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Rituximab for Idiopathic Pulmonary Hemosiderosis: A Systematic Review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 May 2026 and was last updated on 14 May 2026.

INTRODUCTION

Review question / Objective • Population: Patients of any age with confirmed or highly suspected idiopathic pulmonary haemosiderosis (IPH), defined by haemosiderin-laden macrophages on bronchoalveolar lavage or lung biopsy in the absence of capillaritis, immune complex deposition, or identifiable secondary aetiology.
• Intervention: Rituximab (anti-CD20 monoclonal antibody) at any dose or schedule.
• Comparator: None required (single-arm case-level evidence accepted).
• Outcomes: Clinical response (haemoptysis cessation, haemoglobin improvement, radiological improvement); steroid-sparing effect; pulmonary function improvement; relapse frequency; adverse events.

Rationale Idiopathic pulmonary haemosiderosis (IPH) is a rare cause of diffuse alveolar haemorrhage predominantly affecting children and adolescents, with an estimated incidence of 0.24–1.23 per million per annum. Recurrent haemorrhagic exacerbations lead to progressive pulmonary fibrosis and, in severe cases, respiratory failure. Corticosteroids remain the cornerstone of therapy but carry substantial cumulative toxicity in a predominantly paediatric population . Steroid-sparing agents such as hydroxychloroquine, azathioprine, mycophenolate mofetil, and cyclophosphamide are used in refractory or steroid-dependent disease, yet meaningful remission is achieved inconsistently across all second-line options.
Accumulating evidence strongly implicates B-cell-mediated immune dysregulation in IPH pathophysiology. Approximately 25% of patients eventually develop a formal autoimmune diagnosis, and a further subset demonstrate MPO-ANCA seroconversion after years of apparently idiopathic disease.
Rituximab, a chimeric anti-CD20 monoclonal antibody, depletes B lymphocytes and has transformed outcomes in ANCA-associated vasculitis, where it is now guideline-endorsed as equivalent to cyclophosphamide for remission

induction and superior for relapse prevention. Its favourable long-term toxicity profile, guaranteed adherence through intravenous administration, and biological plausibility in a B-cell-driven disease make it a compelling candidate in refractory IPH.
Anecdotal reports of rituximab use in IPH have emerged over the past decade but remain scattered across single-centre reports and conference abstracts from multiple countries, with heterogeneous patient characteristics, dosing schedules, and outcome reporting. No systematic synthesis of this evidence exists. This review therefore addresses a direct clinical evidence gap, providing the first rigorous collation of published rituximab experience in IPH to inform practice and define priorities for future prospective research.

Condition being studied Idiopathic Pulmonary Hemosiderosis is a rare disorder characterized by recurrent episodes of diffuse alveolar haemorrhage resulting from repeated bleeding into the lungs. It predominantly affects children and young adults, although cases have been reported across all age groups. The exact cause remains unknown; however, increasing evidence suggests an underlying immune-mediated mechanism. Clinically, patients commonly present with the classic triad of haemoptysis, iron-deficiency anaemia, and diffuse pulmonary infiltrates, although haemoptysis may be absent in younger children. Recurrent haemorrhagic episodes lead to accumulation of hemosiderin-laden macrophages within the alveoli and can eventually result in interstitial fibrosis, pulmonary hypertension, and respiratory failure.

Diagnosis is based on a combination of clinical presentation, radiological findings, bronchoalveolar lavage demonstrating hemosiderin-laden macrophages, and exclusion of secondary causes of diffuse alveolar haemorrhage such as vasculitis, connective tissue diseases, infections, and cardiac disorders. Corticosteroids remain the cornerstone of treatment and are often effective in controlling acute exacerbations. Additional immunosuppressive agents including azathioprine, hydroxychloroquine, mycophenolate mofetil, and rituximab may be required in recurrent or steroid-dependent disease. Despite advances in therapy, IPH remains associated with significant morbidity due to recurrent relapses and long-term pulmonary damage.

METHODS

Search strategy SEARCH CONCEPT DOMAINS:
Domain 1 — IPH/DAH: MeSH terms: 'Idiopathic Pulmonary Hemosiderosis', 'hemosiderosis, primary pulmonary', 'hemosiderosis, pulmonary'. Free text: 'idiopathic pulmonary hemosiderosis', 'idiopathic pulmonary haemosiderosis', 'pulmonary hemosiderosis', 'pulmonary haemosiderosis', 'IPH', 'diffuse alveolar hemorrhage', 'diffuse alveolar haemorrhage', 'alveolar hemorrhage', 'alveolar haemorrhage'.
Domain 2 — Rituximab: MeSH term: 'cd20 antibody, rituximab'. Free text: 'rituximab', 'anti-CD20', 'CD20 antibody', 'MabThera', 'Rituxan'.
Domains combined with Boolean AND.

Participant or population • Patients of any age (paediatric or adult) and any sex
• Diagnosed with idiopathic pulmonary haemosiderosis based on any combination of: clinical (haemoptysis, iron-deficiency anaemia, bilateral infiltrates on imaging); bronchoscopic (haemosiderin-laden macrophages on BAL, Perls' stain positive); or histopathological (HLM on lung biopsy without capillaritis, immune complex deposition, or vasculitis)
• Systematic exclusion of secondary causes documented (autoimmune screen including ANA, ANCA, anti-GBM, APLA; cardiac evaluation; coagulation; infection).

Intervention Rituximab in any dose/regime.

Comparator No comparator required. Given the orphan nature of IPH, the expected evidence base consists exclusively of uncontrolled case reports and case series without comparator groups. Single-arm case-level evidence is accepted and is consistent with the evidence available for rare disease systematic reviews.
Comparisons between patients treated with different rituximab regimens (e.g., 375 mg/m² × 4 doses vs 1 g × 2 doses) will be performed descriptively within the narrative synthesis if sufficient cases are identified.

Study designs to be included Case reports, case series, conference abstracts, observational studies, metaanalysis and systematic reviews.

Eligibility criteria • Geographic setting: Any country; no geographic restriction
• Clinical setting: Any healthcare setting including primary care, secondary, or tertiary/specialist centre
• Time period: All years to 28 March 2026; no start date restriction
• Age group: Any (neonates, infants, children, adolescents, adults, elderly)
• Language: Any language; non-English reports to be translated

• Publication type: Peer-reviewed journal publications and conference abstracts with extractable data
• Ethical standard: Studies not requiring specific ethical approval (case reports) are included; those where ethical approval or patient consent was explicitly stated to be obtained are noted.

Information sources DATABASES SEARCHED (all searched on 28 March 2026):
• PubMed (MEDLINE) — National Library of Medicine Advanced Search Builder
• Embase — embase.com Advanced Search
• Scopus — scopus.com Advanced Search
GREY LITERATURE:
• Google Scholar
.Reference lists of all included studies will be hand-searched.

Main outcome(s) 1. HAEMOPTYSIS CESSATION: Complete resolution or clinically meaningful reduction (no further episodes requiring medical attention) of haemoptysis after rituximab initiation, at last follow-up. Reported as resolved / improved / unchanged / worsened.
2. HAEMOGLOBIN / ANAEMIA RESOLUTION: Improvement in haemoglobin to age- and sex-appropriate normal range without ongoing transfusion requirement, OR clinically meaningful haemoglobin increment from pre-rituximab baseline. Reported as absolute haemoglobin values (g/dL) at baseline and last follow-up where available.
3. RADIOLOGICAL IMPROVEMENT: Reduction in bilateral ground-glass opacities, consolidation, or other active haemorrhagic infiltrates on chest radiograph or HRCT compared with pre-rituximab imaging. Reported as improved / stable / worsened.
Timing: At last available follow-up point; minimum one assessment post-rituximab required for inclusion.

Additional outcome(s) 1. STEROID-SPARING EFFECT: Reduction in oral corticosteroid dose by ≥50% from pre-rituximab baseline, or complete discontinuation of corticosteroids at any point during follow-up. Reported as steroid dose (mg/day prednisolone equivalent) at baseline and last follow-up; time to steroid discontinuation (months) where reported.
2. PULMONARY FUNCTION IMPROVEMENT: Clinically meaningful improvement (≥10% predicted) in forced vital capacity (FVC), total lung capacity (TLC), or diffusing capacity for carbon monoxide (DLCO) on formal pulmonary function testing compared with pre-rituximab values. Reported as percent predicted values at baseline and last follow-up.
3. RELAPSE FREQUENCY: Number of clinical exacerbations (as defined by treating physicians) per patient per year post-rituximab, compared with pre-rituximab period where data are available.
4. ADVERSE EVENTS ATTRIBUTABLE TO RITUXIMAB: Any undesired clinical or laboratory event occurring after rituximab initiation, including: infusion-related reactions; severe infections; hypogammaglobulinaemia; cytopenias (leucopenia, neutropenia, thrombocytopenia); progressive multifocal leucoencephalopathy (PML); autoimmune complications. Severity graded where reported.
5. DIAGNOSTIC EVOLUTION (EXPLORATORY): Emergence of ANCA positivity or other autoimmune serology during follow-up post-rituximab; renal involvement; development of extra-pulmonary manifestations.

Data management SELECTION PROCEDURE:
All deduplicated records will be imported into Rayyan (Qatar Computing Research Institute) for screening. Two independent reviewers will screen each record at title/abstract stage and full-text stage against the pre-specified eligibility criteria. Disagreements will be resolved through discussion; a third reviewer will arbitrate where consensus cannot be reached. Reasons for full-text exclusion will be recorded. The selection process will be reported using a PRISMA 2020 flow diagram.
DATA EXTRACTION:
Data will be extracted using a pre-specified structured extraction form by two extractors. Discrepancies resolved by discussion with third reviewer.
DATA TO BE EXTRACTED (pre-specified domains):
• Study-level: first author, year, journal, country, study design
• Demographics: age at presentation, age at rituximab initiation, sex
• Diagnosis: diagnostic criteria, confirmation method, HRCT findings, PFT results, autoimmune panel at baseline
• Prior treatments: all agents before rituximab, responses, reason for discontinuation, steroid dose at RTX initiation
• Rituximab regimen: dose, number of infusions, schedule, concurrent medications, maintenance
• Follow-up: duration post-rituximab
• All primary and secondary outcomes
• Adverse events: all events, severity, management, outcome
• Diagnostic evolution: ANCA status during follow-up, extra-pulmonary manifestations.

Quality assessment / Risk of bias analysis Formal risk-of-bias tools designed for interventional studies are not applicable to uncontrolled case reports and case series.

Strategy of data synthesis FORMAL META-ANALYSIS: Not planned. A narrative synthesis will be conducted comprising:
1. Tabular display of all included studies with extracted data across all pre-specified domains.
2. PRISMA 2020 flow diagram of the selection process.
3. Structured narrative synthesis by outcome domain: haemoptysis, haemoglobin, radiology, steroid-sparing, pulmonary function, relapse, and adverse events.

Subgroup analysis PLANNED SUBGROUP / SUBSET ANALYSES (if sufficient cases identified):
1. Age group: Paediatric (< 18 years) vs adult (≥ 18 years), given the known age-specific differences in IPH course and treatment tolerance.
2. Rituximab regimen: Weight-adjusted (375 mg/m² weekly × 4 doses) vs fixed-dose (1 g × 2 doses), to explore whether regimen type influences clinical response
3. ANCA status: ANCA-negative throughout vs ANCA-converting during follow-up, to explore whether the emerging autoimmune phenotype influences rituximab response.

Sensitivity analysis Not applicable.

Language restriction No language limits.

Country(ies) involved India.

Keywords idiopathic pulmonary hemosiderosis; diffuse alveolar haemorrhage; Rituximab, anti-CD20, steroid sparing immunosuppression, pulmonry hemosiderosis, ANCA vasculitis.

Dissemination plans 1. PEER-REVIEWED PUBLICATION: The completed systematic review will be submitted for publication in a peer-reviewed open-access journal. Open-access publication will be requested to maximise availability to clinicians managing rare paediatric lung disease, particularly in low- and middle-income country settings.
2. CONFERENCE PRESENTATION: Findings will be submitted as an abstract to national and international pulmonology and paediatric respiratory medicine meetings.
3. CLINICAL GUIDANCE: The review will be made available to clinical teams managing refractory IPH, including relevant disease-specific patient support organisations and specialist networks.

Contributions of each author
Author 1 - Richa Tyagi - Data extraction and manuscript drafting.
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