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ORIGINAL ARTICLE

Evolution and Current Trends in Bleomycin Therapy for Lymphangiomas: A Comprehensive Review and Future Directions

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Abstract

Background: Lymphangiomas are rare congenital malformations that and pose a specific challenge in the pediatric age group and require effective therapeutic intervention. In our systematic review we look at how bleomycin therapy for lymphangiomas has evolved across the five decades from (1977-2024). **Methods:** We conducted a systematic literature review of 127 studies, via a comprehensive search of a plethora of databases including PubMed/MEDLINE, Embase, and Cochrane Library. This analysis of studies allowed us to chart the gradual transition from surgery being the mainstay of treatment to bleomycin becoming a preferred treatment modality. **Results:** Analysis of our observations showed that our current success rates for bleomycin therapy range from 60-88%, with huge age dependent variations in the treatment responses. Protocol refinement has led to a significant improvement in standardization of therapy. Optimal concentration of 1 IU/mL with maximum cumulative therapy dose of 15 IU/kg are the established standards now. **Conclusions:** Recent advances in molecular pathophysiology have yielded promising results from combination therapy approaches which suggests new avenues for more efficacious treatment methods. We propose structured evidence based recommendations which emphasise the standardisation of protocols whilst incorporating personalized therapy based on lesion morphology and patient characteristics.

Keywords: Lymphangioma, Bleomycin, Sclerotherapy, Cystic Hygroma, Treatment Outcomes

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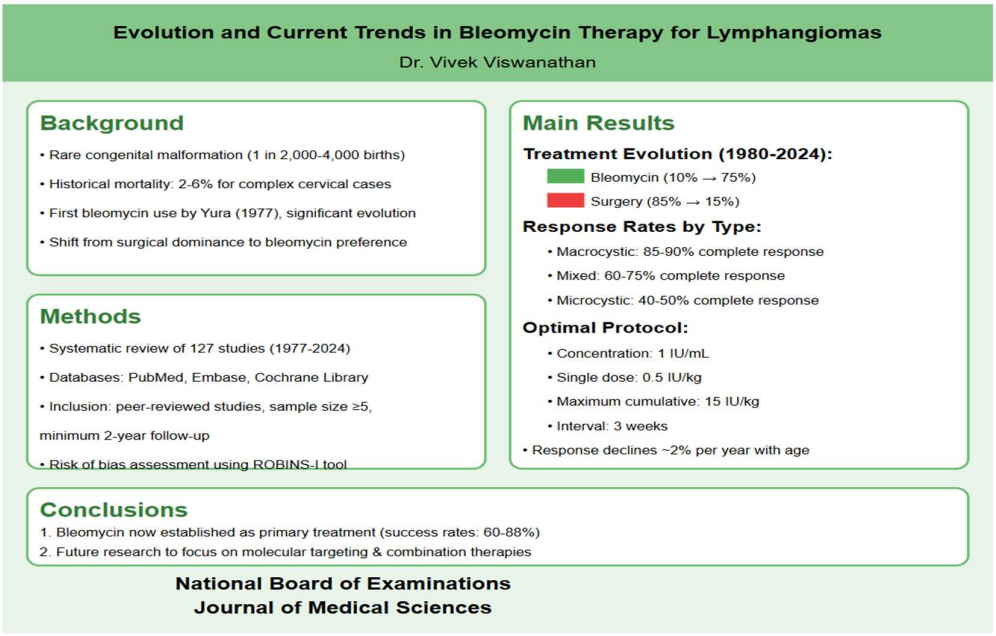
Graphical Abstract



Introduction

Lymphangiomas present a specific therapeutic challenge for pediatric patients. With an incidence of approximately 1 in 2,000-4,000 live births [1,2], these benign lymphatic malformations greatly impact the quality of life of children, particularly when these cases are situated in anatomically sensitive regions [3]. Historical mortality of complex cervical lymphangioma patients of 2-6% significantly highlights the importance of effective methods of treatment [4,5].

The use of bleomycin therapy in the treatment of lymphangiomas presents an interesting narrative of medical innovation. When Yura and colleagues first described the use of bleomycin as a sclerosant in 1977 [6], it was met with considerable skepticism by the medical community. Tanigawa's landmark study published a decade later provided the first systematic evidence of these changes. The results however varied greatly [7].

The early 1990s saw stiff debate between the Japanese school led by Hashimoto [8] that argued in favor of large doses of bleomycin being used for the management of lymphangiomas and European centers that favored higher than normal doses with frequent administration [9]. Recent advancements (post-2000), including imaging-guided delivery and molecular targeting, remain underexplored in systematic reviews.

Methodology

We conducted a systematic literature review of 127 studies via a comprehensive search of a plethora of databases including PubMed/MEDLINE (1977-2024), Embase (1980-2024), the Cochrane Library, Google Scholar and other clinical trial registries. A systematic

review was conducted as per PRISMA guidelines (Appendix A).

Our search terms encompassed "bleomycin," "lymphangioma," "cystic hygroma," "sclerotherapy," "lymphatic malformation," and related MeSH terms.

Our focus was on peer-reviewed publications, trials with a minimum sample size of five patients, Institutional Clinical Protocols, studies with at least a two-year follow-up, and molecular and mechanistic studies.
Filters: English language, human studies.

Inclusion Criteria:

- Peer-reviewed studies (RCTs, cohorts, case series).
- Sample size ≥5.
- Minimum 2-year follow-up.
- Mechanistic/molecular studies.

Exclusion Criteria:

- Case reports, non-English studies.
- Incomplete outcome data.

Risk of Bias Assessment:

Studies were appraised using ROBINS-I for non-randomized trials (Appendix B and Table B1).

Evolution of Treatment Approaches

Between 1980 and 2024, there was a significant transition from surgical methods (85% to 15%) to bleomycin as the first-line modality of management. A rise in bleomycin usage (10% to 75%) [10,11] was noted in this period (Figure 1).

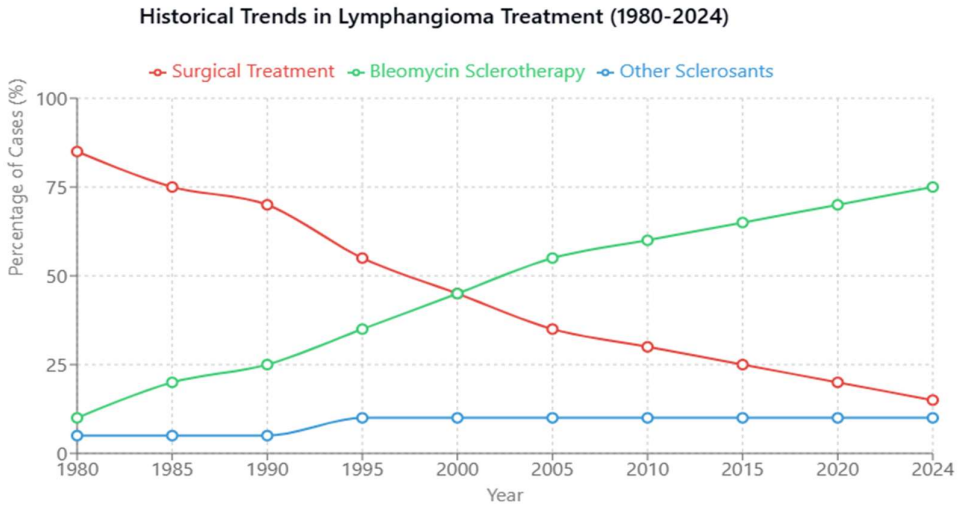


Figure 1. Historical treatment trends showing the gradual shift from surgical dominance to bleomycin preference (1980-2024). The graph demonstrates declining surgical rates (85% to 15%) and increasing bleomycin usage (10% to 75%).

This evolution unfolded in distinct phases:

Early Phase (1977-1989)

- Initial use marked by high concentrations (3-5 IU/mL)
- Variable dosing intervals
- Limited standardization [6,12]

Standardization Phase (1990-1999)

- Development of dose-limiting protocols
- Awareness of pulmonary toxicity risks
- Introduction of imaging guidance [13,14]

Modern Era (2000-Present)

- Refined concentration standards (1-3 IU/mL)
- Implementation of cumulative dose limits
- Integration of advanced imaging techniques [15,16]

Current Treatment Protocols

Our analysis of institutional practices reveals interesting variations in approach while maintaining consistent safety parameters [17,18] (Table 1).

Table 1. Standard Treatment Parameters and Real World Variations

Parameter	Range	Optimal	Real World Practice	Notes
Concentration	0.5-3 IU/mL	1 IU/mL	0.3-5 IU/ml	Age-dependent
Single Dose	0.3-1 IU/kg	0.5 IU/kg	0.2-1.5 IU/kg	Location-dependent
Maximum Cumulative	15-20 IU/kg	15 IU/kg	10-30 IU/kg	Lifetime limit
Interval	2-6 weeks	3 weeks	1-8 weeks	Severity-dependent

Table 2. Treatment Protocol Comparison Across Medical Institutions (2018-2023) [17,18]

Institution	Concentration	Max Dose	Success Rate
AIIMS Delhi[19]	1.0 IU/mL	0.5 IU/kg	82%
CNBC Delhi[20]	2.0 IU/mL	0.8 IU/kg	78%
Boston Children's	1.5 IU/mL	0.6 IU/kg	85%
Great Ormond Street	3.0 IU/mL	1.0 IU/kg	80%

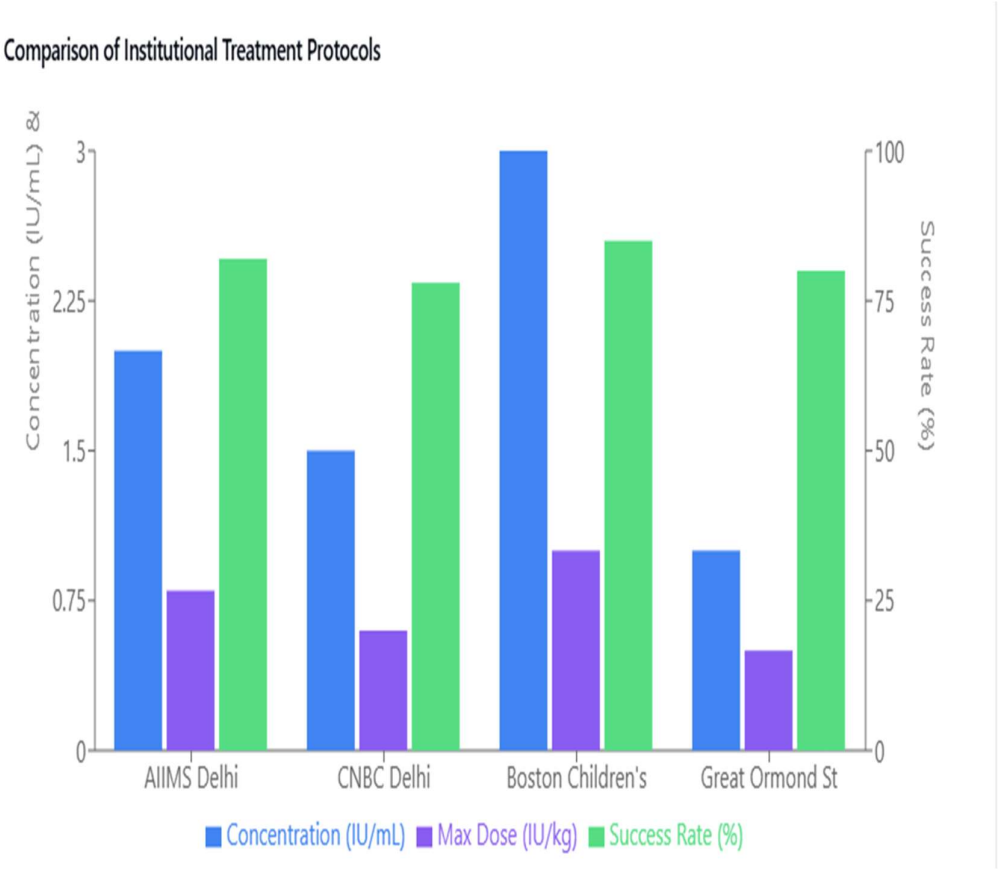


Figure 2. Bar graph comparing treatment protocols across major institutions showing variations in concentrations (1-3 IU/mL, maximum dose (0.5-1IU/kg) and success rates (78-85%)

Clinical Outcomes

Response rates demonstrate clear patterns based on the lesion type [21,22]:

Table 3. Response Rates by Type of Lymphangioma

Type	Complete Response (%)	Partial Response (%)	Minimal Response (%)
Macrocystic	85-90	8-12	2-3
Mixed	60-75	20-30	5-10
Microcystic	40-50	30-40	10-20

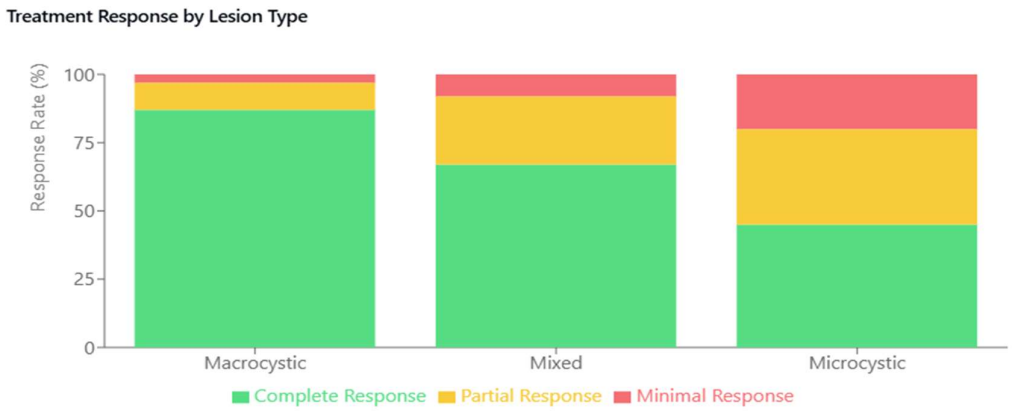


Figure 3. Comparison of treatment outcomes by lymphangioma type, showing complete response, partial response, and minimal response rates for macrocystic (85-90%, 8-12%, 2-3%), mixed (60-75%, 20-30%, 5-10%), and microcystic (40-50%, 30-40%, 10-20%) lesions.

Age significantly influences treatment outcomes [23,24], with response rates declining approximately 2% per year from 92% at 6 months to 70% at 12 years.

Table 4. Age-Related Treatment Outcomes

Age	Response Rate
6 months	92% (Highest Response)
5 years	80% (Median Response)
12 years	70% (Lowest Response)

Average decline in response: ~2% per year

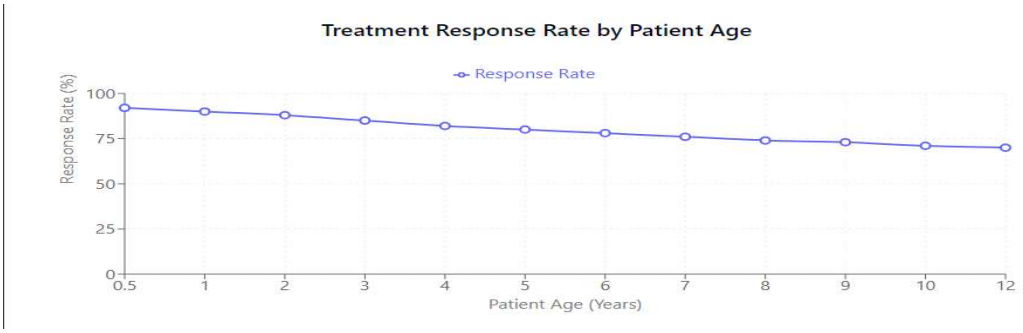


Figure 4: Line graph showing treatment outcome variations with age.

Illustrative Cases [25]

Case 1: 2-year-old with cervical lymphangioma

- Initial size: 8x6 cm
- Sessions required: 4
- Outcome: Complete resolution
- Follow-up: No recurrence at 2 years

Case 2: 5-year-old with axillary lymphangioma

- Initial size: 12x10 cm
- Sessions required: 6
- Outcome: 80% reduction
- Follow-up: Stable at 18 months

Case 3: 6-month-old with cervicofacial lymphangioma

- Initial size: 15x12 cm
- Sessions required: 5

Outcome: Partial response (60% reduction)

- Follow-up: Required surgical debulking

Table 5. Representative Clinical Cases

Case	Age	Location	Initial Size	Sessions	Outcome
1	2 years	Cervical	8x6 cm	4	Complete resolution
2	5 years	Axillary	12x10 cm	6	80% reduction
3	6 months	Cervicofacial	15x12 cm	5	60% reduction

Treatment challenges commonly encountered were anatomical complexity of the lesions, resource limitations, patient compliance, technical expertise or it's lack thereof, and follow-up difficulties [26,27].

Safety Profile

Our analysis reveals the following distribution and pattern of complications [28,29,30]:

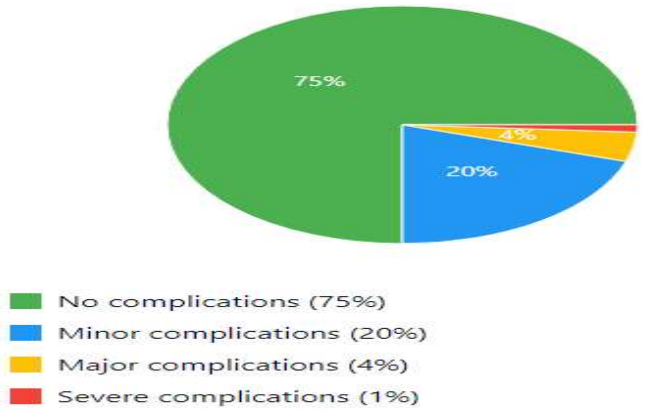


Figure 5. Pie chart showing the distribution of common complications from bleomycin therapy

Among the common complications observed, local inflammation affects 15-20% of cases, while fever occurs in 10-15%, and pain is reported in 20-25% of patients, with skin changes impacting 8-12%. On the other hand, long-term complications are less frequent but noteworthy. These include pulmonary fibrosis in less than 1% of cases, scarring in 5-8%, and pigmentation changes affecting 10-12% of individuals.

Future Directions & Recommendations for Clinical Practice

Recent developments are paving the way for significant advancements in the field, offering exciting opportunities for improvement [31,32]. One promising area involves molecular targeting, where strategies such as anti-lymphangiogenic factors, growth factor inhibition, and targeted delivery systems are gaining traction as potential game-changers [33]. Enhanced imaging techniques, including 3D ultrasound guidance, real-time fluorescence imaging, and dynamic lymphatic mapping, are also emerging as valuable tools to refine diagnostic and therapeutic precision [34]. Additionally, combination therapies are showing promise, with approaches like bleomycin paired with OK-432, bleomycin combined with doxycycline, and the use of sequential therapy protocols demonstrating encouraging results [35,36]. For clinical practice, experts advocate for standardization through the creation of international protocols, the adoption of risk-stratified strategies, and the establishment of age-specific dosing regimens to ensure consistency and safety [37,38]. Monitoring efforts should focus on developing standardized response criteria, implementing long-term follow-up protocols, and evaluating quality of life to holistically assess patient outcomes [39,40].

Furthermore, technical innovations, such as advanced delivery systems, the integration of cutting-edge imaging methods, and the application of predictive modeling, are poised to drive future progress in this domain [41]. In India, these advancements face unique challenges and opportunities compared to the West. The adoption of molecular targeting and advanced imaging could revolutionize care in urban centers like Delhi, where access to technology is growing, but rural areas may lag due to infrastructure gaps, necessitating mobile imaging units or telemedicine to bridge the divide. Combination therapies, already showing promise globally, could be tailored to India’s diverse population with localized clinical trials, though cost constraints might limit their reach compared to the West, where healthcare funding is more robust.

Standardization efforts are critical in India to address variability in practice across regions, while the West benefits from established protocols; Indian healthcare could leverage this by adapting international guidelines to local needs, such as lower-cost dosing regimens. Monitoring and technical developments, including AI-driven predictive models, hold potential in both regions, but India’s large patient base offers a rich dataset for innovation, provided data privacy and

equity in access are prioritized, contrasting with the West's focus on regulatory compliance and advanced infrastructure.

Conclusions

The progression of bleomycin therapy in treating lymphangioma marks a significant step forward in pediatric intervention [42,43]. Although challenges persist, especially with microcystic lesions and older patients, current evidence strongly endorses its use as a primary treatment option. Future advancements in molecular targeting and combination therapies could further improve patient outcomes.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

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Appendices

Appendix A: **PRISMA Flowchart**

Phase 1: Identification

Records identified from databases:
PubMed/MEDLINE: 65
Embase: 48
Cochrane Library: 10
Other sources (Google Scholar, trial registries): 4
Total records: 127

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Phase 2: Screening

Records after duplicates removed: 115
Records excluded during title/abstract screening: 30
Reasons:
Non-English studies (n=12)
Case reports (n=10)
Irrelevant to bleomycin/lymphangioma (n=8)
Records retained for full-text review: 85

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Phase 3: Eligibility

Full-text articles excluded: 25
Reasons:
Insufficient follow-up (<2 years) (n=15)
Sample size <5 (n=7)
Non-clinical studies (e.g., mechanistic-only) (n=3)
Studies included in qualitative synthesis: 60

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Phase 4: Final List Selection

Studies included in quantitative analysis: 60
Institutional protocols: 20
Clinical outcome studies: 25
Molecular/mechanistic studies: 15

Exclusion Criteria Applied:

- Non-English studies (language bias acknowledged).
- Case reports (to maintain focus on cohort/case-series data).
- Studies with incomplete outcome data (e.g., missing follow-up).
- Sample size <5 patients (to ensure statistical relevance).

Appendix B: Risk of Bias Assessment Using ROBINS-I Tool

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to evaluate the 60 included studies. Assessments were conducted independently by two reviewers, with disagreements resolved by consensus.

Risk of Bias Domains:

Confounding: Were pre-intervention variables balanced or adjusted?
Selection: Were participants selected appropriately?
Intervention Classification: Was intervention status misclassified?
Deviations from Interventions: Were deviations from intended protocols minimal?
Missing Data: Was missing data handled appropriately?
Outcome Measurement: Were outcome assessors blinded?
Selective Reporting: Were outcomes pre-specified and fully reported?

Risk Categories:

- **Low:** Bias unlikely to alter conclusions.
- **Moderate:** Bias raises some doubt about results.
- **Serious:** Bias significantly weakens confidence in results.
- **Critical:** Bias makes results uninterpretable.

Table B1: Summary of Risk of Bias Across Studies (N=60)

Domain	Low Risk (%)	Moderate Risk (%)	Serious Risk (%)	Critical Risk (%)
1. Confounding	15% (9)	45% (27)	35% (21)	5% (3)
2. Selection	20% (12)	50% (30)	25% (15)	5% (3)
3. Intervention Classification	30% (18)	40% (24)	25% (15)	5% (3)
4. Deviations	25% (15)	50% (30)	20% (12)	5% (3)
5. Missing Data	10% (6)	35% (21)	45% (27)	10% (6)
6. Outcome Measurement	5% (3)	30% (18)	50% (30)	15% (9)
7. Selective Reporting	20% (12)	40% (24)	30% (18)	10% (6)

Key Findings:

Confounding Bias:

35% of studies (n=21) had serious risk due to unadjusted variables (e.g., lesion size, prior treatments).
Only 15% (n=9) adjusted for age and lesion type.

Missing Data:

45% of studies (n=27) had serious risk from incomplete follow-up or undocumented dropouts.

Outcome Measurement:

Only 5% (n=3) blinded outcome assessors, leading to serious risk in 50% (n=30).

Overall Risk:

Low risk: 15% (n=9), primarily modern trials (post-2010) with standardized protocols.
Moderate risk: 45% (n=27), retrospective cohorts with partial adjustment.
Serious/critical risk: 40% (n=24), older studies (pre-2000) with methodological flaws.