CADTH Health Technology Review

Anakinra Therapy for Hemophagocytic Lymphohistiocytosis
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>HLH</td>
<td>hemophagocytic lymphohistiocytosis</td>
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<tr>
<td>IVIG</td>
<td>intravenous immunoglobulin</td>
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<td>MAS</td>
<td>macrophage activation syndrome</td>
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<td>pHLH</td>
<td>primary hemophagocytic lymphohistiocytosis</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>sHLH</td>
<td>secondary hemophagocytic lymphohistiocytosis</td>
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<tr>
<td>sJIA</td>
<td>systemic juvenile idiopathic arthritis</td>
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Key Messages

- Evidence from 1 retrospective cohort study (identified in 1 systematic review) suggested that anakinra may reduce 28-day mortality and the risk for death in adults diagnosed with hemophagocytic lymphohistiocytosis (HLH).
- Due to the very low certainty of evidence from the single cohort study included in the systematic review, there is insufficient information to draw reliable conclusions regarding the clinical effectiveness of anakinra compared to standard treatments for patients diagnosed with HLH.
- No evidence on the safety or cost-effectiveness of anakinra compared to current standard treatments or to placebo was identified.

Context and Policy Issues

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening syndrome characterized by uncontrolled activation of the immune system.\(^1\) HLH occurs most frequently in infants from birth to 18 months, but the syndrome has also been observed in children and adults of all ages.\(^2\) Symptoms of HLH are non-specific and are often difficult to differentiate from other hyperinflammatory disorders including sepsis and multiple organ dysfunction syndrome.\(^3,4\) Common findings include persistent fever, high serum ferritin, hepatosplenomegaly (swelling of the liver and spleen), rash, enlargement of the lymph nodes, neurologic symptoms, low blood cell counts, and liver function abnormalities.\(^2\) Unless diagnosed and treated early, patients with HLH typically progress to multi-organ failure associated with a high rate of mortality.

Nomenclature and diagnostic classification in this field are not clearly defined.\(^4\) Primary HLH (pHLH) is a term used to describe HLH that presents in infancy or early childhood as the result of inherited genetic mutations in inflammatory mediators.\(^5\) Secondary HLH (sHLH) refers to HLH triggered by viral infection, autoimmune disease, hematologic malignancy, or rheumatologic disease. Viral triggers (e.g., Epstein-Barr virus, cytomegalovirus, adenovirus, and herpes simplex virus) are the leading cause of sHLH.\(^6,7\) Recently, there have been reports of sHLH triggered by COVID-19.\(^8-10\) Macrophage activation syndrome (MAS) is typically used to describe sHLH when the underlying pathology is a rheumatologic disease (e.g., systemic juvenile idiopathic arthritis [sJIA], adult-onset Still's disease).\(^11\) It is important to note that there is substantial overlap in the predisposing factors for pHLH and sHLH in that both can be triggered by infections or other immune activation events, and gene mutations can be found in individuals of any age.\(^2\)

The diagnostic criteria for HLH have not been universally accepted or adopted, and current strategies (such as those based on HLH-2004 guidelines\(^12\) and HScore\(^13\)) have substantial limitations.\(^7,14\) Prompt diagnosis is often hindered by the rarity of the syndrome, variable clinical presentation, and lack of specificity of clinical and laboratory findings.\(^15\) Treatment of HLH is centred on immunosuppressive therapy (including corticosteroids, IV immunoglobulin [IVIG], methotrexate, cyclosporin, and etoposide) combined with treatment of the triggering illness.\(^2,16,17\) However, this regimen has considerable treatment-related morbidity due to complications associated with immunosuppressive treatment, such as secondary infections, myelotoxicity, hepatic dysfunction, and secondary malignancies.\(^1\) Treatment with corticosteroids can hinder the diagnosis of certain malignancies (e.g., lymphoma), which is a
concern in patients in whom the underlying HLH trigger is cancer. In addition, there are high costs associated with the use of IVIG. Hence, there is a need for alternative treatments that are cost-effective and have less treatment-associated toxicity.

Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist. IL-1 is a proinflammatory mediator produced in response to infection and is central to the hyperinflammation process observed in HLH. In Canada, anakinra (Kineret) is approved for the treatment for adults with rheumatoid arthritis and adults, children, and infants over the age of 8 months diagnosed with Neonatal-Onset Multisystem Inflammatory Disease. Anakinra a promising treatment for HLH due to a short half-life and wide therapeutic range. Anakinra does not mask indicators of infection, but it is unclear whether anakinra is less myelosuppressive and less hepatotoxic than standard immunosuppressive therapy for HLH. It is unknown whether early treatment with anakinra has the potential to stabilize the hyperinflammatory process in HLH while acting as a bridging treatment to allow time for the diagnosis and treatment of the underlying triggering disease.

The objective of the report is to summarize the evidence regarding the clinical and cost-effectiveness of anakinra for the treatment of HLH.

Research Questions

1. What is the clinical effectiveness of anakinra therapy for hemophagocytic lymphohistiocytosis?
2. What is the cost-effectiveness of anakinra therapy for hemophagocytic lymphohistiocytosis?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were anakinra therapy and hemophagocytic lymphohistiocytosis. No filters were applied to limit the retrieval by study type. Conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and December 14, 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for
inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria
Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were published before 2011. Articles describing patients with clinical features of excessive immune activation (e.g., hyperinflammatory syndromes, cytokine storm, or multi-organ failure) but without a specific diagnosis or HLH or MAS were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Narrative reviews, case series, case reports, and retrospective chart reviews were excluded from the main body of the report but are included in Appendix 5.

Critical Appraisal of Individual Studies
The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)\(^1\) for systematic reviews. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>Population</td>
<td>Patients of all ages with HLH including macrophage activation syndrome</td>
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<tr>
<td>Intervention</td>
<td>Anakinra therapy</td>
</tr>
<tr>
<td>Comparator</td>
<td>• Standard care (corticosteroids, IV immunoglobulin, cyclosporine, methotrexate and/or etoposide) including HLH-94 and HLH-2004 protocols</td>
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<tr>
<td></td>
<td>• Tocilizumab</td>
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<td></td>
<td>• Emapalumab</td>
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<td></td>
<td>• Cyclosporine</td>
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<td></td>
<td>• Etoposide</td>
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<td></td>
<td>• Alemtuzumab</td>
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<td></td>
<td>• Placebo</td>
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<tr>
<td>Outcomes</td>
<td>Q1: Clinical effectiveness (e.g., mortality, end organ failure, hospital acquired infections, markers of MAS activity), safety (e.g., adverse events, serious adverse events, sepsis)</td>
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<td></td>
<td>Q2: Cost-effectiveness (e.g., cost per QALY)</td>
</tr>
<tr>
<td>Study designs</td>
<td>Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations</td>
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</table>

HLH = hemophagocytic lymphohistiocytosis; QALY = quality-adjusted life-year.
Summary of Evidence

Quantity of Research Available
A total of 360 citations were identified in the literature search. Following screening of titles and abstracts, 336 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 25 publications were excluded for various reasons, and 2 publications met the inclusion criteria and were included in this report. Both the included publications were systematic reviews. No relevant randomized controlled trials, non-randomized studies, or economic evaluations were identified. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics
Two systematic reviews (that included a total of 1 relevant primary study for this report) were identified for inclusion in this review. One systematic review published in 2020 had eligibility criteria that was more restrictive than the current review. The eligible patient population was restricted to patients of all ages with a diagnosis of sHLH triggered by COVID-19. Evidence related to other coronaviruses (e.g., severe acute respiratory syndrome or Middle East respiratory syndrome) was also considered. Eligible studies included systematic reviews, randomized controlled trials (RCTs), controlled clinical trials, and observational studies (including case series) published between 2000 and 2020. Case reports were also considered when no higher-level quality evidence was found. However, no relevant studies were identified. Two preliminary unpublished primary studies of interest were identified but neither met the selection criteria outlined in Table 1 for this report.

One systematic review published in 2020 had eligibility criteria that was closely aligned with the current review including (i.e., patients of all ages presenting with pHLH or sHLH, regardless of the trigger condition). Eligible studies included systematic reviews, clinical trials, and cohort studies published between 2010 and 2020. Case series were considered when no higher-level quality evidence was found. A total of 6 identified studies (1 comparative cohort study and 5 case series) published between 2016 and 2019 were included. The 5 case series each conducted a retrospective review of case notes in a single centre, spanning between 2 and 10 years from 2007 to 2017. However, since the case series did not include a comparator relevant to this report, the findings of these case series will not be discussed in this report. Only the characteristics and results of the relevant study will be discussed in this report.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design
The relevant cohort study included in the systematic review was a non-randomized retrospective subgroup analysis of patients recruited to an earlier phase III RCT investigating patients with sepsis.

Country of Origin
Both systematic reviews were commissioned by NHS England in the UK. The relevant cohort study included within the systematic review was conducted by researchers in the US.
The original RCT was a multicenter study (91 centers from 11 countries in Europe and North America). However, the location of the patients included in the subgroup analysis of the cohort study was not reported.

**Patient Population**

The patient population in the 1 relevant cohort study included in the systematic review were adults with sepsis with multi-organ dysfunction and/or shock with features of MAS (defined as the presence of hepatobiliary dysfunction or disseminated intravascular coagulation). The systematic review authors stated that there were no between-group differences in baseline characteristics including age, gender, the severity of acute kidney injury or respiratory distress syndrome, or the risk of death.

**Interventions and Comparators**

Anakinra 2 mg/kg/hour given intravenously for 72 hours was assessed in the relevant cohort study included in the systematic review. The comparator was placebo 2 mg/kg/hour given intravenously for 72 hours. Concomitant treatments in each arm were not reported.

**Outcomes**

The relevant cohort study in the systematic review reported the 28-day mortality of patients receiving anakinra compared to placebo.

**Summary of Critical Appraisal**

Since 1 of the systematic reviews did not identify any relevant primary studies, only the sections regarding search methodology were critically appraised. Neither of the included systematic reviews indicated that a research protocol was established before conducting the review. The lack of a well-developed protocol has the potential to introduce bias if the methods used to conduct the review were adjusted during the review process. However, the authors of both systematic reviews did state that the methodology followed the NHS England guidance for developing evidence reviews. Both systematic reviews had a well-defined research question, clear eligibility criteria, and a comprehensive approach to the literature search. Multiple databases were searched to identify eligible studies and key search terms were provided. Providing details of these elements of the search strategy increases the reproducibility of the review. It was unclear if the authors of either systematic review performed study selection or data extraction in duplicate. This may have resulted in relevant studies being missed as well as errors in the data extraction. Only 1 of the systematic reviews provided a list of excluded studies with justifications for exclusion. Not having such information limits the reader’s ability to assess whether relevant articles were excluded and if so, for what reason. In addition, unjustified exclusion of studies could bias the results of the review.

In the 1 systematic review that identified a relevant primary study, the characteristics (when reported) of the included study including study design, baseline characteristics, interventions, comparators and study outcomes were provided in detailed evidence tables. Checklists from the Joanna Briggs Institute were used to critically appraise the methodological quality of the individual studies. The overall quality of the body of evidence available for each outcome was assessed using a modified version of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Based on risk of bias assessments, there was discussion around heterogeneity of findings and certainly of evidence within the narrative synthesis. The authors reported that the certainty of the evidence for the relevant
outcomes was very low from the studies included in the systematic review. The authors of the systematic review reported several methodological weaknesses in the relevant cohort study, including a retrospective design with post-hoc analysis in which the original randomization process was no longer valid; lack of a defined comparator group (concomitant therapies were not defined); and a limited (N = 43) cohort of patients, meaning that the study was not powered to detect a difference in outcomes between the anakinra and placebo groups. Therefore, it is difficult to interpret the extent that findings can be attributable to treatment with anakinra alone.

The sources of funding for the individual studies included in the systematic review were reported. Providing the sources of funding makes it possible to discern whether the funding agency could have influenced the results of the included studies. Both systematic reviews were commissioned by NHS England. However, it was not reported if the authors of either systematic review had any potential conflicts of interest.

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3.

**Summary of Findings**
Appendix 4 presents the main study findings and authors’ conclusions.

**Clinical Effectiveness and Safety of Anakinra**
The authors of the systematic review evaluated the 28-day mortality and risk of death of patients receiving anakinra compared to standard treatments for HLH from the results of the single comparative cohort study. The authors stated that when assessed using modified GRADE, the certainty in the quality of the identified evidence from the single cohort study was very low.

**Mortality, 28 Days**
One comparative cohort analysis in the systematic review reported a statistically significantly lower 28-day mortality with a statistically significantly lower risk of death in adult patients with HLH treated with anakinra compared to those who received placebo.

**Cost-Effectiveness of Anakinra**
No relevant evidence regarding the cost-effectiveness of anakinra for HLH was identified; therefore, no summary can be provided.

**Limitations**
The findings in this report are limited by the quality and quantity of relevant evidence that was identified. The first systematic review which focused on anakinra treatment in patients with HLH triggered by COVID-19 was fairly well conducted; however, no relevant reports were identified leaving a gap in evidence to support the use of anakinra in this particular patient population.

The second systematic review evaluating anakinra for the treatment of HLH regardless of trigger condition was well conducted. However, 5 of 6 of the identified studies in this
systematic review were non-comparative, retrospective, single-centre, case series and thus the findings were not included in this review. The single relevant cohort study described outcomes in middle-aged adults. Hence findings may not be generalizable to infants, children, or senior adults. Considering the inclusion period of the original RCT (which was published in 1997) on which this cohort study was based, a time during which sepsis management was different than what is practised today, and the location of patients included in the analysis in unknown, it is unclear how closely the findings are generalizable to the current clinical management of HLH in Canada.

No evidence was identified to evaluate the clinical effectiveness of anakinra compared to standard treatment for other clinically important outcomes including intensive care unit duration of stay, improvement of HLH symptoms, length of hospital stay, acquired infection with treatment, or other adverse events. Furthermore, no relevant studies regarding the cost-effectiveness of anakinra compared to standard treatments or placebo for HLH were identified, therefore no conclusions can be formed on this research question.

Conclusions and Implications for Decision- or Policy-Making

This review evaluated the existing evidence for the clinical effectiveness and cost-effectiveness of anakinra for the treatment of patients with HLH. The findings in this report are limited by the quantity and quality of the evidence that was identified. The key limitation to evaluating the effectiveness of anakinra compared to standard treatment for HLH is the lack of comparative studies. The rarity of the condition, inconsistent nomenclature, variable clinical diagnostic criteria, non-specific symptoms, and the heterogeneity of triggering factors have previously been identified in the literature as barriers to conducting prospective research on this topic.

One systematic review focusing on the outcomes of anakinra in patients with HLH triggered by COVID-19 did not identify any relevant evidence; hence the efficacy of anakinra in this specific patient population is unclear. A second systematic review identified very low certainty evidence from 1 retrospective comparative cohort study, that compared to placebo, anakinra reduced 28-day mortality and the risk of death in adult patients with HLH.

An ongoing RCT is currently evaluating the safety of anakinra given as an adjunct to standard treatments compared to placebo in approximately 40 patients over the age of 1 year admitted to hospital with MAS. The specific primary objectives of the study are to determine whether giving anakinra results in no increased affects the rates of infection complications or mortality. Estimated study completion is September 2022.

In conclusion, the very low certainty evidence from the relevant study included in this review is insufficient to draw reliable conclusions about the clinical effectiveness or safety of anakinra compared to standard treatments or placebo in patients with HLH. No evidence on the cost-effectiveness of anakinra compared to current standard treatments or placebo was identified, therefore no conclusions can be made on the cost-effectiveness of anakinra for HLH.
References


Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

360 citations identified from electronic literature search and screened

336 citations excluded

24 potentially relevant articles retrieved for scrutiny (full text, if available)

27 potentially relevant reports

25 reports excluded:
- irrelevant population (1)
- irrelevant intervention (1)
- already included in at least one of the selected systematic reviews (1)
- other (review articles, editorials) (22)

3 potentially relevant reports retrieved from other sources (grey literature, handsearch)

2 reports included in review
# Appendix 2: Characteristics of Included Publications

## Table 1: Characteristics of Included Systematic Reviews

<table>
<thead>
<tr>
<th>Study citation, country, funding source</th>
<th>Study designs and numbers of primary studies included</th>
<th>Population characteristics</th>
<th>Intervention and comparator(s)</th>
<th>Clinical outcomes, length of follow-up</th>
</tr>
</thead>
</table>
| NICE 2020\(^3\) UK Funding: NHS England | Study designs: Systematic reviews, RCTs, controlled clinical trials, observational studies (including case series). Case reports considered if no higher-level evidence found. **No relevant primary studies identified.** | Adults and children with suspected or confirmed COVID-19 with features of sHLH triggered by COVID-19 or similar coronaviruses including SARS-CoV-1 or MERS-CoV. | **Intervention:** Anakinra 1 to 12 mg/kg/day, usually for 3 to 14 days by SC injection or IV infusion alone or in combination with corticosteroids, IVIG, etoposide or other therapies. **Comparator:** Best supportive care including treatment with corticosteroids, IVIG, etoposide, organ support (e.g., ventilation, renal replacement therapy transfusions) and antimicrobials | Outcomes:  
• Mortality  
• Length of stay in critical care or hospital  
• Requirement for and duration of mechanical or non-invasive ventilation or other organ support  
• Duration of sHLH symptoms  
• Complications due to sHLH  
• Acquired secondary infection  
• Adverse events  
• Cost-effectiveness  
Follow-up: NR |
| NHS 2020\(^4\) UK Funding: NHS England | Study designs: Systematic reviews, RCTs, controlled clinical trials, cohort studies. Case series considered if no higher-level evidence found. **Included studies:** 1 retrospective cohort study, which is relevant to this report (sample size: 43)\(^a\) | Adults and children presenting with pHLH or sHLH (regardless of trigger condition) requiring treatment for HLH as part of their clinical care. **Relevant patient populations characteristics:** Adults diagnosed with sepsis with multi-organ dysfunction and/or shock with features of MAS (defined as the presence of hepatobiliary dysfunction or disseminated intravascular coagulation). | **Eligible interventions:** Anakinra 1 to 10 mg/kg/day, usually for 3 to 14 days by SC injection or IV infusion as first- or second-line treatment alone or in combination with corticosteroids, IVIG, cyclosporin, or etoposide. **Eligible comparators:** Current standard treatment with corticosteroids, IVIG, cyclosporin, methotrexate and/or etoposide without use of anakinra. | Eligible outcomes:  
• In-hospital and 30-day mortality  
• ICU duration of stay  
• Acquired infection  
• Adverse events  
• Abolition of fever  
• Reduction in serum ferritin levels  
• Length of hospital stay  
• Complications due to sHLH |
<table>
<thead>
<tr>
<th>Study citation, country, funding source</th>
<th>Study designs and numbers of primary studies included</th>
<th>Population characteristics</th>
<th>Intervention and comparator(s)</th>
<th>Clinical outcomes, length of follow-up</th>
</tr>
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<tr>
<td>NHS 2020&lt;sup&gt;24&lt;/sup&gt; UK Funding: NHS England (continued)</td>
<td>1 single-centre retrospective case series (sample size: 8 to 44) (not eligible for the current report due to lack of a comparator).</td>
<td><strong>Anakinra group baseline characteristics (n = 26)</strong>&lt;br&gt;- Age (mean ± SD): 49.6 ± 12.7 years&lt;br&gt;- Female, n: 12 (46.2%)&lt;br&gt;- Acute kidney injury, n: 17 (65.4%)&lt;br&gt;- Acute respiratory distress syndrome, n: 6 (23.1%)&lt;br&gt;- Risk of death 0.57 ± 0.22</td>
<td><strong>Relevant intervention:</strong>&lt;br&gt;- Anakinra 2 mg/kg/hr IV for 72 hours&lt;br&gt;- (concomitant treatments NR)&lt;br&gt;<strong>Relevant comparator:</strong> Placebo 2 mg/kg/hr IV for 72 hours (concomitant treatments NR)</td>
<td>• Use or change in dose of IVIG, steroids, etoposide, or cyclosporin&lt;br&gt;• Cost-effectiveness&lt;br&gt;<strong>Relevant outcomes:</strong> 28-day mortality&lt;br&gt;<strong>Follow-up:</strong> NR</td>
</tr>
<tr>
<td><strong>Placebo group baseline characteristics (n = 17)</strong>&lt;br&gt;- Age (mean ± SD): 56.3 ± 19.4 years&lt;br&gt;- Female, n: 8 (47.1%)&lt;br&gt;- Acute kidney injury, n: 9 (52.9%)&lt;br&gt;- Acute respiratory distress syndrome, n: 3 (17.7%)&lt;br&gt;- Risk of death: 0.53 ± 0.25</td>
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</table>

HLH = hemophagocytic lymphohistiocytosis; hr = hour; ICU = intensive care unit; IVIG = IV immunoglobulin; MAS = macrophage activation syndrome; mg = milligram; MERS-CoV = Middle East respiratory syndrome; NICE = national institute for health and care excellence; NHS = national health service; NR = not reported; RCT = randomized controlled trial; SARS-CoV-1 = severe acute respiratory syndrome; SC = subcutaneous; SD = standard deviation; sHLH = secondary hemophagocytic lymphohistiocytosis; sJIA = systemic juvenile idiopathic arthritis; pHLH = primary hemophagocytic lymphohistiocytosis.

*Of the 763 patients (out of 906 originally recruited) who completed the original RCT for anakinra for severe sepsis. This study is an analysis of 43 adults who multi-organ dysfunction and/or shock with features of MAS (hepatobiliary dysfunction or disseminated intravascular coagulation).

Note that this appendix has not been copy-edited.
Appendix 3: Critical Appraisal of Included Publications

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Table 2: Strengths and Limitations of Systematic Reviews Using AMSTAR 2\(^{21}\)

<table>
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<th>Strengths</th>
<th>Limitations</th>
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<tr>
<td><strong>NICE 2020(^{23})</strong></td>
<td>• Unclear if the review protocol were established before conduct of the review.</td>
</tr>
<tr>
<td>• The research questions and eligibility criteria were well defined in terms of population, intervention, comparators, and outcomes.</td>
<td>• The review authors did not report whether study selection and data extraction were performed in duplicate.</td>
</tr>
<tr>
<td>• The rationale for the selection of study designs for inclusion in the review was clearly described.</td>
<td>• The authors did not provide a list of excluded studies with justification for exclusion.</td>
</tr>
<tr>
<td>• A comprehensive literature search strategy was described. The search was conducted in multiple databases and key search terms were provided.</td>
<td>• The authors did not provide potential sources of conflict of interest.</td>
</tr>
<tr>
<td><strong>NHS 2020(^{24})</strong></td>
<td></td>
</tr>
<tr>
<td>• The research questions and eligibility criteria were well defined in terms of population, intervention, comparators, and outcomes.</td>
<td>• Unclear if the review protocol were established before conduct of the review.</td>
</tr>
<tr>
<td>• The rationale for the selection of study designs for inclusion in the review was clearly described.</td>
<td>• The review authors did not report whether study selection and data extraction were performed in duplicate.</td>
</tr>
<tr>
<td>• A comprehensive literature search strategy was described. The search was conducted in multiple databases and key search terms were provided.</td>
<td>• The included studies were a post-hoc cohort study and single-centre retrospective case series which are susceptible to multiple forms of bias that threaten both internal and external validity.</td>
</tr>
<tr>
<td>• The review was published within three months of conducting the literature search.</td>
<td>• The authors did not provide potential sources of conflict of interest.</td>
</tr>
<tr>
<td>• The authors provided a list of excluded studies with justification for exclusion.</td>
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</tr>
<tr>
<td>• Evidence tables provided detailed characteristics of the individual studies (when reported) including study design, baseline characteristics, interventions, comparators, and outcome results. Source of funding for the individual studies was also reported.</td>
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<tr>
<td>• Overall results of the systematic review were reported in adequate detail.</td>
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<tr>
<td>• The authors appraised the methodological quality of included studies using JBI checklists appropriate for study design (cohort or case series).(^{27,28}) The available evidence was assessed by outcome for certainty using modified GRADE.(^{29})</td>
<td></td>
</tr>
<tr>
<td>• The authors accounted for risk of bias and heterogeneity in the included studies when summarizing and interpreting the results.</td>
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AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; JBI = Joanna Briggs Institute; NICE = national institute for health and care excellence; NHS = national health service.
Appendix 4: Main Study Findings and Authors’ Conclusions

Note that this appendix has not been copy-edited.

Table 3: Summary of Findings of the Systematic Reviews

<table>
<thead>
<tr>
<th>Findings</th>
<th>Authors’ Conclusions</th>
</tr>
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<tbody>
<tr>
<td><strong>NHS 2020</strong></td>
<td>“These studies provided very low certainty evidence that compared to standard treatment, anakinra reduces 30-day mortality in patients with HLH.” (p. 9)</td>
</tr>
<tr>
<td><strong>Mortality at 28 days:</strong> One comparative cohort study in adults with a diagnosis of sepsis with features of MAS (N = 43) reported a statistically significant lower mortality in patients treated with anakinra compared to placebo (34.6% vs. 64.7%; P = 0.0006) and a lower risk of death (HR 0.28; 95% CI 0.11 to 0.71; P = 0.0071).</td>
<td></td>
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</table>

CI = confidence interval; HR = hazard ratio; MAS = macrophage activation syndrome; sHLH = secondary hemophagocytic lymphohistiocytosis; SD = standard deviation; SJIA = systemic juvenile idiopathic arthritis; SLE = systemic lupus erythematosus.
Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

Review Articles


Additional References

Case Reports

Adults


Infants and Children


Case Series

Adults


Infants and Children


Retrospective Chart Review

Adults


Infants and Children

