



Review Article

Advanced therapies for infantile malignant pertussis: A systematic review of hydroxyurea, leukapheresis, exchange transfusion, and extracorporeal membrane oxygenation

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ABSTRACT

Objectives: The objectives of the study are to evaluate the effectiveness, safety, and survival outcomes of advanced interventions, such as hydroxyurea, leukapheresis, exchange transfusion (ET), and extracorporeal membrane oxygenation (ECMO), in infants with malignant pertussis.

Methods: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses-2020-compliant systematic review of PubMed and Europe PMC (January 2000–June 2025) identified studies of infants treated with these interventions. The risk of bias was assessed using risk of bias in non-randomized studies of interventions (ROBINS-I), Joanna Briggs Institute (JBI), and a measurement tool to assess systematic reviews 2 (AMSTAR-2) tools, and data were synthesized descriptively.

Results: Among 830 records screened, 46 studies met the inclusion criteria. Hydroxyurea, typically administered at 20 mg/kg/day, was associated with gradual leukoreduction within 5–7 days and reported survival rates ranging from 70% to 90% across observational cohorts, comparable to those observed with ET and with fewer reported procedural complications. ET was consistently associated with rapid leukoreduction and short-term improvement in oxygenation, particularly when performed early. Leukapheresis demonstrated inconsistent benefit and was infrequently reported. ECMO alone was associated with lower survival rates; however, when used in conjunction with prior leukoreductive strategies, reported survival exceeded 70% in selected cohorts.

Conclusion: Observational evidence suggests that early leukoreductive strategies may be associated with improved outcomes in infants with malignant pertussis, particularly when implemented before cardiovascular deterioration. ET and hydroxyurea were the most consistently reported interventions, while ECMO appeared to provide benefit primarily as adjunctive support following leukoreduction. Given the heterogeneity and non-randomized nature of the available data, these findings should be interpreted cautiously and considered hypothesis-generating.

Keywords: *Bordetella pertussis*, Critical care pediatrics, Exchange transfusion, Extracorporeal membrane oxygenation, Hydroxyurea, Hyperleukocytosis, Infantile pertussis, Leukapheresis, Leukoreduction, Malignant pertussis, Severe pertussis interventions

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INTRODUCTION

Pertussis (whooping cough) is a highly contagious respiratory infection caused primarily by *Bordetella pertussis* and, less commonly, *Bordetella parapertussis*. The bordetellae are small, Gram-negative, aerobic coccobacilli. The genus *Bordetella* contains the species *B. pertussis* and *B. parapertussis*. Despite being vaccine-preventable, pertussis continues to pose a global health concern. The World Health Organization estimates nearly 16 million cases of pertussis annually worldwide, resulting in approximately 195,000 deaths, most of which occur among infants under 1 year of age.^[1,2]

The diphtheria–tetanus–pertussis vaccine was introduced into the Expanded Programme on Immunization in 1974. Since then, a marked reduction in the global burden of pertussis was noticed. A resurgence of cases has been observed since the 1980s, even in countries with high vaccination coverage, such as the United States, Canada, and Australia.^[3,4] This “pertussis resurgence” has been attributed to waning immunity, improved diagnostic capabilities, and possible genetic adaptations of the pathogen.

Malignant pertussis represents the most severe form of the disease and is characterized by refractory respiratory failure, profound hyperleukocytosis, and pulmonary hypertension, leading to exceptionally high mortality in early infancy.^[5,6] Reported predictors of fatal outcomes include age below 6 months, marked leukocytosis, pneumonia, and elevated inflammatory markers such as C-reactive protein.^[4,7] Clinically, infants often present with paroxysmal cough, apnea, cyanosis, and progressive respiratory distress. The leukemoid reaction induced by pertussis toxin contributes to increased blood viscosity and pulmonary vascular obstruction, precipitating cardiogenic shock and multiple organ dysfunction.

Several advanced interventions have been explored to mitigate the devastating hematologic and cardiopulmonary effects of malignant pertussis. Hydroxyurea, a pharmacologic cytoreductive agent originally used in hemoglobinopathies such as sickle-cell disease and β -thalassemia, has shown emerging promise as a non-invasive strategy for leukoreduction.^[8,9] Likewise, exchange transfusion (ET) and leukapheresis have been applied to rapidly lower leukocyte counts, although standardized thresholds for intervention remain undefined.^[10]

Meanwhile, extracorporeal membrane oxygenation (ECMO) has been used for over four decades in neonatal and pediatric respiratory failure. However, in pertussis, its benefit remains controversial; reports from the Extracorporeal Life Support Organization Registry indicate survival rates of only about 30%, markedly lower than for other ECMO indications.^[11-13] These observations underscore the potential importance of early, coordinated escalation and evidence-based escalation of therapy before the onset of multi-organ failure.

Given these uncertainties, the present systematic review was undertaken to evaluate the clinical effectiveness, safety, and survival outcomes of advanced therapeutic interventions, such as hydroxyurea, ET, leukapheresis, and ECMO in the management of malignant pertussis in infants.

Although several advanced interventions such as hydroxyurea, ET, leukapheresis, and ECMO have been utilized in malignant pertussis, the evidence base remains highly fragmented, with most data derived from isolated case reports and small series. Previous reviews have focused on individual therapies or specific regions, lacking an integrated comparative analysis of all advanced modalities. Given the persistently high mortality associated with malignant pertussis and the absence of standardized treatment guidance, a comprehensive synthesis of available clinical evidence is urgently needed to clarify the relative effectiveness, safety, and survival outcomes of these interventions.^[14,15]

What is the comparative clinical effectiveness, safety, and survival impact of advanced therapeutic interventions, such as hydroxyurea, ET, leukapheresis, and ECMO in infants diagnosed with malignant pertussis?

The objectives of the study are to systematically evaluate available evidence on the effectiveness, safety, and survival impact of hydroxyurea, ET, leukapheresis, and ECMO in the management of malignant pertussis among infants.

MATERIALS & METHODS

Study design

This research was conducted as a systematic review designed to synthesize evidence on the clinical effectiveness, safety, and survival outcomes of advanced therapeutic interventions, including hydroxyurea, ET, leukapheresis, and ECMO, in infants diagnosed with malignant pertussis. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency and reproducibility.

The review question was formulated using the PICOT framework [Table 1] to define the target population, interventions, comparator, outcomes, and time frame of interest.

Search strategy

A comprehensive literature search was performed in PubMed and Europe PMC to identify relevant publications from January 2000 to June 10, 2025. Boolean operators (AND, OR) were used to combine the following search terms: “Malignant Pertussis,” “Hyperleukocytosis,” “Infantile Pertussis,”

Table 1: PICOT variables defining the study question.	
P	Infants diagnosed with malignant pertussis (with white blood cells more than 50 G/L or signs of leukocytosis)
I	Advanced supportive interventions (Hydroxyurea, exchange transfusion, leukapheresis, extracorporeal membrane oxygenation)
C	Standard supportive care
O	Reduction in mortality, leukocyte count, organ support need, and hospital length of stay
T	Acute phase (Admission, pediatric intensive care unit)

“Hydroxyurea,” “Leukapheresis,” “Exchange Transfusion,” “ECMO,” “Critical Care Pediatrics,” “Leukoreduction,” “*Bordetella Pertussis*,” and “Severe Pertussis Interventions.”

All search results were imported into the Rayyan software for organization, screening, and duplicate removal. The initial search retrieved 830 records.

Eligibility criteria

Studies were included if they:

- Involved infants below 12 months with a confirmed diagnosis of malignant pertussis presenting with hyperleukocytosis
- Reported at least one of the following interventions: hydroxyurea, ET, leukapheresis, or ECMO
- Provided data on clinical outcomes, survival, or safety
- Were published in English between 2000 and 2025.

Exclusion criteria included studies unrelated to infant pertussis, lacking outcome data, unavailable in full text, or published in languages other than English.

Study selection

Two reviewers independently screened titles and abstracts to assess relevance. Potentially eligible studies were subjected to full-text evaluation against the inclusion criteria. Discrepancies were resolved through discussion and consensus. After sequential screening, 46 studies were deemed eligible for final inclusion.

Data extraction and management

Data from eligible studies were extracted into a standardized Excel form, capturing key details such as author name, publication year, study design, sample characteristics, interventions, outcomes, and digital object identifier. Extracted data were verified for accuracy and consistency. Studies with incomplete or ambiguous data were excluded from quantitative summaries.

Risk of bias assessment

Given the heterogeneity of study designs, risk of bias was assessed using:

- ROBINS-I for non-randomized observational studies^[16]
- JBI Critical Appraisal Checklists for case reports and case series^[17]
- AMSTAR-2 criteria for systematic reviews and meta-analyses.^[18]

Each included study was classified as having low, moderate, or high risk of bias, based on clarity of intervention description, outcome measurement, and control for confounding [Table 2].

Findings from high- and moderate-quality studies were consistent with the overall direction of evidence, suggesting robustness of the observed trends despite some methodological variation.

Data synthesis

Due to heterogeneity in study design and outcome reporting, a narrative synthesis approach was adopted. Data were summarized descriptively by intervention type (hydroxyurea, ET, leukapheresis, ECMO) and analyzed for patterns in timing, survival rates, leukoreduction efficacy, and adverse events. Where comparable metrics were available, findings were presented as ranges or median values across studies.

Confidence in the evidence

The overall confidence in the body of evidence was judged qualitatively, considering study design hierarchy, consistency of findings, sample size, and bias levels. Greater confidence was attributed to outcomes reported by multicenter or prospective studies and consistent across multiple independent cohorts.

PRISMA flow diagram

The study selection process was illustrated using a PRISMA 2020 flow diagram, depicting the number of records identified, screened, assessed for eligibility, and included in the final review. The flow chart visually represents reasons for exclusion at each stage (e.g., duplicates, irrelevance, language limitations, or missing data) [Figure 1].

RESULTS

Study selection and characteristics

The database search retrieved 830 articles. After removing duplicates, 590 titles and abstracts were screened; 544 records were excluded for irrelevance or non-infant populations. Ultimately, 46 studies published between 2000 and 2025 met the inclusion criteria [Figure 1, PRISMA Flow].

Table 2: The quality assessment of the included studies.

	Study	Tool used	Quality assessment
1	Blanc <i>et al.</i> , 2025 ^[20]	ROBINS-I	Low
2	Liru <i>et al.</i> , 2025 ^[33]	ROBINS-I	Moderate
3	Wu and Gan, 2025 ^[22]	ROBINS-I	Moderate
4	Lalaoui <i>et al.</i> , 2025 ^[34]	JBI Critical Appraisal Checklist	High
5	Huo <i>et al.</i> , 2025 ^[23]	ROBINS-I	Moderate
6	Akçay <i>et al.</i> , 2025 ^[35]	ROBINS-I	Moderate
7	Cousin <i>et al.</i> , 2025 ^[19]	AMSTAR 2	Moderate
8	Hu <i>et al.</i> , 2024 ^[36]	ROBINS-I	Moderate
9	de Winter <i>et al.</i> , 2024 ^[37]	ROBINS-I	Moderate
10	Alhumaid <i>et al.</i> , 2024 ^[38]	JBI Critical Appraisal Checklist	High
11	Falsaperla <i>et al.</i> , 2024 ^[39]	ROBINS-I	Moderate
12	Shi <i>et al.</i> , 2023 ^[40]	JBI Critical Appraisal Checklist	High
13	Long and Lowe, 2022 ^[41]	JBI Critical Appraisal Checklist	High
14	Son <i>et al.</i> , 2021 ^[42]	ROBINS-I	Moderate
15	Şık <i>et al.</i> , 2020 ^[28]	ROBINS-I	Moderate
16	Kavitha <i>et al.</i> , 2020 ^[43]	ROBINS-I	Moderate
17	Rossetti <i>et al.</i> , 2020 ^[26]	ROBINS-I	Moderate
18	Maitre <i>et al.</i> , 2018 ^[21]	ROBINS-I	Moderate
19	Tian <i>et al.</i> , 2018 ^[44]	JBI Critical Appraisal Checklist	High
20	Shi <i>et al.</i> , 2018 ^[45]	JBI Critical Appraisal Checklist	High
21	Bailly <i>et al.</i> , 2017 ^[46]	ROBINS-I	Moderate
22	Teagarden <i>et al.</i> , 2017 ^[47]	JBI Critical Appraisal Checklist	High
23	Krawiec <i>et al.</i> , 2017 ^[48]	JBI Critical Appraisal Checklist	High
24	Chantreuil <i>et al.</i> , 2015 ^[49]	JBI Critical Appraisal Checklist	High
25	Winter <i>et al.</i> , 2015 ^[50]	JBI Critical Appraisal Checklist	High
26	Assy <i>et al.</i> , 2015 ^[51]	JBI Critical Appraisal Checklist	High
27	Kuperman <i>et al.</i> , 2014 ^[24]	JBI Critical Appraisal Checklist	High
28	Al Hanshi <i>et al.</i> , 2014 ^[52]	JBI Critical Appraisal Checklist	High
29	Rocha <i>et al.</i> , 2014 ^[53]	JBI Critical Appraisal Checklist	High
30	Borgi <i>et al.</i> , 2014 ^[54]	ROBINS-I	Moderate
31	Nieves <i>et al.</i> , 2013 ^[55]	ROBINS-I	Moderate

(Contd...)

Table 2: (Continued).

	Study	Tool used	Quality assessment
32	Berger <i>et al.</i> , 2013 ^[56]	ROBINS-I	Low
33	Taffarel <i>et al.</i> , 2012 ^[57]	ROBINS-I	Moderate
34	Martinez <i>et al.</i> , 2011 ^[58]	JBI Critical Appraisal Checklist	High
35	Berthomieu <i>et al.</i> , 2010 ^[59]	JBI Critical Appraisal Checklist	High
36	Rowlands <i>et al.</i> , 2010 ^[25]	JBI Critical Appraisal Checklist	High
37	Couchot <i>et al.</i> , 2009 ^[60]	JBI Critical Appraisal Checklist	High
38	Vaessen <i>et al.</i> , 2006 ^[61]	JBI Critical Appraisal Checklist	High
39	Donoso <i>et al.</i> , 2006 ^[62]	ROBINS-I	Moderate
40	Grzeszczak <i>et al.</i> , 2006 ^[27]	JBI Critical Appraisal Checklist	High
41	De Berry <i>et al.</i> , 2005 ^[63]	ROBINS-I	Moderate
42	Inwald <i>et al.</i> , 2004 ^[64]	ROBINS-I	Moderate
43	Romano <i>et al.</i> , 2004 ^[65]	ROBINS-I	Moderate
44	Halasa <i>et al.</i> , 2003 ^[66]	ROBINS-I	Moderate
45	Pooboni <i>et al.</i> , 2003 ^[67]	ROBINS-I	Moderate
46	Smith and Vyas, 2000 ^[68]	JBI Critical Appraisal Checklist	High

ROBINS-I: Risk of bias in non-randomized studies of interventions, JBI: Joanna Briggs institute, AMSTAR 2: A measurement tool to assess systematic reviews 2

The included literature comprised retrospective and prospective cohorts ($n = 24$), case series ($n = 12$), case reports ($n = 9$), and one meta-analysis^[19] conducted across Europe, North America, the Middle East, and Asia. Most studies involved infants <6 months presenting with malignant pertussis and hyperleukocytosis ($>50 \times 10^9/L$) complicated by respiratory failure or pulmonary hypertension.

Quality assessment

Quality appraisal using ROBINS-I, the JBI checklist, and AMSTAR-2 indicated 17 studies of high, 21 of moderate, and 8 of low methodological quality [Table 2]. High-quality studies consistently emphasized timely leukoreduction and multimodal management as key survival predictors. Despite heterogeneity in study design, the included studies generally suggested an association between earlier recognition, timely intervention, and more favorable outcomes.

Hydroxyurea therapy

Hydroxyurea emerged as a promising pharmacologic leukoreductive therapy. Across seven studies,^[5,20,21] doses

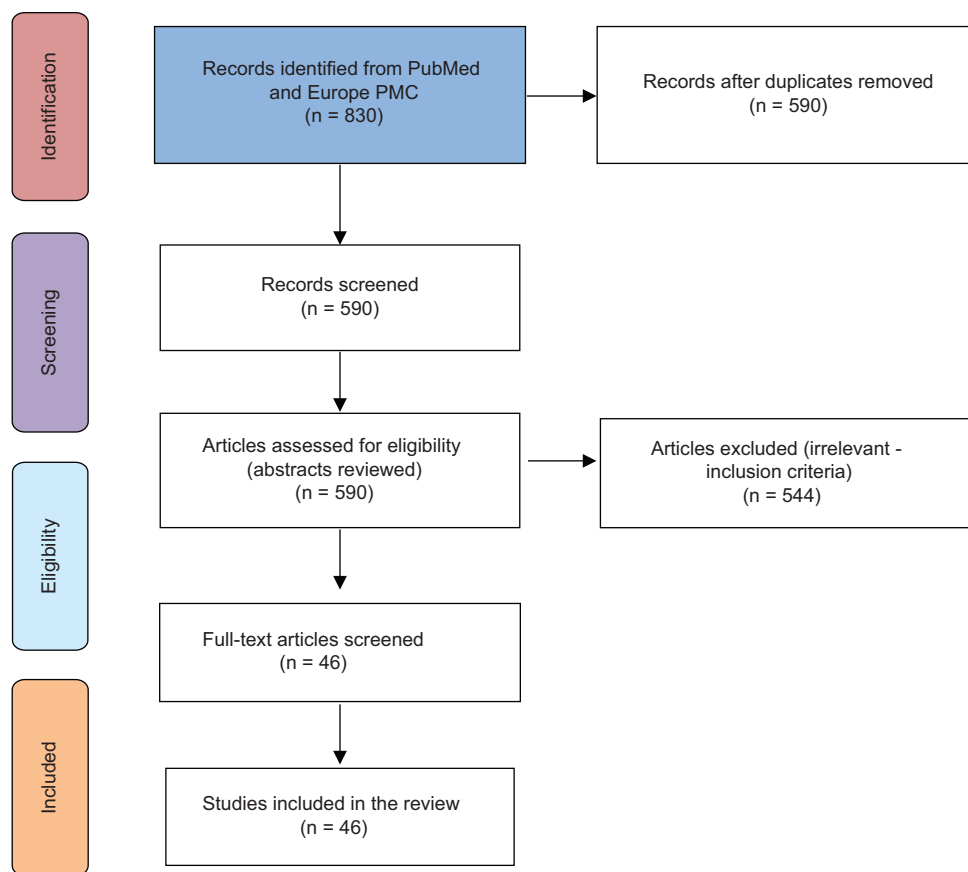


Figure 1: PRISMA 2020 flow diagram of the study selection process, including reasons (with counts) for full-text exclusions based on the predefined eligibility criteria.

of approximately 20 mg/kg/day achieved significant white blood cell (WBC) reduction within 5–7 days. Reported survival ranged 70–90% [Tables 3 and 4], with mortality 10–30%, comparable to ET but with fewer procedural risks.

Blanc *et al.*,^[20] documented full hematologic recovery in all treated infants, while Maitre *et al.*,^[21] reported similar results when hydroxyurea was combined with leukapheresis or ET. These data suggest that hydroxyurea is a viable first-line or bridging option in centers where transfusion or ECMO is not immediately available.

ET

ET was the most frequently employed intervention, described in over 20 studies.^[22–25] It produced rapid leukoreduction within 2–6 h and improved pulmonary pressures [Tables 3–5].

Wu and Gan^[22] observed a 72% survival in ET recipients versus 42% with conservative care, while Huo *et al.*,^[23] found that ET within 24 h of pediatric intensive care unit admission halved mortality (22% vs. 46%). Complications included fluid imbalance, coagulopathy, and rebound leukocytosis, reported by Rowlands *et al.*,^[25] Overall, ET remains a cornerstone

Table 3: Pooled findings of the advanced intervention use and survival ranges.

Intervention	Number of studies	Mortality range (%)
Hydroxyurea	7+	10–30
Exchange transfusion	20+	15–50
Leukapheresis	Few (<5)	0–30*
Extracorporeal membrane oxygenation	10+	5–45

*Very limited data; ranges are unstable and influenced by case selection and timing.

Table 4: Outcome for combined interventions.

Combination therapy	Reported survival benefit
ET+ECMO	Survival >70% in centers using early intervention protocols
Hydroxyurea+ET	Moderate survival benefit with better stability in resource-limited settings
Leukapheresis+ECMO	Very limited data; survival reported inconsistently

ECMO: Extracorporeal membrane oxygenation, ET: Exchange transfusion

Table 5: Mortality rates of the advanced interventions in infantile malignant pertussis.

Intervention	Best outcome if used	Mortality when used early (%)	Mortality when used late (%)
Hydroxyurea	Before leukocytosis/pulmonary HTN	<20	40–60
Exchange transfusion	Early hyperleukocytosis stage	<30	>60
Extracorporeal membrane oxygenation	Before cardiac arrest	<40	>70

therapy, especially when initiated before cardiovascular collapse in infants with WBC > 100 × 10⁹/L.

Leukapheresis

Leukapheresis appeared in only three reports.^[21,26,27] Although transient leukocyte reduction occurred, outcomes were inconsistent, and procedural instability was common. Rossetti *et al.*,^[26] noted short-term respiratory improvement after early leukapheresis in a premature infant; however, the survival benefit was marginal [Table 3]. Given its technical complexity and hemodynamic risks, leukapheresis remains experimental and unsuitable as standard therapy for neonates.

ECMO

Ten studies^[11,28,29] evaluated ECMO as rescue therapy for refractory failure. Overall survival ranged 30–60% [Tables 4 and 6] and depended heavily on timing and concurrent leukoreduction.

Domico *et al.*,^[11] reported 28% survival among 200 ECMO-treated infants, but mortality decreased markedly when ET or hydroxyurea preceded ECMO (OR 3.36; *P* = 0.03). Cousin *et al.*,^[29] observed similar improvement when ECMO was combined with early ET and optimized ventilation. Major complications included bleeding, infection, and neurologic injury, underscoring the need for precise timing and multimodal coordination.

Comparative effectiveness and timing

Comparative synthesis of all included interventions [Table 4] suggested that earlier multimodal approaches were often associated with better outcomes across observational cohorts. Hydroxyurea and ET appeared to offer complementary leukoreduction mechanisms, while ECMO was generally utilized as supportive therapy to bridge cardiorespiratory stabilization in selected cases.

In some reports, centers adopting early-escalation approaches combining ET + ECMO or hydroxyurea + mechanical ventilation reported survival exceeding 70%, whereas lower survival rates were more frequently reported when interventions were delayed or applied as single-modality strategies. Temporal patterns [Table 5] suggested that initiation within 48 hours of clinical deterioration was associated with more favorable outcomes, while late ECMO

Table 6: Risks associated with advanced interventions in infantile malignant pertussis.

Intervention	Risks
Hydroxyurea	Mild myelosuppression, needs monitoring.
Exchange transfusion	Coagulopathy, fluid shifts, and rebound leukocytosis.
Leukapheresis	Hemodynamic instability, technical complexity.
Extracorporeal membrane oxygenation	Bleeding, infection, neurologic injury.

initiation without prior leukoreduction was commonly associated with poorer survival. Figure 2 provides survival rates (minimum–maximum) of each intervention in infantile malignant pertussis, based on data synthesized from the included studies.^[19-64]

Quantitative summary of outcomes

A pooled summary of reported survival outcomes and complications for each advanced therapy is presented in Table 6. Across included studies, hydroxyurea was associated with gradual leukoreduction with minimal reported toxicity; ET was associated with rapid leukocyte reduction but carried higher procedural risks; leukapheresis was infrequently reported with inconsistent outcomes; and ECMO outcomes were generally more favorable when integrated with prior leukoreduction rather than when used as isolated rescue therapy.

Overall, these findings may help inform an early-escalation framework grounded in the complementary roles of hydroxyurea, ET, and ECMO, and they underscore the need for future multicenter prospective studies to clarify optimal timing and sequencing. Key findings of each study are summarized in Table 7.

Key findings

Early multimodal intervention may be beneficial

Observational studies consistently suggest improved survival when leukoreduction (via hydroxyurea or ET) is initiated early in the disease course, before cardiovascular compromise.

Table 7: Summary of included studies and interventions for malignant pertussis, 2000–2025.

No	Authors/ Year	Title of the article	Research design	Intervention
1	Blanc <i>et al.</i> , 2025 ^[20]	Hydroxyurea for Malignant Pertussis in Critically Ill Children.	Prospective study.	Hydroxyurea; Exchange transfusion; ECMO.
2	Liru <i>et al.</i> , 2025 ^[33]	Clinical characteristics of pertussis in infants and risk factors for respiratory support.	Retrospective study.	Exchange transfusion.
3	Wu and Gan, 2025 ^[22]	Clinical characteristics and impact of exchange transfusion in infant pertussis with extreme leukocytosis.	Retrospective study.	Exchange transfusion.
4	Lalaoui <i>et al.</i> , 2025 ^[34]	Neonatal malignant pertussis and exchange transfusion: A case report.	Case report.	Exchange transfusion.
5	Huo <i>et al.</i> , 2025 ^[23]	Risk factors and mortality in children with severe pertussis: the role of exchange transfusion in a pediatric intensive care unit.	Retrospective study.	Exchange transfusion.
6	Akçay <i>et al.</i> , 2025 ^[35]	Severe pertussis infections in pediatric intensive care units: a multicenter study	Retrospective study.	Exchange transfusion.
7	Cousin <i>et al.</i> , 2025 ^[19]	Pertussis infection in critically ill infants: meta-analysis and validation of a mortality score.	Meta-analysis study.	ECMO.
8	Hu <i>et al.</i> , 2024 ^[36]	Application of exchange transfusion in neonates with severe pertussis and hyperleukocytosis.	Retrospective study.	Exchange transfusion.
9	de Winter <i>et al.</i> , 2024 ^[37]	Use and Waste of Reconstituted Whole Blood Exchange Transfusions: An 11-year National Observational Study.	Retrospective cohort study.	Exchange transfusion.
10	Alhumaid <i>et al.</i> , 2024 ^[38]	International treatment outcomes of neonates on extracorporeal membrane oxygenation (ECMO) with persistent pulmonary hypertension of the newborn (PPHN): A systematic review.	Review study.	ECMO.
11	Falsaperla <i>et al.</i> , 2024 ^[39]	Extracorporeal Membrane Oxygenation as Life Support in Neonatal Respiratory Failure: A Single-Center Cohort Study and a Systematic Review	Cohort and review study.	ECMO.
12	Shi <i>et al.</i> , 2023 ^[40]	Risk Factors of Exchange Blood Transfusion in Infants with Severe Pertussis.	Case series.	Exchange transfusion.
13	Long and Lowe, 2022 ^[41]	Severe Pertussis Infection with Hyperleukocytosis in a 10-month-old Unvaccinated Amish Female: A Case Report.	Case report.	Exchange transfusion; Leukapheresis.
14	Son <i>et al.</i> , 2021 ^[42]	Exchange transfusion in the management of critical pertussis in young infants: a case series.	Case series.	Exchange transfusion.
15	Şık <i>et al.</i> , 2020 ^[28]	The clinical characteristics and prognosis of pertussis among unvaccinated infants in the pediatric intensive care unit.	Retrospective study.	ECMO.
16	Kavitha <i>et al.</i> , 2020 ^[43]	Clinical Profile of Critical Pertussis in Children at a Pediatric Intensive Care Unit in Northern India.	Retrospective study.	Exchange transfusion.
17	Rossetti <i>et al.</i> , 2020 ^[26]	Early Leukapheresis Depletion in an Ex-Premature with Severe Acute Respiratory Distress Syndrome Due to Bordetella Pertussis and Coronavirus Infection.	Case report.	Leukapheresis.
18	Maitre <i>et al.</i> , 2018 ^[21]	Leukemoid Reaction in Infant Pertussis: Is There a Place for Hydroxyurea? A Case Report.	Case report.	Hydroxyurea; Exchange transfusion; Leukapheresis.
19	Tian <i>et al.</i> , 2018 ^[44]	Fatal malignant pertussis with hyperleukocytosis in a Chinese infant: A case report and literature review.	Case report and review study.	Exchange transfusion.
20	Shi <i>et al.</i> , 2018 ^[45]	Extracorporeal membrane oxygenation with prone position ventilation successfully rescues infantile pertussis: a case report and literature review.	Case report and review study.	ECMO.

(Contd...)

Table 7: (Continued).

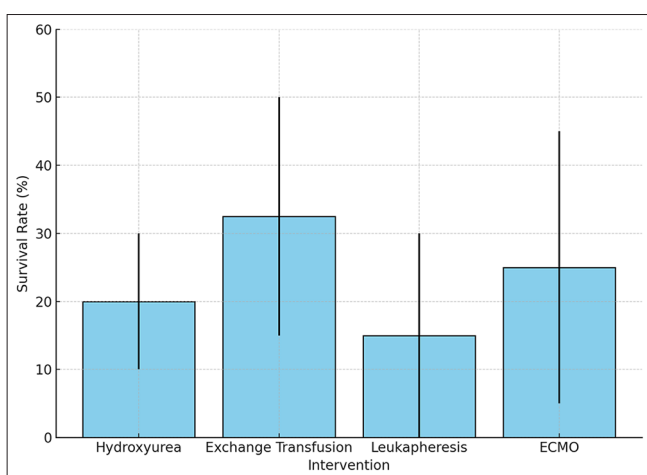
No	Authors/ Year	Title of the article	Research design	Intervention
21	Bailly <i>et al.</i> , 2017 ^[46]	Development and Validation of a Score to Predict Mortality in Children Undergoing Extracorporeal Membrane Oxygenation for Respiratory Failure: Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction Score.	Retrospective cohort study.	ECMO.
22	Teagarden <i>et al.</i> , 2017 ^[47]	Thiamine Deficiency Leading to Refractory Lactic Acidosis in a Pediatric Patient.	Case report.	ECMO.
23	Krawiec <i>et al.</i> , 2017 ^[48]	Intrapulmonary Percussive Ventilation as an Airway Clearance Technique during Venoarterial Extracorporeal Life Support in an Infant with Pertussis.	Case report.	ECMO.
24	Chantreuil <i>et al.</i> , 2015 ^[49]	Malignant pertussis and exchange transfusion.	Case report.	Exchange transfusion; ECMO.
25	Winter <i>et al.</i> , 2015 ^[50]	Risk Factors Associated with Infant Deaths from Pertussis: A Case-Control Study.	Retrospective cohort study.	Exchange transfusion; ECMO.
26	Assy <i>et al.</i> , 2015 ^[51]	Severe Neonatal Pertussis Treated by Leukodepletion and Early Extracorporeal Membrane Oxygenation.	Case report.	Exchange transfusion; ECMO.
27	Kuperman <i>et al.</i> , 2014 ^[24]	Severe pertussis and hyperleukocytosis: is it time to change for exchange?	Case report.	Exchange transfusion.
28	Al Hanshi <i>et al.</i> , 2014 ^[52]	Severe Pertussis Pneumonia managed with Exchange Transfusion.	Case report.	Exchange transfusion.
29	Rocha <i>et al.</i> , 2014 ^[53]	Neonatal extracorporeal membrane oxygenation: Initial experience of Hospital de São João.	Case series.	ECMO.
30	Borgi <i>et al.</i> , 2014 ^[54]	Predictors of Mortality in Mechanically Ventilated Critical Pertussis in a Low-Income Country.	Retrospective study.	Exchange transfusion.
31	Nieves <i>et al.</i> , 2013 ^[55]	Exchange blood transfusion in the management of severe pertussis in young infants.	Case series.	Exchange transfusion.
32	Berger <i>et al.</i> , 2013 ^[56]	Critical pertussis illness in children: a multicenter prospective cohort study.	Prospective cohort study.	Exchange transfusion.
33	Taffarel <i>et al.</i> , 2012 ^[57]	(Severe pertussis, progression, and exchange transfusion as an alternative treatment. Case reports).	Retrospective study.	Exchange transfusion.
34	Martinez <i>et al.</i> , 2011 ^[58]	Early blood exchange transfusion in malignant pertussis: a case report.	Case report.	Exchange transfusion.
35	Berthomieu <i>et al.</i> , 2010 ^[59]	Malignant pertussis: 3 case reports.	Case series.	Exchange transfusion.
36	Rowlands <i>et al.</i> , 2010 ^[25]	Impact of rapid leukodepletion on the outcome of severe clinical pertussis in young infants.	Retrospective study.	Exchange transfusion; ECMO.
37	Couchot <i>et al.</i> , 2009 ^[60]	Extracorporeal membranous oxygenation in severe infant pertussis: a case report.	Case report.	ECMO.
38	Vaessen <i>et al.</i> , 2006 ^[61]	Clinical case of the month. Fatal pertussis infection in a 2-month-old infant.	Case report.	Exchange transfusion.
39	Donoso <i>et al.</i> , 2006 ^[62]	Exchange transfusion to reverse severe pertussis-induced cardiogenic shock.	Case series.	Exchange transfusion.
40	Grzeszczak <i>et al.</i> , 2006 ^[27]	Leukopheresis therapy for severe infantile pertussis with myocardial and pulmonary failure.	Case report.	Leukapheresis.
41	De Berry <i>et al.</i> , 2005 ^[63]	Pertussis with severe pulmonary hypertension and leukocytosis treated with extracorporeal membrane oxygenation.	Case report.	ECMO.
42	Inwald <i>et al.</i> , 2004 ^[64]	Open lung biopsy in neonatal and pediatric patients referred for extracorporeal membrane oxygenation (ECMO).	Retrospective study.	ECMO.

(Contd...)

Table 7: (Continued).

No	Authors/Year	Title of the article	Research design	Intervention
43	Romano <i>et al.</i> , 2004 ^[65]	Pertussis pneumonia, hypoxemia, hyperleukocytosis, and pulmonary hypertension: improvement in oxygenation after a double volume exchange transfusion.	Case report.	Exchange transfusion.
44	Halasa <i>et al.</i> , 2003 ^[66]	Fatal pulmonary hypertension associated with pertussis in infants: does extracorporeal membrane oxygenation have a role?	Retrospective study.	ECMO.
45	Pooboni <i>et al.</i> , 2003 ^[67]	Extracorporeal life support in pertussis	Retrospective study.	ECMO.
46	Smith and Vyas, 2000 ^[68]	Early infantile pertussis; increasingly prevalent and potentially fatal.	Case series.	ECMO.

ECMO: Extracorporeal membrane oxygenation

**Figure 2:** Survival rates (minimum–maximum) of each intervention in infantile malignant pertussis, based on data synthesized from the included studies.

Hydroxyurea shows potential as a feasible option

Hydroxyurea was associated with gradual leukoreduction and favorable survival ranges in several cohorts and may represent a practical option, particularly where invasive procedures are not immediately available.

ET is widely used in practice

ET was the most frequently reported intervention and was associated with rapid leukoreduction, particularly when performed early.

Leukapheresis demonstrates limited and inconsistent benefit

Available evidence suggests variable outcomes and substantial procedural challenges, limiting its routine applicability.

ECMO appears most effective as adjunctive therapy

ECMO outcomes were more favorable when combined with early leukoreduction, rather than when used as isolated rescue therapy.

DISCUSSION

This systematic review provides an integrated synthesis of available evidence on advanced therapeutic interventions for malignant pertussis in infants, drawing on data from 46 studies published over a 25-year period. Collectively, the findings indicate that hyperleukocytosis in pertussis is not simply a laboratory abnormality but is closely associated with the development of severe respiratory failure, pulmonary hypertension, and increased mortality, particularly in infants younger than 2 months. Hydroxyurea exerts its effect through inhibition of ribonucleotide reductase, leading to reduced leukocyte production and blood viscosity, which may contribute to improvement in pulmonary vascular resistance and microvascular flow in malignant pertussis. By examining hydroxyurea, ET, leukapheresis, and ECMO together, this review offers a consolidated perspective on early escalation strategies used in the management of this life-threatening condition.

Across several included studies, hydroxyurea was associated with progressive leukoreduction over 5–7 days, with reported survival rates ranging from 70% to 90% and mortality between 10% and 30%.^[5,20,21] These observations suggest that hydroxyurea may represent a non-invasive and relatively accessible pharmacologic option, particularly in resource-limited settings where immediate access to ET or ECMO is not available. In contrast to the broader leucodepletion review by Annayev *et al.*,^[30] which did not demonstrate a significant survival difference between treated and untreated groups (47.5% vs. 41.7%), the present synthesis highlights

the potential role of hydroxyurea in stabilizing infants before more invasive interventions and in minimizing risks related to fluid shifts and electrolyte imbalance. Nevertheless, differences in patient severity and timing of initiation across studies limit definitive conclusions.

Consistent with prior analyses,^[31] the reviewed literature supports an association between rapid leukocytosis, a lymphocyte-to-neutrophil ratio below 1, and echocardiographic evidence of pulmonary hypertension with poorer clinical outcomes. Early hematologic and echocardiographic assessment may therefore assist in identifying infants at higher risk who could benefit from earlier consideration of leukoreductive strategies before progression to multiorgan dysfunction. In addition, evolving antimicrobial resistance patterns further emphasize the importance of prompt diagnosis and comprehensive supportive care, as pharmacologic treatment alone may be insufficient to counteract disease severity once marked hyperleukocytosis has developed.^[32]

ET remains the most extensively reported leukoreductive intervention, with support from more than 20 studies.^[22,23,25] ET is consistently associated with rapid leukocyte reduction within 2–6 h and short-term improvements in oxygenation and pulmonary hemodynamics. Importantly, timing appears to play a critical role, as outcomes were more favorable when ET was performed before the onset of circulatory collapse or initiation of ECMO. Coquaz-Garoudet *et al.*,^[31] reported 100% survival among infants receiving early ET compared with no survivors in delayed cases (Relative Risk [RR] = 0.18). Although procedural complications such as rebound leukocytosis and coagulopathy have been described, ET continues to be widely utilized in clinical practice for infants with WBC counts exceeding $100 \times 10^9/L$ when appropriate hemodynamic and electrolyte monitoring is available.

Although leukapheresis offers a theoretical advantage through selective leukocyte removal, its application in malignant pertussis was limited to three reports.^[21,26,27] Reported outcomes were inconsistent, with only transient clinical improvement and frequent procedural instability in neonates. These findings, in line with Annayev *et al.*,^[30] underscore the technical complexity and vascular access challenges associated with leukapheresis in this age group. In addition, reported complications such as thrombocytopenia and hypocalcemia (Cousin *et al.*, 2024)^[29] further limit its routine applicability in young infants.

ECMO was evaluated in 10 studies^[11,28] and was most commonly employed as salvage support for refractory respiratory or cardiovascular failure. Survival outcomes varied considerably and were strongly influenced by both timing and integration with leukoreductive therapy. Domico *et al.*,^[11] reported a survival rate of 28% when ECMO was

used alone, with a threefold improvement observed when ET or hydroxyurea preceded ECMO initiation (odds ratio [OR] = 3.36, $P = 0.03$). Similarly, Cousin *et al.*,^[19] reported improved outcomes when ECMO was introduced earlier in combination with ET and optimized ventilatory strategies. Earlier case reports and small retrospective series have also described the use of exchange transfusion and ECMO in infants with severe pertussis complicated by hypoxemia, hyperleukocytosis, and pulmonary hypertension, demonstrating transient physiological improvement in some cases but overall variable and often poor survival outcomes.^[65-68] These findings suggest that ECMO may be most effective when used as a supportive bridge within a multimodal treatment framework rather than as an isolated intervention.

Variation in reported survival across studies likely reflects differences in disease severity, timing of intervention, and use of combined therapeutic approaches. Lower survival rates, such as those reported for ECMO alone, were more commonly observed when intervention occurred late in critically unstable infants, whereas higher survival rates were associated with earlier initiation alongside leukoreductive strategies. Similarly, variability in outcomes following ET and hydroxyurea may be influenced by baseline severity, timing of therapy, and concurrent multimodal management.

- Hydroxyurea may be considered an accessible first-line or bridging therapy when ET or ECMO is delayed or unavailable
- ET is widely used in clinical practice as an early leukoreductive intervention, particularly when initiated before cardiovascular compromise
- Leukapheresis has shown limited and inconsistent benefit and is not routinely applied due to technical and physiologic limitations
- ECMO is most often utilized in salvage situations and appears to provide benefit primarily when used in combination with early leukoreduction
- Observational data suggest that early, integrated escalation strategies, initiating hydroxyurea (HU) or ET before clinical deterioration and escalating to ECMO when necessary, may be associated with improved survival.

Overall, this review highlights that outcomes in malignant pertussis may depend less on a single intervention and more on the timing, integration, and accessibility of supportive and leukoreductive strategies. Hydroxyurea appears to be a practical adjunct in settings where immediate access to advanced extracorporeal support is limited, while ET remains the most frequently reported and commonly used intervention for rapid leukoreduction in published cohorts. A time-sensitive, integrated approach has been reported in several studies and may provide a useful foundation for future multicenter protocols and more standardized management pathways.

Limitations

This review has several limitations that should be acknowledged. First, the majority of included studies were case reports and small case series, which inherently increase the risk of publication bias, as successful outcomes are more likely to be reported. Second, there was substantial heterogeneity in how malignant pertussis, hyperleukocytosis, and timing of interventions were defined across studies, which may have contributed to variability in outcomes. Third, confounding by indication is possible, since more severely ill infants were more likely to receive advanced interventions such as ECMO or ET, potentially underestimating their effectiveness. Finally, due to the high degree of methodological and clinical heterogeneity, a quantitative meta-analysis could not be performed, and results were therefore synthesized narratively.

CONCLUSION

Observational evidence suggests that early leukoreductive strategies may be associated with improved outcomes in infants with malignant pertussis, particularly when initiated before cardiovascular deterioration. ET and hydroxyurea were the most consistently reported interventions and were associated with leukocyte reduction and favorable survival ranges across studies. ECMO appeared to provide benefit mainly when used as adjunctive support following leukoreduction, whereas leukapheresis showed limited and inconsistent results. Given the heterogeneity and non-randomized nature of the available data, these findings should be interpreted cautiously and regarded as hypothesis-generating. Further prospective multicenter studies are required to better define optimal timing and treatment sequencing in this rare condition.

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