Chest radiograph on admission (a) demonstrated bilateral infiltrates, which corresponded to bilateral ground glass opacities and interstitial thickening on a CT performed the same day (b). After 1 month,

pulmonary infiltrates were consistently more severe, despite multiple courses of antibiotics and diuresis (c). After treatment with etoposide and dexamethasone, infiltrates resolved by the time of discharge (d)

Principles of Management

HLH is a group of disorders characterized by aberrant immune activation leading to uncontrolled inflammation and, in many cases, critical illness. The underlying causes of HLH have been divided into primary causes, which encompass genetic defects in immune system regulation and often

present in the neonatal period or early childhood, and secondary causes, which may be related to autoimmune disease, viral infection, or malignancy [1, 2]. However, there is growing appreciation that many adolescent and adult patients develop HLH due to the interaction of an underlying genetic defect with an environmental trigger, such as viral infection with Epstein-Barr virus or cytomegalovirus [3].

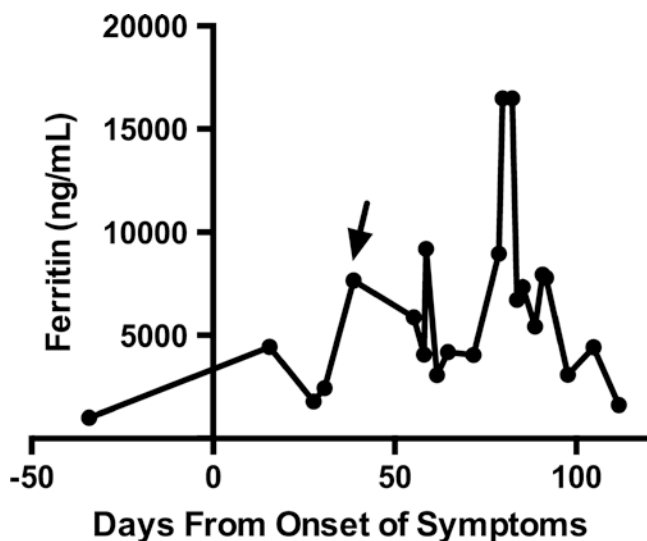


Fig. 79.2 Degree of hyperferritinemia varied significantly over the patient's hospital course, with marked elevations at the time of diagnosis (arrow) and relapse of HLH

HLH Presentation and Diagnosis

Presentation

In adults, HLH often presents with dramatic, but nonspecific, features of including fever, organomegaly, cytopenias, kidney injury, and altered mental status [4, 5]. As many as 2 out of 3 patients with HLH will present with severe coagulation disorders including disseminated intravascular coagulation and hypofibrinogenemia, many with associated severe bleeding [6]. As illustrated in the case above, in our experience rapid fluctuating hemodynamic instability and hypoxic respiratory failure are also common features resulting from the abnormal inflammatory response. These presenting symptoms and laboratory findings overlap significantly with severe sepsis. It is not uncommon for adult patients with HLH to have recently been hospitalized for presumed sepsis, and HLH is entertained as a diagnosis after one or more unexplained relapses. The most important step in recognizing HLH in the critically ill patient, therefore, is to consider it in the differential diagnosis alongside more common causes of shock and respiratory failure.

Diagnosis

While primary HLH is a genetic disorder and may be diagnosed by molecular testing with a suggestive family history and clinical presentation, secondary HLH is a clinical syndrome with diverse causes. Diagnostic criteria for HLH are currently based on the selection criteria for the HLH-2004 trial, which enrolled pediatric patients (Table 79.1 [7]).

The presence of fever, organomegaly, cytopenia, and hypertriglyceridemia or hypofibrinogenemia, while nonspe-

Table 79.1 Diagnostic criteria for HLH derived from the HLH-2004 study. Adapted from [2]

HLH-2004 diagnostic criteria
A. Molecular diagnosis consistent with HLH
Or
B. Five of the 8 criteria listed below
1. Fever >38.5 °C
2. Splenomegaly
3. Cytopenias affecting 2 of 3 lineages in peripheral blood (RBC, platelets, or neutrophils)
4. Hypertriglyceridemia or hypofibrinogenemia
5. Hemophagocytosis in biopsy of the bone marrow, spleen, or liver
6. Low or absent NK cell activity
7. Hyperferritinemia
8. Elevated sCD25 (soluble IL-2 receptor)

cific, are widely accepted as helpful criteria in defining the syndrome. The presence of hemophagocytosis, despite lending HLH its name, is also nonspecific [8]. The search for appropriate biomarkers, then, remains an area of active and important investigation, as detailed below. In practice, the most critical information leading to the diagnosis of HLH is often derived from following the patient over several days, observing the response, or lack thereof, to treatment for sepsis or other common conditions, and the relationship of biomarkers to the patient's evolving clinical condition.

HLH Treatment

Treatment

The largest trial of HLH treatment are the HLH-94 and HLH-2004 trials, which investigated the treatment of HLH with etoposide, dexamethasone, and cyclosporine in children and adolescents [7, 9]. Long-term follow-up of the HLH-2004 trial suggested that intensified cyclosporine regimens and the addition of intrathecal steroids with reduced time to HSCT did not improve outcome significantly in the pediatric population [10]. Etoposide and dexamethasone have become the mainstay of treatment in adult patients with HLH. Anti-thymocyte globulin has also been used in combination with steroids, cyclosporine and intrathecal chemotherapy [11]. A recent consensus review on malignancy-associated HLH suggests tailoring treatment to the underlying trigger, performance status, organ function and additional therapies the patient is receiving [12]. Early consultation with a hematologist and center experienced in the treatment of HLH is critical, both because immunomodulatory therapy for HLH is an area of active investigation, and because bone marrow transplantation is considered the curative therapy for patient with a known or suspected genetic cause of HLH.

Early therapies for HLH may be limited by end-organ damage present at the time of diagnosis, especially liver and

kidney injury. As highlighted in the case presented here, treatment with high dose steroids may provide adequate temporizing therapy, allowing the patient to stabilize and ultimately receive definitive therapy.

HLH Outcomes

Outcomes

As the case above highlights, adult patients in the ICU are often diagnosed with HLH after several episodes of apparent improvement followed by worsening, with periods of critical illness. The most comprehensive longitudinally studied cohort of patients with HLH was enrolled in the HLH-1994 study, which exclusively studied children under age 16 [13]. In this cohort, cumulative 5-year mortality was 46%, with 25% mortality within 8 weeks of diagnosis. Survival was 66% among those patients who underwent HSCT. HLH in adults is far more likely to be secondary than HLH in the pediatric population, though late presentations of primary HLH are possible [3]. Among critically ill patients who receive etoposide for treatment of HLH, a near 50% survival rate has been reported [14]. A multi-center seven-year series of 68 adult HLH cases described a median overall survival of 4 months [15]. While survival to discharge in many adult cohorts mirrors the pediatric population, long-term mortality in secondary HLH may be more reflective of underlying malignancy [16, 17].

Evidence Contour

Outcomes and Prognosis

Short-term mortality from HLH depends strongly on local treatment resources and supportive care, and varies widely among single-center studies from 50 to nearly 80% prior to discharge [4, 18]. Across centers, however, HLH related to malignancy is found to have the highest mortality, followed by autoimmune and then infectious causes. In a single center descriptive study, the worst prognosis was found in patients with malignancy associated HLH and extreme hyperferritinemia with a median survival of 7 months [19]. In a North American tertiary care center, patients with HLH secondary to causes other than malignancy had a median survival of 48 months, compared to less than 2 months in cases associated with malignancy [20]. Severity of illness at the time of diagnosis of HLH also appears to bear on outcome despite treatment, with thrombocytopenia, marked hyperferritinemia, and shock at ICU admission associated with mortality [14, 20]. In a single center study of 162 patients with HLH, in multivariate analyses age, lymphoma, decreasing platelet count and not having etoposide administered as part of treatment were all associated with increased mortality [21].

Diagnosis and Biomarker Testing

As highlighted in the case presentation, diagnosis of HLH is often difficult and delayed. Multiple conditions share at least several of the diagnostic criteria of HLH. Genetic testing has been proposed as a means for improving diagnosis and therefore treatment of HLH. Using a high-throughput sequencing strategy of 12 genes linked to HLH researchers developed a screening test with 97.3% sensitivity in detecting known genetic mutations for HLH [22]. However, when utilized in a prospective cohort of adult HLH patients, only 40% of patients had an identifiable mutation, highlighting the lack of clear genetic cause in adult HLH.

Specific biomarkers for HLH would likely shorten time to diagnosis and therapy. Bone marrow hemophagocytosis, while lending its name to HLH, is neither sensitive nor specific for the disorder [8]. NK cell activity and sIL-2R levels are part of the HLH diagnostic criteria, but these laboratory studies are available in only a few reference laboratories. Ideally, biomarker testing would rely on commonly and rapidly available assays, such as those for determining ferritin levels.

In the pediatric population, hyperferritinemia (>10,000 mcg/L) has a greater than 90% specificity for HLH [23]. However, a recent retrospective study demonstrated that HLH is diagnosed in only 14.2% of adults and 48.9% of children with ferritin >10,000 mcg/L suggesting this biomarker is less specific than previously thought [24]. In patients diagnosed with HLH, ferritin levels reflect disease course and activity, and in children a marked decrease in ferritin (>96%) portends decreased short term mortality during HLH treatment [25]. In critically ill adults, however, the increased prevalence of conditions which elevate ferritin, such as infection, malignancy, autoimmune disease, liver injury and chronic blood transfusion make hyperferritinemia a nonspecific finding for HLH [26, 27]. Only 3% of hospitalized patients with elevated ferritin levels (>2000 ng/mL) will have a diagnosis of HLH; patients are more likely to have liver injury or infection with elevated ferritin alone [28].

In addition, particular causes of secondary HLH may be associated with variable biomarker patterns. For example, HLH due to lymphoma may present with a high ratio of sIL-2R to ferritin compared to other causes [29]. Given that HLH is a disorder of immune dysregulation, efforts have been made to differentiate HLH from infection based on cytokine patterns in the pediatric population [30]. Whether this approach will be fruitful in adults requires further study.

Treatment

There are no randomized controlled trials for the treatment of adult HLH. Treatment regimens have been adapted from the

HLH-94 and HLH-2004 studies that primarily included children. A trial of salvage therapy of doxorubicin-etoposide-methylprednisolone in adults with mostly non-familial refractory HLH, demonstrated an overall response rate of 75%, with 29 of 48 patients surviving to undergo disease specific therapy [31]. A recent case series reported the use of the interleukin 1 antagonist, anakinra, with steroids and IVIG in eight critically ill patients with HLH and demonstrated a hospital survival rate of 50% [32]. Additional research on non-etoposide based treatment regimens may therefore be warranted for critically ill patients with multiple organ failure. Alemtuzumab, a humanized monoclonal antibody targeting CD52, has been used as a salvage therapy for refractory adult HLH [33] and is being evaluated as part of an ongoing clinical trial for primary therapy in combination with etoposide (Clinicaltrials.gov identifier NCT02385110). Other biologics and small molecules are currently being evaluated for various forms of HLH (ruxolitinib NCT02400463, tocilizumab NCT02007239, emapalumab NCT01818492).

Other Inflammatory Syndromes in the ICU

While HLH is associated with a wide variety of primary and secondary etiologies, several other sepsis-like syndromes have been identified in specific clinical contexts.

Macrophage Activation Syndrome (MAS)

As mentioned earlier, secondary HLH (sHLH) occurs in the setting of other medical conditions. MAS is a form of sHLH associated with autoimmune disease [34]. In children, it is a well-recognized complication of systemic juvenile idiopathic arthritis (sJIA) [35].

Presentation

In adults, MAS is commonly seen with rheumatologic diseases such as in systemic lupus erythematosus and Adult Onset Still's Disease (AOSD), the latter being characterized clinically by quotidian fevers, arthralgia, salmon-pink skin rash, sore throat, lymphadenopathy and organomegaly [36]. Nearly half of all MAS/sHLH patients are critically ill requiring mechanical ventilator or vasoactive support [14].

Diagnosis

Clinically, MAS/sHLH is difficult to diagnose, though should be suspected in critically ill, persistently febrile patients. While there are suggested diagnostic criteria for MAS complicating sJIA [37], there are no such criteria for MAS in adult rheumatologic disease. Recently, a 9 variable scoring system (HScore) has been developed for use in identifying adults with sHLH (Table 79.2) [38]. An HScore of

Table 79.2 H-Score criteria for identifying secondary HLH/MAS

Variable	Criteria (points)
Underlying immunosuppression ^a	No (0), Yes (18)
Temperature	<38.4 (0), 38.4–39.4 (33), >39.4 (38)
Organomegaly	No (0), hepatomegaly or splenomegaly (23), hepatomegaly and splenomegaly (39)
Number of cytopenias ^b	1 lineage (0), 2 lineages (24), 3 lineages (34)
Ferritin (ng/mL)	<2000 (0), 2000–6000 (35), >6000 (40)
Triglyceride (mg/dL)	<132 (0), 132–354 (41), >354 (64)
Fibrinogen (mg/dL)	>250 (0), ≤250 (30)
Aspartate aminotransferase (AST, IU/L)	<30 (0), ≥30 (19)
Hemophagocytosis features on bone marrow aspirate	No (0), Yes (35)

Adapted from Fardet et al. 2014 *Arthritis & Rheumatology*, available at <http://saintantoine.aphp.fr/score/>

^aHuman immunodeficiency virus, long-term immunosuppression

^bHemoglobin <9.2 (g/dL), leukocyte count <5 (K/μL), platelet count <110 (K/μL)

≥169 corresponds to a sensitivity of 93% and specificity of 86% for identifying patients with sHLH.

Treatment

Treatment should be performed in consultation with hematologic experts as there is no validated approach to treatment of adult patients with MAS/sHLH. The foundation of treatment is high dose steroids (1 g methylprednisolone daily for 3–5 days), although many patients may require additional therapy [39]. Use of the IL-1 receptor antagonist, anakinra, has shown benefit in MAS associated with sJIA [40], and may be useful in adult MAS/sHLH. Additional therapies include IVIG, rituximab (in EBV associated disease), and cyclosporine [34].

A macrophage activation-like syndrome (MALS) has been described in patients with sepsis who have an HScore of >151 and/or had evidence of disseminate intravascular coagulation and hepatobiliary dysfunction [41]. Presence of MALS was associated with an increased risk of death within the first 10 days of sepsis. A Ferritin level of >4420 ng/mL was associated with a 97% specificity for MALS diagnosis in these patients. Interestingly, sepsis patients with MAS features including HBD/DIC have a mortality benefit in the phase III clinical trial using anakinra [42]. However, its utility in treating patients with sepsis with MAS features requires validation in future clinical trials.

Cytokine Release Syndrome

Chimeric antigen receptor (CAR) T cells are now being used in treatment of leukemia and lymphoma. While effective in

inducing bone marrow remission [43–45], CAR-T cells may be associated with the development of cytokine release syndrome (CRS) which frequently requires treatment in the ICU.

Presentation

This syndrome is characterized by fevers, hypotension, capillary leak, neurotoxicity and death [46]. Neurologic side effects can be particularly devastating and include encephalopathy, aphasia, obtundation and seizures [44]. Rates of CRS are variable among studies ranging from 35% to 100%, with about 1 in 4 patients developing severe symptoms [45]. Development of CRS is associated with higher tumor burden (>20% bone marrow blasts) and higher doses of CAR-T cells [47].

Diagnosis

Diagnostic criteria for CRS due to CAR-T cells have been developed (Table 79.3) [44], but generally this syndrome should be suspected in patients receiving CAR-T therapy who develop evidence of fever or end organ damage. Given the common nature of this side effect, grading scales for symptom severity and treatment algorithms have been proposed. At our institution, we consider ICU admission for Grade 2 toxicity and require ICU admission for Grade 3 and 4 toxicities (Table 79.4). After initial studies demonstrated efficacy of interleukin-6 receptor blocking monoclonal antibody, tocilizumab, in severe CRS related to CAR-T cell therapy [48], it has been commonly used

Table 79.3 Diagnostic Criteria for CRS

Fevers for at least 3 consecutive days
Two cytokine max fold changes of at least 75 or one cytokine max fold change of at least 250
At least one clinical sign of toxicity including:
Hypotension or initiation of an intravenous vasoactive pressor or,
Hypoxia <90% or,
Neurologic toxicity (including mental status change, obtundation, and seizure)

Adapted from [44]

Table 79.4 Toxicity severity for cytokine release syndrome

Grade	Symptoms
Grade 1	Symptoms non-life threatening, symptomatic treatment only
Grade 2	Symptoms requiring and responding to moderate intervention: Oxygen requirement <40%, hypotension responding to IV fluids or low dose of one vasopressor, grade II organ toxicity
Grade 3	Symptoms requiring and responding to aggressive intervention, including oxygen requirement ≥40%, hypotension requiring high dose or multiple vasoactives, grade III organ toxicity, grade IV transaminitis
Grade 4	Life-threatening symptoms with requirement for mechanical ventilatory support or grade 4 organ toxicity (except transaminitis)
Grade 5	Death

Grade II–IV refers to Common Terminology Criteria for Adverse Events (CTCAE v4.0)

Adapted from [49]

as a first line agent in patients with symptoms that include progressive hypoxia and hypotension. Management is usually performed in the context of established protocols at the institution administering the CAR-T therapy.

Idiopathic Pneumonia Syndrome

IPS is a complication of allogeneic hematopoietic cell transplant (HCT) that commonly leads to respiratory failure requiring management in the intensive care unit. It is defined as an idiopathic pneumonia-like syndrome with evidence of widespread alveolar injury in the absence of other common etiologies of respiratory failure including infection [50]. The pathophysiology of IPS is unclear, though it has been suggested that direct toxic effects of HCT conditioning regimens, occult infection, and certain inflammatory cytokines including TNF α may play a role.

Presentation

Clinically, patients may present with symptoms of pneumonia, hypoxic respiratory failure and multi-lobe infiltrates on chest imaging. IPS usually presents in the first 3 months after hematopoietic cell transplant (HCT), though later presentations more than 100 days post-HCT have also been reported [51]. The historical incidence is 3–15% with traditional myeloablative conditioning and lower with modern non-myeloablative regimens [50]. In one retrospective cohort study, median time to onset was 23 days (IQR 13–48 days) from HCT and two-year mortality was 85% [52].

Diagnosis

There is no pathognomonic pattern of histologic alveolar injury and patients are rarely able to tolerate lung biopsy. Therefore, diagnosis relies on exclusion of other etiologies that may cause multi-lobe infiltrates and respiratory failure. Bronchoalveolar lavage (BAL) should be performed and tested for common bacterial (including acid-fast bacilli, *Nocardia*, *Legionella*) and non-bacterial (CMV, RSV, PCP, HSV, VZV, influenza, parainfluenza, human metapneumovirus, rhinovirus, coronavirus, HHV6, *Chlamydia*, *Mycoplasma* and *Aspergillus*) organisms [50]. The importance of this testing is emphasized by the fact that 57% of BAL specimens from IPS patients had detectable bacterial or viral pathogens using modern techniques [53]. Thus, lower respiratory tract sampling may be one of the most important diagnostics an intensivist can offer. To reach a diagnosis of IPS, patients must also have an absence of cardiac dysfunction, acute renal failure or iatrogenic fluid overload contributing to their pulmonary dysfunction.

Treatment

Current treatment for IPS includes supportive care for hypoxic respiratory failure and systemic corticosteroids. Response rates in recent clinical trials were 67% for high

dose steroids, with a median time to response of 7 days [54]. Steroid treatment is typically with 2 mg/kg/day methylprednisolone equivalents continued intravenous for the three days with subsequent oral dosing and then tapering after day 7. The TNF α binding protein etanercept has been used in combination with steroids, demonstrating improvements in response to therapy and early survival in small single center studies [55–57]. In 2014 a phase III clinical trial of adult IPS, etanercept did not provide additional benefit over steroids alone, though enrollment in this trial was prematurely ended and definitive conclusions regarding use of etanercept in IPS cannot be made from this trial alone. Notably, etanercept use was not associated with increased risk of opportunistic infection or malignancy relapse compared with placebo controls. Veno-venous extracorporeal membrane oxygenation use has been reported in both early and late IPS, though its efficacy and impact on outcomes is unclear [58, 59]. For patients who do not respond to steroids and anti-TNF α therapies the treatment is also unclear. IL-6 is elevated in the plasma of patients with IPS [60] and it has been suggested that the IL-6 inhibitor, tocilizumab, may have some benefit in treating or preventing IPS [61].

Conclusion

Several important clinical syndromes, including HLH, MAS, IPS, and CRS can mimic sepsis and cause critical illness through immune dysregulation in the absence of infection. Identification of these syndromes requires a high index of suspicion, awareness of the clinical context and risk factors, as well as careful exclusion of infection and attention to response to empiric therapies. While prognosis in these syndromes is often uncertain, recent evidence indicates that patient survival in the presence of excellent supportive care is strongly driven by the underlying disease rather than the sepsis-like syndrome itself.

References

- Janka GE, Lehmborg K. Hemophagocytic syndromes – an update. *Blood Rev.* 2014;28:135–42.
- Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood.* 2011;118:4041–52.
- Wang Y, et al. Genetic features of late onset primary hemophagocytic lymphohistiocytosis in adolescence or adulthood. *PLoS One.* 2014;9:e107386.
- Li J, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. *Medicine (Baltimore).* 2014;93:100–5.
- Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet.* 2014;383:1503–16.
- Valade S, et al. Coagulation disorders and bleedings in critically ill patients with hemophagocytic lymphohistiocytosis. *Medicine (Baltimore).* 2015;94:e1692.
- Henter J-I, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48:124–31.
- Goel S, Polski JM, Imran H. Sensitivity and specificity of bone marrow hemophagocytosis in hemophagocytic lymphohistiocytosis. *Ann Clin Lab Sci.* 2012;42:21–5.
- Henter J-I, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood.* 2002;100:2367–73.
- Bergsten E, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood.* 2017;130:2728–38.
- Stephan J, et al. Treatment of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins, steroids, and cyclosporin A. *Blood.* 1993;82:2319–23.
- Daver N, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. *Cancer.* 2017;123:3229–40.
- Trottestam H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood.* 2011;118:4577–84.
- Buyse S, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. *Intensive Care Med.* 2010;36:1695–702.
- Schram AM, et al. Haemophagocytic lymphohistiocytosis in adults: a multicentre case series over 7 years. *Br J Haematol.* 2016;172:412–9.
- Han A-R, et al. Lymphoma-associated hemophagocytic syndrome: clinical features and treatment outcome. *Ann Hematol.* 2007;86:493–8.
- Yu J-T, et al. Lymphoma-associated hemophagocytic lymphohistiocytosis: experience in adults from a single institution. *Ann Hematol.* 2013;92:1529–36.
- Rivière S, et al. Reactive hemophagocytic syndrome in adults: a multicenter retrospective analysis of 162 patients. *Am J Med.* 2014;127:1118–25. <https://doi.org/10.1016/j.amjmed.2014.04.034>.
- Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol.* 2015;90:220–4.
- Otrock ZK, Eby CS. Clinical characteristics, prognostic factors and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol.* 2014:1–5.
- Arca M, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. *Br J Haematol.* 2015;168:63–8.
- Tesi B, et al. Targeted high-throughput sequencing for genetic diagnostics of hemophagocytic lymphohistiocytosis. *Genome Med.* 2015;7:130.
- Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2008;50:1227–35.
- Otrock ZK, et al. Elevated serum ferritin is not specific for hemophagocytic lymphohistiocytosis. *Ann Hematol.* 2017;96:1667–72.
- Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. *Pediatr Blood Cancer.* 2011;56:154–5.
- Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: new insights into diagnosis and management. *J Intensive Care Med.* 2014;30:401–12. <https://doi.org/10.1177/0885066613517076>.
- Schram AM, et al. Marked hyperferritinemia does not predict for HLH in the adult population. *Blood.* 2015;125:1–19. <https://doi.org/10.1182/blood-2014-10-602607>.
- Schaffner M, Rosenstein L, Ballas Z, Suneja M. Significance of Hyperferritinemia in hospitalized adults. *Am J Med Sci.* 2017;354:152–8.

29. Tsuji T, Hirano T, Yamasaki H, Tsuji M, Tsuda H. A high sIL-2R/ferritin ratio is a useful marker for the diagnosis of lymphoma-associated hemophagocytic syndrome. *Ann Hematol.* 2014;93:821–6.
30. Xu X-J, et al. Diagnostic accuracy of a specific cytokine pattern in hemophagocytic lymphohistiocytosis in children. *J Pediatr.* 2012;160:984–90.e1.
31. Wang Y, et al. Multicenter study of combination DEP regimen as a salvage therapy for adult refractory hemophagocytic lymphohistiocytosis. *Blood.* 2015;126:2186–92.
32. Wohlfarth P, et al. Interleukin 1 receptor antagonist Anakinra, intravenous immunoglobulin, and corticosteroids in the management of critically ill adult patients with hemophagocytic lymphohistiocytosis. *J Intensive Care Med.* 2019;34(9):723–31. <https://doi.org/10.1177/0885066617711386>.
33. Marsh RA, et al. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. *Pediatr Blood Cancer.* 2013;60:101–9.
34. Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology.* 2018;58:5–17. <https://doi.org/10.1093/rheumatology/key006>.
35. Minoia F, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol.* 2014;66:3160–9.
36. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. *Autoimmun Rev.* 2014;13:708–22.
37. Ravelli A, et al. Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European league against rheumatism/American College of Rheumatology/Paediatric rheumatology international trials organisation Collaborat. *Arthritis Rheumatol.* 2016;68:566–76.
38. Fardet L, et al. Development and validation of the HScore, a score for the diagnosis of reactive Hemophagocytic syndrome. *Arthritis Rheumatol.* 2014;66:2613–20.
39. Fukaya S, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. *Rheumatology (Oxford).* 2008;47:1686–91. <https://doi.org/10.1093/rheumatology/ken342>.
40. Ringold S, et al. Update of the 2011 American College of Rheumatology Recommendations for the treatment of juvenile idiopathic arthritis recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum.* 2013;65:2499–512.
41. Kyriazopoulou E, et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. *BMC Med.* 2017;15:172.
42. Shakoory B, et al. Interleukin-1 receptor blockade is associated with reduced mortality in Sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial*. *Crit Care Med.* 2016;44:275–81.
43. Maude SL, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014;371:1507–17.
44. Davila ML, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med.* 2014;6:224ra25.
45. Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant.* 2019;25:e123–7.
46. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood.* 2016;127:3321–30.
47. Turtle CJ, et al. CD19 CAR-T cells of defined CD4+ : CD8+ composition in adult B cell ALL patients. *J Clin Invest.* 2016;11:1–16.
48. Grupp SA, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med.* 2013;368:1509–18.
49. Lee DW, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124:188–95.
50. Panoskaltzis-Mortari A, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *Am J Respir Crit Care Med.* 2011;183:1262–79.
51. Thompson J, et al. Etanercept and corticosteroid therapy for the treatment of late-onset idiopathic pneumonia syndrome. *Biol Blood Marrow Transplant.* 2017;23:1955–60.
52. Vande Vusse LK, Madtes DK, Bolgiano D, Watkins TR. The association between platelet transfusion and idiopathic pneumonia syndrome is unaffected by platelet product type. *Transfusion.* 2016;56:489–96.
53. Seo S, et al. Idiopathic pneumonia syndrome after hematopoietic cell transplantation: evidence of occult infectious etiologies. *Blood.* 2015;125:3789–97.
54. Yanik GA, et al. Randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor: enbrel (etanercept) for the treatment of idiopathic pneumonia syndrome after allogeneic stem cell transplantation: blood and marrow transplant clinical trials network protocol. *Biol Blood Marrow Transplant.* 2014;20:858–64.
55. Yanik GA, et al. The impact of soluble tumor necrosis factor receptor etanercept on the treatment of idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Blood.* 2008;112:3073–81.
56. Yanik G, et al. Etanercept (Enbrel) administration for idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2002;8:395–400.
57. Tizon R, et al. High-dose corticosteroids with or without etanercept for the treatment of idiopathic pneumonia syndrome after Allo-SCT. *Bone Marrow Transplant.* 2012;47:1332–7.
58. Koinuma T, Nunomiya S, Wada M, Koyama K, Suzuki T. Concurrent treatment with a tumor necrosis factor-alpha inhibitor and veno-venous extracorporeal membrane oxygenation in a post-hematopoietic stem cell transplant patient with idiopathic pneumonia syndrome: a case report. *J Intensive Care.* 2014;2:48.
59. Liao W-I, Tsai S-H, Chiu S-K. Successful use of extracorporeal membrane oxygenation in a hematopoietic stem cell transplant patient with idiopathic pneumonia syndrome. *Respir Care.* 2013;58:e6–10.
60. Yanik GA, et al. TNF-receptor inhibitor therapy for the treatment of children with idiopathic pneumonia syndrome. A joint pediatric blood and marrow transplant consortium and Children's oncology group study (ASCT0521). *Biol Blood Marrow Transplant.* 2015;21:67–73.
61. Teshima T. The primacy of IL-6 in IPS? *Blood.* 2015;125:2320–2.