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An Evidence-Based Guideline Improves Outcomes for Patients With Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Maria L. Taylor[1], Kacie J. Hoyt[2], Joseph Han[3], Leslie Benson[4], Siobhan Case[5], Mia T. Chandler[1], Margaret H. Chang[5], Craig Platt[1], Ezra M. Cohen[1], Megan Day-Lewis[1], Fatma Dedeoglu[1], Mark Gorman[4], Jonathan S. Hausmann[6], Erin Janssen[1], Pui Y. Lee[1], Jeffrey Lo[1], Gregory P. Priebe[7], Mindy S. Lo[1], Esra Meidan[1], Peter A. Nigrovic[5], Jordan E. Roberts[1], Mary Beth F. Son[1], Robert P. Sundel[1], Maria Alfieri[8], Jenny Chan Yeun[8], Damilola M. Shobiye[8], Barbara Degar[9], Joyce C. Chang[1], Olha Halyabar[1], Melissa M. Hazen[1], and Lauren A. Henderson[1]

ABSTRACT. ***Objective.*** To compare clinical outcomes in children with hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) who were managed before and after implementation of an evidence-based guideline (EBG).

Methods. A management algorithm for MAS-HLH was developed at our institution based on literature review, expert opinion, and consensus building across multiple pediatric subspecialties. An electronic medical record search retrospectively identified hospitalized patients with MAS-HLH in the pre-EBG (October 15, 2015, to December 4, 2017) and post-EBG (January 1, 2018, to January 21, 2020) time periods. Predetermined outcome metrics were evaluated in the 2 cohorts.

Results. After the EBG launch, 57 children were identified by house staff as potential patients with MAS-HLH, and rheumatology was consulted for management. Ultimately, 17 patients were diagnosed with MAS-HLH by the treating team. Of these, 59% met HLH 2004 criteria, and 94% met 2016 classification criteria for MAS complicating systemic juvenile idiopathic arthritis. There was a statistically significant reduction in mortality from 50% before implementation of the EBG to 6% in the post-EBG cohort ($P = 0.02$). There was a significant improvement in time to 50% reduction in C-reactive protein level in the post-EBG vs pre-EBG cohorts (log-rank $P < 0.01$). There were trends toward faster time to MAS-HLH diagnosis, faster initiation of immunosuppressive therapy, shorter length of hospital stay, and more rapid normalization of MAS-HLH–related biomarkers in the patients post-EBG.

Conclusion. While the observed improvements may be partially attributed to advances in treatment of MAS-HLH that have accumulated over time, this analysis also suggests that a multidisciplinary treatment pathway for MAS-HLH contributed meaningfully to favorable patient outcomes.

Key Indexing Terms: hemophagocytic lymphohistiocytosis, macrophage activation syndrome

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[1]M.L. Taylor, BS, M.T. Chandler, MD, C. Platt, MD, PhD, E.M. Cohen, MD, M. Day-Lewis, RN, MSN, CPNP, F. Dedeoglu, MD, E. Janssen, MD, PhD, P.Y. Lee, MD, PhD, J. Lo, MD, M.S. Lo, MD, PhD, E. Meidan, MD, J.E. Roberts, MD, M.B.F. Son, MD, R.P. Sundel, MD, J.C. Chang, MD, MSCE, O. Halyabar, MD, M.M. Hazen, MD, L.A. Henderson, MD, MMSc, Division of Immunology, Boston Children's Hospital, Boston, Massachusetts; [2]K.J. Hoyt, MSc, Division of Immunology, Boston Children's Hospital, Boston, Massachusetts, and Virginia Tech Carilion School of Medicine, Roanoke, Virginia; [3]J. Han, BS, Icahn School of Medicine at Mount Sinai, New York, New York; [4]L. Benson, MD, M. Gorman, MD, Division of Neurology, Boston Children's Hospital, Boston, Massachusetts, [5]S. Case, MD, M.H. Chang, MD, PhD, P.A. Nigrovic, MD, Division of Immunology, Boston Children's Hospital, and Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Boston, Massachusetts; [6]J.S. Hausmann, MD, Division of Immunology, Boston Children's Hospital, and Division of Rheumatology and Clinical Immunology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [7]G.P. Priebe, MD, Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts; [8]M. Alfieri, MPH, J. Chan Yeun, MSPH, D.M. Shobiye, MPH, Department of Pediatric Quality Program, Boston Children's Hospital, Boston, Massachusetts; [9]B. Degar, MD, Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

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Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are related disorders defined by hyperinflammation. HLH and MAS are characterized by T cell and macrophage activation, which lead to exuberant release of proinflammatory cytokines.[1-6] HLH occurs in individuals with gene defects that impair cytotoxicity (familial HLH [FHL]), but it can also develop in highly inflammatory states, such as infection and malignancy (secondary HLH).[7-14] MAS is a form of secondary HLH that complicates rheumatologic disorders.[6] Regardless of terminology, these conditions share an underlying pathology defined by excessive inflammation.[3,4,15]

There are multiple obstacles that make the management of MAS-HLH challenging. MAS-HLH typically evolves in the setting of an infection, malignancy, or autoimmune condition where some degree of inflammation is expected. The telltale signs of hyperinflammation can be incorrectly attributed to the triggering illness, resulting in a delayed or missed MAS-HLH diagnosis.[16-18] The multiorgan involvement of MAS-HLH often necessitates multidisciplinary care, which may be difficult to coordinate.[4,19] While MAS-HLH was traditionally treated with chemotherapy, there are now multiple anticytokine agents available that have demonstrated promise with less associated toxicity.[20-26] This plethora of options, coupled with the lack of studies directly comparing chemotherapy- vs nonchemotherapy-based protocols, can generate uncertainty and delays in selecting first-line therapies. These complexities are compounded by the rapid pace of disease escalation that is characteristic of MAS-HLH. Any delay in the institution of immunosuppression can result in significant morbidity for the patient.

To address the challenges intrinsic to managing MAS-HLH, we implemented an evidence-based guideline (EBG) through consensus building across multiple pediatric subspecialties.[27] The objectives of this effort were to facilitate the early diagnosis and the rapid initiation of immunomodulation in MAS-HLH while reducing practice variability. Herein, we compare quality of care metrics in patients with MAS-HLH before and after the launch of the EBG and show that use of this guideline was associated with improved clinical outcomes.

METHODS

The methods used to develop the MAS-HLH EBG have been described previously.[27] The EBG was launched on December 4, 2017. The pre-EBG time period was defined as October 15, 2015, to December 4, 2017. The post-EBG time period extended from January 1, 2018, to January 21, 2020. Study subjects were identified retrospectively through an electronic medical record (EMR) search algorithm that captured all patients admitted to the hospital with a consult note from rheumatology and/or oncology, temperature ≥ 38.2 °C, and ferritin level ≥ 500 ng/mL. An attending rheumatologist reviewed the chart of each patient. Patients were included in the analysis if the treating team diagnosed the child with new-onset MAS-HLH. For patients with multiple admissions for MAS-HLH, the index hospitalization with the first rheumatology/oncology consult note was included. Clinical characteristics were gathered and entered into a REDCap database. Quality improvement (QI) metrics were prespecified during development of the EBG and were calculated and recorded for each patient[27] (Table 1). The process measures included time to MAS-HLH diagnosis/treatment, and the primary outcome measures included duration of illness, severity of illness, and time to normalization of laboratory variables. We also tracked the number of rheumatology/oncology consults to measure resource utilization. A complete treatment response was defined as full control of MAS-HLH and hospital discharge without the need to add further immunomodulatory treatments. The study was approved by the institutional review board at Boston Children's Hospital (IRBP00020692).

Continuous variables were compared using Mann-Whitney *U* tests. Fisher exact tests were used to compare categorical variables. Kaplan-Meier survival curves were used to estimate the time from admission to MAS-HLH diagnosis, time from admission to initiation of MAS-HLH–directed therapy, time to 50% reduction in ferritin value from the peak ferritin level during admission, and time to 50% reduction in C-reactive protein (CRP) value from the peak CRP level during admission. For the CRP and ferritin survival analyses, patients were included if they had abnormal values for these variables that were trended over time. Censoring occurred at the time of hospital discharge or death if 50% reduction in ferritin or CRP levels was not observed. Two patients had prolonged hospital admissions for indications other than MAS-HLH and were excluded from the analysis for length of hospital stay, time to MAS-HLH diagnosis/treatment, and duration of fever. Log-rank tests were used to compare differences in survival distributions between the pre- and post-EBG groups. GraphPad Prism version 8.0 (GraphPad Software) was used for the statistical analyses.

RESULTS

Implementation of an EBG for the management of MAS-HLH. As described previously, we developed a collaborative approach to the diagnosis and treatment of patients hospitalized for MAS-HLH at our institution.[27] Briefly, a multidisciplinary work

Table 1. Prespecified quality metrics to evaluate the MAS-HLH EBG.

Recognition and treatment of MAS-HLH
Time from admission to MAS-HLH diagnosis (days)
Time from admission to initiation of MAS-HLH–directed therapy (days)
Duration of illness
Fever duration (days)
Length of hospital stay (days)
Hospital readmission within 60 days (Y/N)
Severity of illness
Need for higher level of care (Y/N)
Mortality during admission (Y/N)
Mortality at a later time (Y/N)
Normalization of MAS-HLH laboratory variables
Time to decrease in ferritin by 50% (days)
Ferritin decrease by 50% during admission (Y/N)
Time to decrease in CRP by 50% (days)
Time to CRP < 1 mg/dL (days)
Normalization of platelet count during the admission (Y/N)
Normalization of liver function tests during the admission (Y/N)

CRP: C-reactive protein; EBG: evidence-based guideline; HLH: hemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome; N: no; Y: yes.

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Address correspondence to Dr. L.A. Henderson, 1 Blackfan Circle, Karp Family Research Building, 10th Floor, Boston, MA 02115, USA. Email: Lauren.Henderson@childrens.harvard.edu.

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group used nominal group technique to achieve consensus and create a clinical algorithm for MAS-HLH. Entry criteria (fever, ferritin ≥ 500 ng/mL) were developed to alert the house staff when to consider MAS-HLH in a hospitalized patient. The rheumatology consult team was identified as the "gatekeeper" and assumed the responsibility of coordinating the diagnostic evaluation for MAS-HLH. First-line immunomodulatory treatments were recommended in the EBG based on the acuity of illness and risk for infection. To facilitate implementation of the EBG, campaign materials were developed and educational sessions were held with house staff and subspecialty providers. The EBG was launched in December 2017 and updated in January 2021 (Supplementary File S1, available with the online version of this article).

Identification of patients managed by the EBG. An EMR search algorithm was developed to systematically identify patients who entered the MAS-HLH EBG. In the post-EBG period, 86 inpatients with a rheumatology or oncology consult note, fever ≥ 38.2 °C, and ferritin ≥ 500 ng/mL were flagged as potential MAS-HLH cases. Upon further chart review, 57 entered the EBG, and rheumatology was consulted for an evaluation for MAS-HLH (Figure 1; Supplementary Table S1, available with the online version of this article). After assessment, 30 patients underwent a diagnostic evaluation for MAS-HLH, and 17 were ultimately considered to have MAS-HLH by the treating providers. The same EMR search was used to find 81 potential patients with MAS-HLH in the pre-EBG period (Figure 1; Supplementary Table S1). After chart review, 30 individuals were found to have undergone a diagnostic evaluation for MAS-HLH, and 10 received a diagnosis of MAS-HLH.

Clinical characteristics of patients with MAS-HLH. The most common clinical manifestations of MAS-HLH were persistent fevers, rash, and hepatosplenomegaly (Table 2). The median ferritin level was 12,188 ng/dL and 3082 ng/dL in pre-EBG and post-EBG groups, respectively. CRP and alanine transaminase (ALT) values were higher whereas the fibrinogen level was lower in the pre-EBG group. In the pre-EBG patients, 3 of 10 met HLH 2004 diagnostic criteria and 7 of 10 fulfilled the 2016 classification criteria for MAS complicating systemic juvenile idiopathic arthritis (sJIA).[21,28] Specialized studies required to fulfill the HLH 2004 criteria were not sent in full on many pre-EBG patients, potentially explaining the low number of pre-EBG patients who qualified for the HLH diagnosis. Natural killer cell function, bone marrow biopsy, and genetic sequencing were performed in 4 of 10, 3 of 10, and 5 of 10 pre-EBG patients, respectively. For children in the post-EBG group, 10 of 17 and 16 of 17 met the HLH 2004 and 2016 MAS classification criteria, respectively. Nearly one-quarter of patients in the pre- and post-EBG cohorts had a preexisting diagnosis of sJIA. Infection was identified in a majority of cases (approximately 80%) as the trigger for MAS-HLH. Two of the 17 children in the post-EBG group had an underlying malignancy as the cause of MAS-HLH. During the diagnostic evaluation, almost 25% of patients in the post-EBG cohort were found to have a genetic cause of MAS-HLH with biallelic, pathogenic variants uncovered in *PRF1* (n = 1), *UNC13D* (n = 1), *STAT2* (n = 1), and *COG4* (n = 1), while a single child with a heterozygous and disease-causing variant in *NLRC4* was identified in the pre-EBG cohort.

HLH- and MAS-directed treatment in the pre- and post-EBG cohorts. Eight patients in the pre-EBG period and 15 in the post-EBG cohort received immunomodulatory therapy for MAS-HLH. Of note, 4 children with MAS-HLH who were not treated with immunosuppression experienced a clinical improvement without intervention (n = 3) or after treatment of the underlying condition that triggered the MAS-HLH (n = 1; see Supplementary Table S2 for more information, available with the online version of this article). The management recommendations outlined in the EBG were followed in 16 of 17 patients. The single deviation occurred in a child with immune dysregulation who was managed by oncology without rheumatology's input.

The EBG provides a list of immunomodulatory medications that can be used alone or in combination as first-line treatment of MAS-HLH, including anakinra, intravenous Ig (IVIG), cyclosporine (CSA), tacrolimus, and glucocorticoids (GCs). After implementation of the EBG, IVIG (n = 6), interleukin (IL)-1 blockade (n = 6), and GCs (n = 5) were the most commonly selected medications for the initial treatment of MAS-HLH (Figure 2). IL-1 blockade and IVIG were used at higher frequencies in the post-EBG group. The increased use of IVIG was notable (10% of pre-EBG vs 35% of post-EBG patients). IVIG monotherapy was selected as first-line treatment in patients who were either noncritically ill (4 of 6 patients treated with IVIG) or in patients where there was a high degree of concern for an invasive infection (4 of 6). More patients in the pre-EBG cohort received the HLH 2004 protocol (20% of pre-EBG vs 6% in the post-EBG groups). Tocilizumab (TCZ) was not included in the EBG recommendations and it was prescribed for 1 pre-EBG and no post-EBG patients. Twenty-five percent of pre-EBG compared to 67% of post-EBG patients had a complete response to first-line therapy, although this difference was not statistically significant ($P = 0.09$, Fisher exact test).

Clinical outcomes after implementation of an EBG for MAS-HLH. A goal of the EBG was to decrease the time to MAS-HLH diagnosis and treatment. The median time from hospital admission to MAS-HLH diagnosis was 4 days (IQR 31.3 days) in the pre-EBG period compared to 2 days (IQR 3.5 days) in the post-EBG era, although this difference did not achieve statistical significance (Figure 3A). Similarly, there was a nonsignificant trend toward faster initiation of treatment in the post-EBG group with a median time from admission to the initiation of MAS-HLH-directed therapy of 5 days (IQR 40.0 days) in the pre-EBG cohort compared to 2 days (IQR 5.0 days) after EBG launch (Figure 3B).

To evaluate the duration of illness before and after implementation of the EBG, we measured fever duration, length of hospital admission, and need for readmission to the hospital after discharge. The median number of febrile days was 4 in the pre-EBG group compared to 5 in the post-EBG group, while the length of hospital stay was 28 days vs 11 days in these 2 groups, respectively (Figures 3C,D). There was wide variability

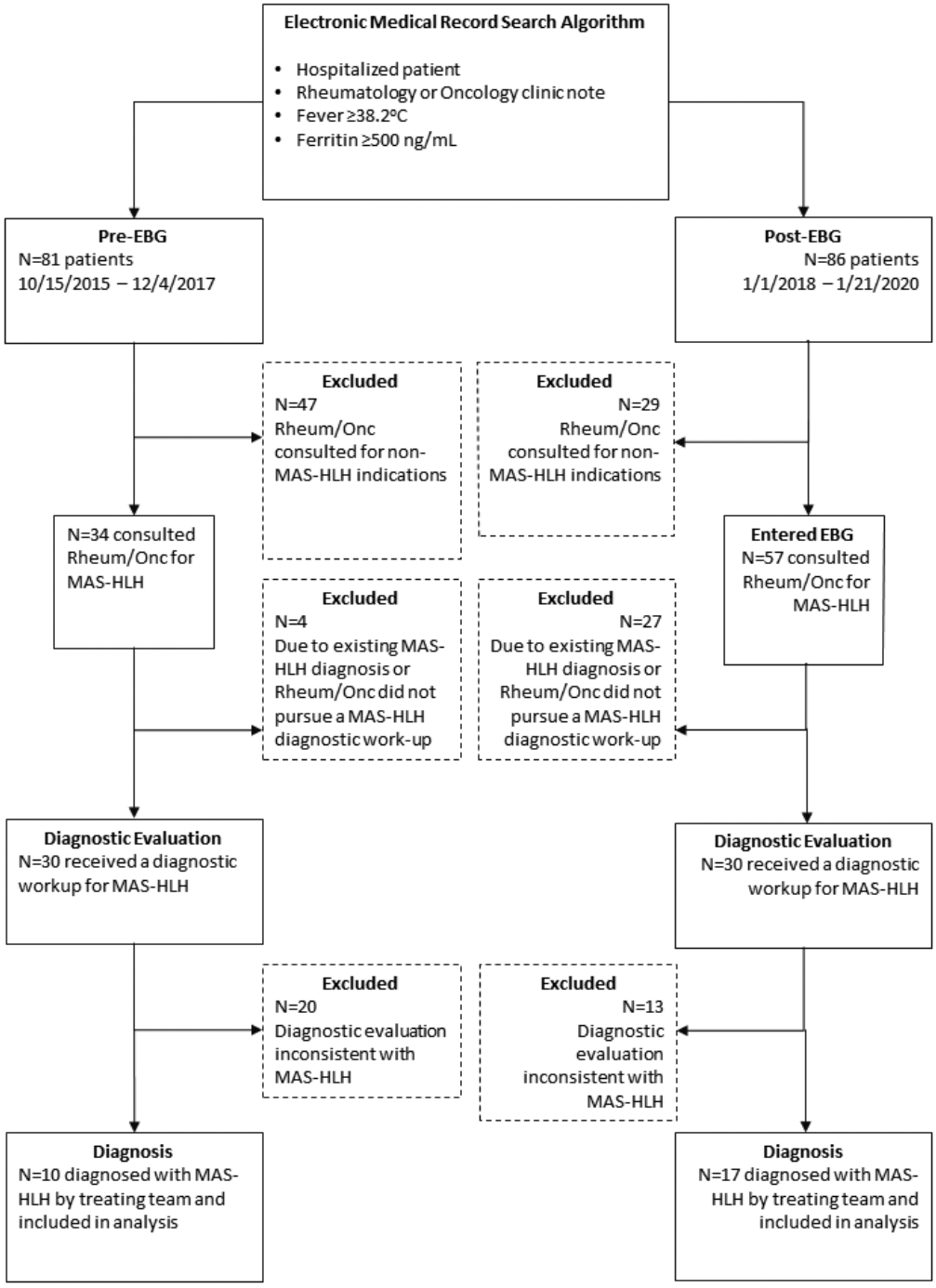

Figure 1. Inclusion and exclusion of patients identified in the electronic medical record search algorithm. EBG: evidence-based guideline; HLH: hemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome; Onc: oncology; Rheum: rheumatology.

in number of days with fever and length of admission in both pre- and post-EBG patients, thereby limiting comparisons. During the pre-EBG period, 1 patient was readmitted for MAS-HLH within 60 days of the discharge date. After initiation of the EBG, 5 of 17 patients in the post-EBG cohort were readmitted for active MAS-HLH.

Laboratory biomarkers of MAS-HLH were assessed in both cohorts. During hospital admission, liver function tests normalized in 20% of pre-EBG and 29% of post-EBG patients. Thrombocytopenia resolved during the hospital stay in 50% compared to 65% of children in the pre- vs post-EBG groups. There was a trend toward faster decline in ferritin values in

children enrolled in the EBG (Figure 3E). There was a statistically significant improvement in time to 50% decrease in CRP level (log-rank $P < 0.01$; Figure 3F). The median time to a CRP of < 1 mg/dL could not be estimated given the large proportion of patients who did not achieve this event during hospital admission.

A greater proportion of patients in the pre-EBG group were directly admitted to the intensive care unit (ICU; 6 of 10, 60%)

Table 2. Clinical characteristics of patients with MAS-HLH.

	Pre-EBG, n = 10	Post-EBG, n = 17
Age, mean ± SD	10.0 ± 9.2	9.5 ± 7.7
Sex, n (% female)	8 (80)	8 (47)
Clinical manifestations		
Persistent fever	7 (70)	17 (100)
Rash	5 (50)	5 (29)
HSM	5 (50)	5 (29)
Coagulopathy	5 (50)	3 (18)
Neurologic involvement	2 (20)	4 (24)
Preexisting rheumatologic diagnosis		
sJIA	2 (20)	4 (24)
SLE	1 (10)	1 (6)
Autoinflammatory[a]	1 (10)	0 (0)
KD	0 (0)	0 (0)
Other[b]	0 (0)	1 (6)
MAS-HLH trigger		
Infection	8 (80)	14 (82)
Autoimmune/autoinflammatory flare	2 (20)	0 (0)
Malignancy	0 (0)	2 (12)
Other[c]	4 (40)	2 (12)
Cytopenias[d]	4 (40)	12 (71)
Highest ferritin level, ng/dL[e,f], median (range)	12,188 (6741-100,000)	3082 (526-36,040)
Highest CRP level, mg/dL[e], mean ± SD	16.3 ± 12.0	6.0 ± 5.8
Highest ALT level, units/L[e], mean ± SD	409 ± 549	226 ± 255
Lowest fibrinogen level, mg/dL[e], mean ± SD	192 ± 93	211 ± 168
Abnormal elevation in sIL2R level	7 (70)	10 (59)
Abnormal NK cell function	2 (20)	3 (18)
Hemophagocytosis	2 (20)	4 (24)
HLH 2004 criteria[3]	3 (30)	10 (59)
2016 MAS classification criteria[g,2]	7 (70)	16 (94)
Identified genetic diagnosis		
FHL[h]	0 (0)	2 (12)
PID[i]	0 (0)	1 (6)
Other[j]	1 (20)	1 (6)

Values are n (%) unless otherwise indicated. [a] In the pre-EBG group, there was 1 patient with an undifferentiated autoinflammatory disorder. [b] In the post-EBG group, there was 1 patient with ANCA vasculitis. [c] Other triggers for MAS-HLH included decreased immunosuppression for the underlying rheumatologic disorder (n = 1), renal failure (n = 1), a history of atypical hemolytic uremic syndrome (n = 1), and cystic fibrosis status post lung transplant (n = 1) in the pre-EBG group and decreased immunosuppression for the underlying rheumatologic disorder (n = 1), an unknown preexisting primary immunodeficiency (n = 1) in the post-EBG group. [d] Cytopenias affecting ≥ 2 of 3 lineages in the peripheral blood with hemoglobin < 9 gm/dL, platelets < 100×10^3/mL, and neutrophils < 1×10^3/mL. [e] The highest or lowest indicated laboratory value recorded during the hospital admission. [f] Two patients in the pre-EBG group had a ferritin level > 100,000 ng/dL, which was considered a value of 100,000 to calculate the median ferritin level. [g] Patient fulfilled the 2016 MAS classification criteria except for sJIA diagnosis. [h] In the post-EBG group, biallelic mutations in *PRF1* (n = 1) and *UNC13D* (n = 1) were found. [i] In the post-EBG group, a patient with pathogenic and homozygous variants in *STAT2* was found. [j] In the pre-EBG group, other genetic diagnosis uncovered during the diagnostic evaluation included a pathogenic and heterozygous variant in *NLRC4* (n = 1). In the post-EBG group, 1 patient had compound heterozygous mutations in *COG4*. ALT: alanine aminotransferase; ANCA: antineutrophil cytoplasmic antibody; CRP: C-reactive protein; EBG: evidence-based guideline; FHL: familial HLH; HLH: hemophagocytic lymphohistiocytosis; HSM: hepatosplenomegaly; KD: Kawasaki disease; MAS: macrophage activation syndrome; NK: natural killer; PID: primary immunodeficiency; sIL2R: soluble interleukin 2 receptor; sJIA: systemic juvenile idiopathic arthritis; SLE: systemic lupus erythematosus.

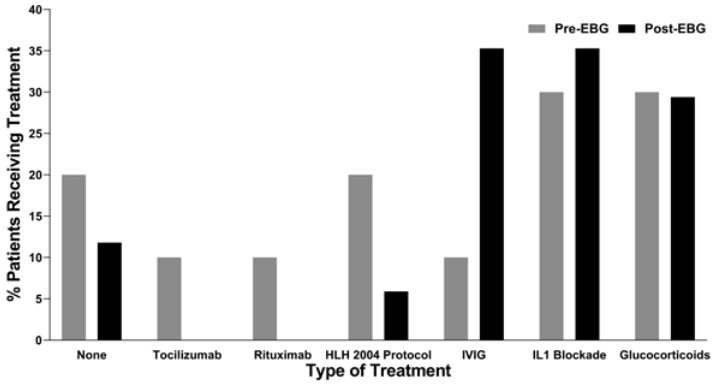

Figure 2. First-line immunomodulatory treatment for HLH and MAS. The bar graph depicts the proportion of patients in the pre- and post-EBG cohorts treated with the given medications. EBG: evidence-based guideline; HLH: hemophagocytic lymphohistiocytosis; IL: interleukin; IVIG: intravenous immunoglobulin; MAS: macrophage activation syndrome.

compared to the post-EBG cohort. Of the 6 pre-EBG patients initially managed on the pediatric ward, 2 were transferred to the ICU at a later time. In the post-EBG group, 12 of 17 (71%) of patients were admitted to the pediatric ward. Of these 12 post-EBG patients, 6 were transferred to the ICU.

There was a statistically significant difference in mortality between the pre- and post-EBG cohorts. Half of the pre-EBG patients (5 of 10, 50%) died during hospital admission while there was only 1 fatality in the post-EBG group (1 of 17, 6%; $P = 0.02$, Fisher exact test; Table 3). Patients in the pre-EBG group were 8.5 times more likely to die from MAS-HLH during admission than individuals in the post-EBG cohort (risk ratio 8.5, 95% CI 1.6-50.9). During a subsequent hospital admission, an additional patient (n = 1) in the post-EBG group died from sJIA-related interstitial lung disease.

DISCUSSION

Children with MAS-HLH typically present with life-threatening hyperinflammation and multiorgan dysfunction, requiring coordinated subspecialty care. To facilitate the recognition of MAS-HLH and improve clinical outcomes, a pathway for the management of MAS-HLH was developed at our institution. As part of the EBG, predetermined QI measures were instituted to track outcomes. Compared to the pre-EBG era, children treated for MAS-HLH in the post-EBG period had a significantly faster improvement in CRP level and reduction in mortality. In addition, there was a nonstatistically significant trend toward earlier diagnosis, faster initiation of MAS-HLH–directed therapies, and shorter length of hospital stay in the post-EBG group. Hyperferritinemia, thrombocytopenia, and transaminitis also resolved in a greater proportion of children in the post-EBG cohort. These findings suggest that implementation of a guideline created through consensus building across multiple pediatric subspecialties improved outcomes for children with MAS-HLH.

A key component of the MAS-HLH EBG included efforts to increase awareness of MAS-HLH among house staff and consultant services through educational materials, clinical conferences, and electronic order sets. These efforts appeared to have had an effect on consults for MAS-HLH. In the 25.6 months prior to establishment of the guideline, 34 patients were referred to a subspecialist for consideration of a diagnosis of MAS-HLH (Figure 1). In the 24.7 months after the EBG became active, consults for MAS-HLH were requested for 57 children (Figure 1). At MAS-HLH diagnosis, children in the post-EBG group tended to have lower markers of disease activity compared to pre-EBG patients, including lower ferritin, ALT, and CRP levels, along with higher fibrinogen values (Table 2). This would suggest that patients with MAS-HLH were recognized faster and directed to subspecialty care earlier in the disease course after establishment of the EBG. Indeed, the median time from hospital admission to MAS-HLH diagnosis was 2 days in the post-EBG group compared to 4 days in the pre-EBG group. Once recognized, children with MAS-HLH were quickly treated with immunomodulatory therapy, often on the same day as diagnosis. The median time from admission to the initiation of MAS-HLH–directed therapy was 2 days in the post-EBG patients. We suspect a significant driver in the trend toward faster diagnosis and treatment of MAS-HLH after implementation of the EBG was a change in referral pattern that resulted in quicker engagement with experts in hyperinflammation along with clinical decision support in the form of the EBG.

A second major goal of the EBG was to reduce variability in the management of MAS-HLH. Prior to the initiation of the EBG, multiple services could be consulted for a patient with suspected MAS-HLH. The EBG established rheumatology as the "gatekeeper" to engage for the initial management of MAS-HLH. These recommendations were followed, as 16 of 17 patients diagnosed with MAS-HLH in the post-EBG period had an initial consult with rheumatology. For treatment, the EBG provided a list of medications that could be used alone or in combination for first-line immunomodulatory therapy in MAS-HLH. Of note, patients with FHL were excluded from these treatment recommendations and directed to oncology for treatment. Patients treated for MAS-HLH in the post-EBG cohort received first-line immunomodulatory treatments as

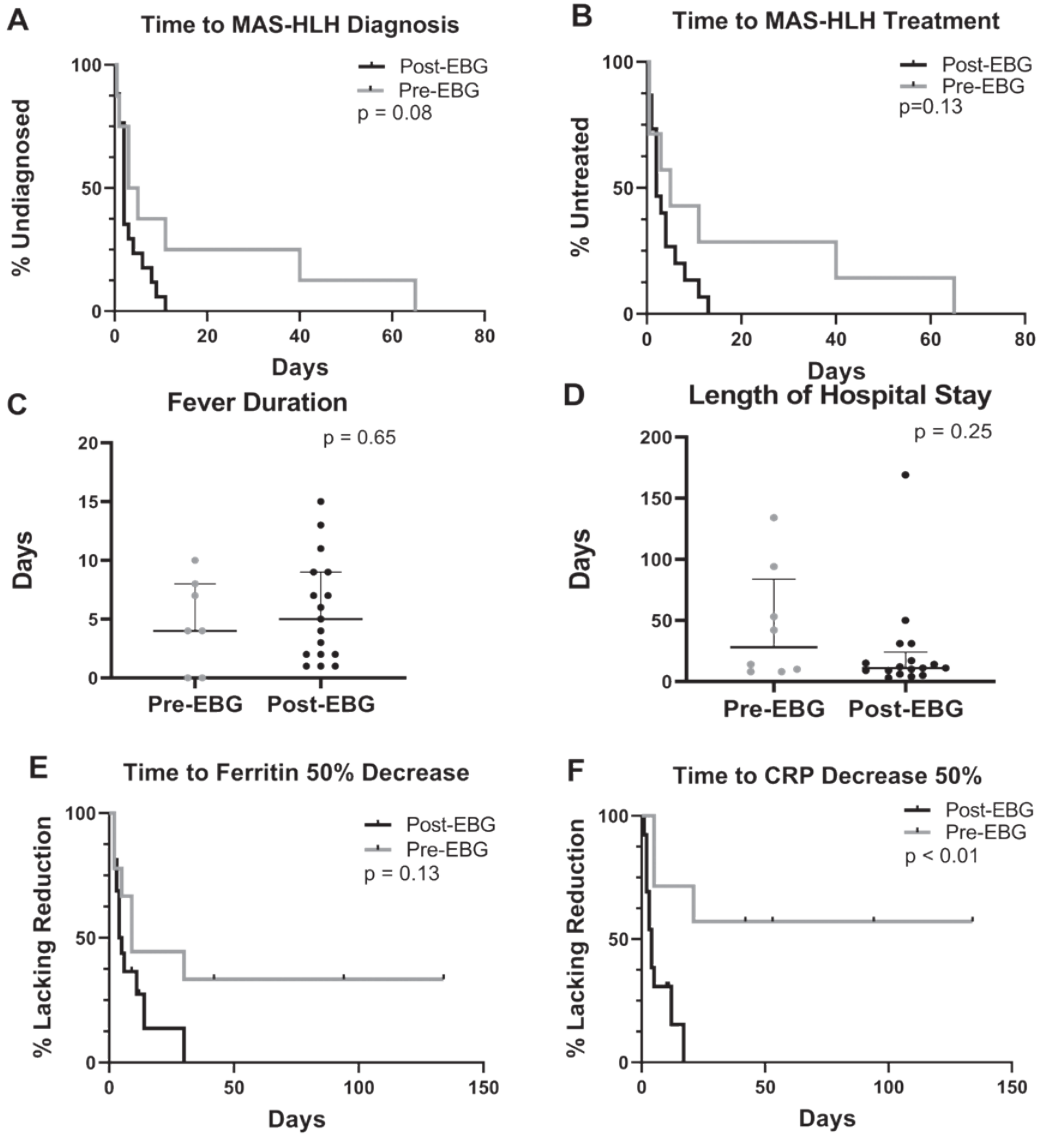

Figure 3. Clinical outcomes in the pre- and post-EBG cohorts. Kaplan-Meier estimates of the cumulative probability of (A) remaining without a diagnosis of MAS-HLH over days since hospital admission stratified by pre- (n = 8) and post-EBG (n = 17) cohorts, or (B) remaining without MAS-HLH–directed immunomodulatory therapy over days since hospital admission, stratified by pre-EBG (n = 7) and post-EBG (n = 15) cohorts. (C) Median number of febrile days with IQR in the pre- and post-EBG patients. (D) Median length of hospital admission with IQR in the pre- and post-EBG patients. (E) Cumulative probability of not yet achieving 50% reduction in ferritin over days since peak ferritin level, by pre-EBG (n = 9) and post-EBG (n = 16) cohorts. (F) Cumulative probability of not yet achieving 50% reduction in CRP over days since peak CRP level, by pre-EBG (n = 7) and post-EBG (n = 13) cohorts. The *P* values represent log-rank tests comparing survival curves. CRP: C-reactive protein; EBG: evidence-based guideline; HLH: hemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome.

per guideline recommendations (GCs [n = 5], IL-1 blockade [n = 6], and IVIG [n = 6]; Figure 2). Interestingly, IVIG use increased most dramatically. Treatment with IVIG for MAS has been reported in the literature, but it is not thought to be as effective as GCs and anakinra.[29,30] IVIG was included in the EBG to provide a therapeutic option for patients with moderate levels of illness where immunosuppression might not be warranted because of concern for a serious underlying infection. Indeed, IVIG was given to such patients in the post-EBG group, and its increased use may reflect lower disease severity in patients diagnosed earlier in the disease course. TCZ was not recommended in the EBG given limited evidence supporting the efficacy of the medication for this indication.[6] In keeping with the guidelines, no patients with MAS-HLH received TCZ in the post-EBG cohort. A smaller proportion of patients received etoposide-based therapy in the post-EBG (1 of 17, 6%) vs pre-EBG (2 of 10, 20%) groups. The single child treated with the HLH 2004 protocol in the post-EBG group had homozygous and

Table 3. Mortality in the pre- and post-MAS-HLH EBG cohorts.

	Pre-EBG, n = 10	Post-EBG, n = 17	RR, 95% CI
Mortality during admission	5 (50)	1 (6)	8.5 (1.6-50.9)
Mortality at a later time	0 (0)	1 (6)	0.0 (0.0-6.0)

Values are n (%) unless otherwise indicated. EBG: evidence-based guideline; HLH: hemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome; RR: risk ratio.

pathogenic mutations in *PRF1*. In contrast, the patients treated with etoposide in the pre-EBG group included a child with autoinflammation with infantile enterocolitis as a result of a heterozygous variant in *NLRC4* and another patient with an unknown inflammatory disorder. In total, these findings indicate that the recommendations outlined in the MAS-HLH EBG were largely followed in clinical practice.

The medications recommended in the EBG are now routinely used by rheumatologists to treat MAS in the context of autoimmune/autoinflammatory diseases.[30-34] Increasingly, these medications are used to treat nonrheumatologic forms of secondary HLH.[23,24,29,35] Kumar and coauthors proposed a treatment algorithm for secondary HLH in adults, recommending GCs, anakinra, IVIG, and/or CSA as first-line treatments.[24] In children, Eloseily et al reported favorable outcomes (73% survival) in a retrospective, single-center cohort of 44 children who received anakinra for MAS-HLH.[23] In this study, 36% of patients lacked an underlying rheumatologic diagnosis, suggesting that anakinra was effective and safe in secondary HLH not associated with an autoimmune condition.[23] The exception was malignancy-associated HLH, where the mortality rate was 100%.[23] In our post-EBG cohort, 67% had a full response to first-line therapy. The survival rate was 94% during the index hospital admission, which compares favorably to historical cohorts of children with MAS-HLH where survival rates have ranged from 44% to 73%.[23,36,37] Six children in the post-EBG group (35% of the cohort) had a rheumatologic diagnosis and there were no fatalities in this subset (Table 2). Of the remaining 11 patients, 2 had FHL and were treated by oncology. The remaining 9 patients with secondary HLH fared well with the approach outlined in the EBG. The single death occurred in a child who received IV GCs as first-line treatment for HLH secondary to a new diagnosis of acute myeloid leukemia, supporting the findings of Eloseily et al that malignancy-associated HLH has a poor prognosis.[23] A second child with sJIA-related lung disease died during a subsequent hospitalization. Our favorable experience in using nonchemotherapy-based protocols as first-line treatment for MAS and secondary HLH provides further support for this approach in children.

Several interesting clinical characteristics were noted in this MAS-HLH cohort. The association between malignancy and secondary HLH is well known in adults but not commonly considered in the pediatric population.[12] A previous case series reported by Lehmberg et al showed that an oncologic process was found in 8% of pediatric HLH cases, a rate much higher than previously appreciated.[7] In our post-EBG cohort, close to 12% of children were noted to have malignancy as a trigger for the MAS-HLH (Table 2). These findings coupled with the high mortality rates in malignancy-associated HLH highlight the importance of considering an oncologic evaluation in children with new-onset MAS-HLH.[23,38] Our EBG recommends genetic testing in most patients with MAS-HLH. A genetic diagnosis was uncovered in approximately 25% of patients in the post-EBG cohort. The high frequency of causative variants in children with MAS-HLH indicates a need for systematic genetic evaluation in this population.

Our findings should be interpreted in light of several limitations of this study. The EBG was implemented and evaluated at a single quaternary center and may not be generalizable to other institutions. A small number of patients were included in the pre- and post-EBG cohorts, reflecting the relative rarity of MAS-HLH. The small sample size limited our power to detect more modest effect sizes and did not allow for techniques to adjust for differences in the study groups, such as propensity score matching. The post-EBG patients demonstrated lower levels of MAS-HLH biomarkers, indicating that these patients were less severely ill than children in the pre-EBG group. Thus, it is possible that the improved outcomes noted after EBG implementation were related to differences in disease severity across the 2 groups. We believe the decreased disease severity in the post-EBG patients is attributable to earlier disease recognition because of the educational efforts launched with the EBG, but we are unable to prove this definitively. We were also unable to account for death as a competing risk, which likely resulted in an overestimate of the probability of 50% CRP or ferritin reduction in the pre-EBG cohort because of the large proportion of deaths. An improved understanding of the biology of MAS-HLH coupled with advancements in diagnostic tools and treatments have likely contributed to improved quality of care and more favorable outcomes over time. In an effort to address potential bias because of these secular trends, we restricted the pre-EBG group to the 2 years before initiation of the EBG. Finally, there may be unforeseen costs associated with implementing an intervention. In the case of this EBG, there was a greater number of rheumatology/oncology consults for MAS-HLH, and many of these patients were not ultimately diagnosed with MAS-HLH. This represents an increase in resource utilization that needs to be weighed against the benefits of the EBG. In the implementation phase of the EBG, we focused on process and outcome measures. As we accumulate more patients, we plan to add balancing metrics, including adverse events related to earlier and more aggressive treatment of MAS-HLH.

In summary, implementation of a multidisciplinary, consensus-based guideline for the management of MAS-HLH was associated with improved clinical outcomes, including a reduction in mortality. These findings highlight the importance of a collaborative and streamlined approach to the diagnosis and treatment of MAS-HLH.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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