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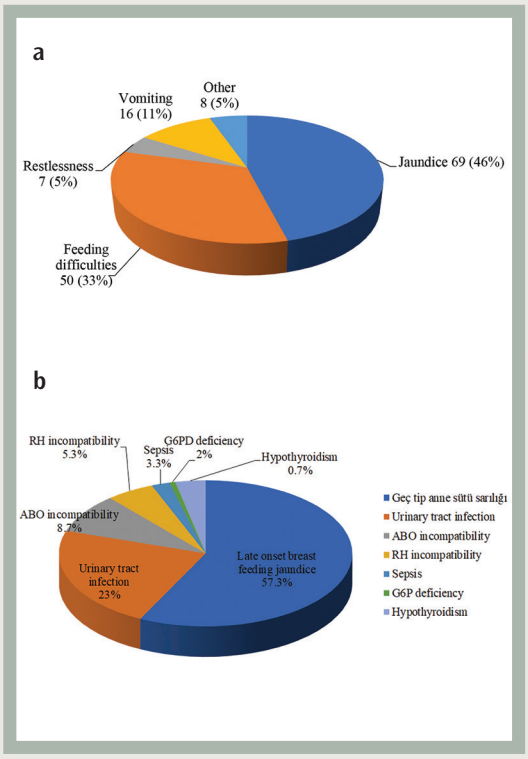


**Cover Image.** (a) Presenting complaints reported by caregivers at the time of hospital admission (b) Late-onset breast milk jaundice

*G6PD: Glucose-6-phosphate dehydrogenase*

Sinem Özdemir et al.
Prolonged Jaundice in Term Newborns: Evaluation of Etiological and Clinical Characteristics
Page Number: 52-58

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# Cost-Effectiveness of Gene and Cell Therapies: Evaluation Methods in the Single-Dose, High-Price Paradigm

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## ABSTRACT

Gene and cell therapies represent a paradigm shift in medicine, offering the prospect of durable or curative benefit from a single administration; however, they are associated with unprecedented upfront prices, routinely exceeding two to three million US dollars per patient. This combination—a one-time intervention whose clinical value accrues over a lifetime while its full cost is incurred immediately—strains the conventional methods of pharmacoeconomic evaluation and confronts payers with acute affordability and equity challenges. This review examines how the cost-effectiveness of these therapies is assessed within the single-dose, high-price paradigm and what methodological adaptations the paradigm demands. We first describe the economic distinctiveness of one-time therapies and the core analytic problems they raise: the profound uncertainty about the durability of effect; the reliance on single-arm trials and surrogate endpoints; the disproportionate influence of the discount rate; and the limitations of the quality-adjusted life-year (QALY) in capturing value for severe, rare paediatric conditions. We then synthesise the published economic evidence through detailed case studies of spinal muscular atrophy (onasemnogene abeparvovec) and Duchenne muscular dystrophy (delandistrogene moxeparvovec), and through further exemplars in chimeric antigen receptor T-cell therapy, haemophilia, and sickle-cell disease and β-thalassaemia. Reported incremental cost-effectiveness ratios vary enormously—from dominant or highly cost-effective to several million euros per QALY—driven chiefly by assumptions about durability, comparator cost, and discounting. We review novel financing and access mechanisms, including outcomes-based agreements, annuity payments, and public access models, and situate the discussion within the context of divergence in international health technology assessment, recent market withdrawals, and the Turkish reimbursement environment. Robust, transparent, and durability-sensitive economic evaluation, coupled with innovative payment models, will be essential to reconcile access with sustainability.

**Keywords:** Gene therapy, cell therapy, cost-effectiveness analysis, spinal muscular atrophy, Duchenne muscular dystrophy, health technology assessment

## Introduction

Gene and cell therapies—often grouped, particularly in Europe, under the regulatory heading of advanced therapy medicinal products (ATMPs)—have moved from experimental promise to clinical reality with remarkable speed. In 2024 alone the US Food and Drug Administration approved nine new cellular and gene therapy products, spanning oncology, haematology, neurology, and inherited genetic disorders (1). These therapies differ fundamentally from conventional pharmaceuticals. Rather than modifying the disease through chronic administration, they aim to correct or compensate for the underlying genetic defect through a single

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CAM & SAKURA MEDICAL JOURNAL

intervention, offering the prospect of durable and, in some cases, curative benefit. This therapeutic promise, however, is inseparable from an economic one: a one-time treatment that replaces years or decades of chronic therapy and is delivered at a price that reflects the displaced lifetime value in a single invoice.

The magnitude of these prices is unprecedented in medicine. Onasemnogene abeparvovec (Zolgensma) for spinal muscular atrophy (SMA) entered the market in 2019 at approximately US$2.1 million, then the most expensive drug in the world; delandistrogene moxeparvovec (Elevidys) for Duchenne muscular dystrophy (DMD) was subsequently priced above US$3 million; the haemophilia gene therapy etranacogene dezaparvovec reached roughly US$3.5 million; and the gene-edited sickle-cell and β-thalassaemia therapies exagamglogene autotemcel (Casgevy) and lovotibeglogene autotemcel (Lyfgenia) carry list prices of approximately US$2.2 million and US$3.1 million respectively (2,3). For health systems accustomed to evaluating incremental therapies costing thousands of dollars per year, these figures represent a categorical, rather than merely quantitative, departure.

This departure creates a distinctive analytic problem for pharmacoeconomics. The discipline's standard tool, cost-effectiveness analysis (CEA), compares the incremental cost of an intervention with its incremental health benefit and is most often expressed as the incremental cost-effectiveness ratio (ICER), reported as cost per quality-adjusted life-year (QALY). When benefits accrue over a lifetime but costs are incurred at a single moment, and when the durability of those benefits is genuinely uncertain because the therapies are so new, the resulting ICER becomes exquisitely sensitive to modelling assumptions that conventional short-course therapies never tested so severely (4,5). Simultaneously, even a therapy that is cost-effective by conventional thresholds may be unaffordable when its entire cost falls in a single budget year for a cohort of patients, decoupling cost-effectiveness from budget impact in ways that challenge payers directly (6).

This review addresses how the value of gene and cell therapies is assessed within this single-dose, high-price paradigm, with particular attention to the exemplary neuromuscular conditions, SMA and DMD, where gene therapy has advanced furthest and generated the richest economic literature. We examine the economic distinctiveness of one-time therapies, the methodological challenges of their evaluation, the published cost-effectiveness evidence across therapeutic areas, the novel payment models developed in response to them, and the international and Turkish policy context. The aim is to provide clinicians, pharmacologists, and health-policy researchers with an integrated understanding of both the analytic methods and their real-world consequences for patient access.

### Literature Search

This article is a narrative review, and the supporting evidence was identified through a structured but non-systematic literature search. We searched PubMed/MEDLINE, Embase, and the Cochrane Library, supplemented by Google Scholar and targeted screening of the grey literature, including health technology assessment (HTA) reports from bodies such as the National Institute for Health and Care Excellence (NICE) and the Institute for Clinical and Economic Review (ICER). The search covered publications from January 2010 to June 2026, and no lower date restriction was applied to foundational methodological references. Search terms combined the concepts of therapies and economic evaluation—including "gene therapy," "cell therapy," "advanced therapy medicinal products," "cost-effectiveness analysis," "quality-adjusted life-year," "incremental cost-effectiveness ratio," "health technology assessment," and "outcomes-based agreement"—with the names of specific conditions and products, such as SMA, onasemnogene abeparvovec, DMD, delandistrogene moxeparvovec, chimeric antigen receptor T-cell (CAR-T) therapy, haemophilia, and sickle-cell disease. We prioritised English-language, peer-reviewed economic evaluations, systematic reviews, and authoritative HTA or policy documents that were most relevant to the single-dose, high-price paradigm, and we hand-searched the reference lists of included articles to identify further sources. Given the narrative design, no formal risk-of-bias appraisal or quantitative meta-analysis was undertaken.

### The Economic Distinctiveness of One-Time Therapies

The defining economic feature of gene and cell therapies is the temporal separation of cost and benefit. A single administration generates a stream of health gains—averted disease progression, avoided complications, extended survival, and, critically, avoided expensive chronic therapies—that may extend across a patient's entire life. However, the full acquisition cost is realised immediately. In conventional pharmacoeconomic terms, this means that the value proposition of a one-time therapy rests almost entirely on two quantities that are, at the point of launch, deeply uncertain: the durability of the clinical effect and the cost of the standard of care it displaces (4,7).

Durability is the primary source of uncertainty. If the effect of a gene therapy persists for life, its lifetime value may be substantial, potentially justifying a high price by offsetting decades of chronic treatment. If the effect wanes after several years, such that re-treatment or a return to chronic therapy is required, the value collapses. Because these therapies are recent, long-term follow-up is typically unavailable at the time of assessment, and analysts must extrapolate from a few years of trial data across a lifetime horizon (5,7). A systematic review of CEA of haemophilia gene therapies found that favourable results were driven overwhelmingly by the assumption that the therapeutic effect would remain durable for at least ten years, offsetting the high cost of standard factor-replacement or emicizumab therapy; when durability assumptions were relaxed, modelled value fell substantially (8).

The cost of the displaced standard of care is the second determinant, and it explains much of the variation in reported cost-effectiveness across conditions. Where the chronic alternative is itself extraordinarily expensive—such as nusinersen for SMA, which requires repeated intrathecal dosing indefinitely—a one-time therapy can appear cost-effective or even cost-saving despite its high price, because it avoids a still larger cumulative expenditure (9). Where the standard of care is comparatively inexpensive, as in some sickle-cell populations, budget-neutrality over realistic contract horizons becomes far harder to achieve even when the therapy delivers major health gains (3). The economic case for a one-time therapy is thus as much a statement about the counterfactual it replaces as about the therapy itself.

## Methodological Challenges in Economic Evaluation

The single-dose, high-price paradigm exposes several methodological pressure points in conventional CEA, summarised in Table 1; evaluations of these therapies should in turn adhere to established reporting standards to ensure transparency and cross-study comparability (10).

### Durability and Extrapolation

Given only short-term trial data, analysts must select extrapolations of survival and effect persistence over a lifetime. The choice of parametric survival model, the assumed waning of effect, and the handling of re-treatment can swing the ICER dramatically. Good practice, as articulated by value-assessment bodies, is to present both optimistic and conservative durability scenarios rather than a single point estimate, and to make the durability assumption explicit and central to the analysis (5,11).

### Discounting

Because benefits are delayed relative to costs, the discount rate exerts an unusually large influence on the cost-effectiveness of one-time therapies; sensitivity analyses repeatedly identify it as among the most influential parameters (5). This has prompted debate about whether a lower or differential discount rate should apply to therapies with durable, front-loaded costs and back-loaded benefits. The prevailing methodological view is that there is insufficient theoretical justification for a gene-therapy-specific discounting rule, and that any change to discounting should be applied consistently across technologies rather than selectively; nonetheless, the sensitivity of results to this choice must be transparently reported (5,12).

### Single-arm Trials and Surrogate Endpoints

Many pivotal gene-therapy trials are single-arm studies in small rare-disease populations, using surrogate endpoints such as motor-milestone achievement or biomarker expression rather than long-term functional or survival outcomes (13,14). This complicates the estimation of comparative effectiveness and forces reliance on naive or matched comparisons with natural-history or standard-of-care cohorts, introducing bias and uncertainty into the incremental benefit that underpins the ICER (14).

**Table 1. Methodological challenges in evaluating one-time gene and cell therapies and mitigating approaches**

| Challenge | Why it matters | Mitigating approach |
|---|---|---|
| Durability uncertainty | Value depends on whether effect lasts a lifetime | Optimistic and conservative durability scenarios; registries |
| Discounting | Delayed benefit vs. immediate cost makes ICER highly rate-sensitive | Transparent sensitivity analysis; consistent cross-technology rules |
| Single-arm trials/surrogates | Weak comparative and long-term evidence | Matched natural-history comparisons; post-approval data |
| QALY limitations | Under-captures severity, rarity, family spillover | Alternative metrics (e.g., equal-value life-years); societal weights |
| Perspective | Payer view omits caregiver/productivity benefit | Report payer and societal perspectives |
| Affordability vs. cost-effectiveness | Concentrated cost causes budget shock | Budget impact analysis; novel payment models |

*QALY: Quality-adjusted life-year, ICER: Incremental cost-effectiveness ratio*

### Valuing Benefit: the QALY and Its Limits

The QALY, the standard measure of health benefit, has recognised limitations when applied to severe, rare, and often paediatric conditions. Eliciting utilities in infants is methodologically difficult; conventional cost-effectiveness thresholds may not reflect societal preferences for treating very severe or ultra-rare diseases; and the QALY may inadequately capture value elements such as the value of hope, family spillover effects, and the option value of survival. Some analysts have adopted alternative or supplementary metrics, such as equal-value life-years gained, to mitigate concerns that conventional QALY-based valuation systematically undervalues therapies for the most severely affected (6,12,15).

### Perspective and Cost Offsets

The perspective of the analysis—the healthcare payer perspective versus the broader societal perspective—materially affects results because gene therapies often generate substantial non-medical benefits, including averted caregiver burden and preserved productivity, that a narrow payer perspective excludes. Analyses that adopt a societal perspective frequently yield more favourable results, and in some cases render a therapy dominant, than those confined to direct healthcare costs (12). Transparency about perspective, and ideally the presentation of multiple perspectives, is therefore essential.

### Case Study: Spinal Muscular Atrophy

SMA, a leading inherited cause of infant mortality resulting from biallelic loss of the *SMN1* gene, has become the paradigmatic testing ground for the economics of gene therapy. Three disease-modifying therapies now exist: the antisense oligonucleotide nusinersen and the small molecule risdiplam, both requiring chronic administration, and the one-time gene-replacement therapy onasemnogene abeparvovec (16). The pivotal single-dose gene-replacement trials transformed the natural history of the most severe infantile form, and evidence increasingly indicates that outcomes are best when treatment is initiated pre-symptomatically, often following newborn screening (13,17).

The economic evaluations of onasemnogene abeparvovec illustrate the central themes of this review. An early US CEA modelling the gene therapy against nusinersen in SMA type 1 estimated undiscounted lifetime survival of 37.2 vs. 9.7 life-years and found the gene therapy cost-effective across a price range of US$2.5–5.0 million, with ICERs ranging from dominant (cost-saving) to approximately US$31,000 per QALY—results driven by the avoidance of the very high lifetime cost of chronic nusinersen (9). In the United Kingdom, the NICE appraised onasemnogene abeparvovec for pre-symptomatic SMA through its highly specialised technology programme; using a confidential discounted price, both the company and the external assessment group produced ICERs below £100,000 per QALY, and the therapy was recommended subject to a commercial access arrangement (18). Analyses of newborn screening for SMA, which enables the pre-symptomatic treatment associated with the greatest benefit, have found screening to be dominant—improving outcomes while saving costs—from a hospital-payer perspective (17).

The contrast with the chronic comparator is instructive. A comparative analysis of nusinersen reimbursement across eleven jurisdictions found ICERs ranging from roughly €465,000 to €6.4 million per QALY for early-onset SMA and up to €10.6 million per QALY for later-onset disease; despite none of these estimates meeting conventional cost-effectiveness thresholds, every jurisdiction reimbursed the drug, most through managed-entry agreements (19). This experience demonstrates that for severe, ultra-rare paediatric conditions, formal cost-effectiveness has often not been the binding constraint on access; instead, negotiated agreements and explicit societal valuation of severity and rarity have driven positive decisions—an environment into which one-time gene therapies now enter, bringing their own distinctive economics.

### Case Study: Duchenne Muscular Dystrophy

DMD, an X-linked disorder caused by mutations in the dystrophin gene that lead to progressive muscle degeneration, respiratory failure, and cardiomyopathy, has followed SMA into the gene-therapy era, albeit with a more contested evidence base. Corticosteroids remain the standard of care and the most cost-effective and best-evidenced treatment, supplemented by exon-skipping oligonucleotides and, more recently, the micro-dystrophin gene therapy delandistrogene moxeparvovec, approved through an accelerated pathway on the basis of surrogate biomarker expression (20). The accelerated approval of several DMD therapies on surrogate endpoints, sometimes with uncertain demonstrated clinical benefit, exemplifies the tension between rapid access and robust value demonstration that pervades this field (20).

An early US CEA of delandistrogene moxeparvovec estimated that the therapy added approximately 10.3 discounted (26.4 undiscounted) equal-value life-years relative to standard care, and used threshold analysis—rather than an established price, which was not yet set—to estimate a maximum value-based treatment cost of approximately US$5 million at a willingness-to-pay of US$500,000 per equal-value life-year gained (21). The use of equal-value life-years

and an elevated threshold reflects deliberate methodological choices intended to accommodate the severity and rarity of DMD and illustrates how the analytic framework itself becomes a locus of value judgment in this setting. Because the therapy's price subsequently exceeded US$3 million and its clinical benefit remains debated, DMD has become a focal case for the broader question of whether accelerated approval on surrogate endpoints can be reconciled with the durable clinical benefit that high one-time prices implicitly presuppose (20,21).

### Further Exemplars: CAR-T, Haemophilia, and Haemoglobinopathies

Beyond neuromuscular disease, the economics of one-time and short-course cellular and gene therapies have been examined across several fields, with widely divergent conclusions (Table 2).

### CAR-T Therapies

Tisagenlecleucel was among the first CAR-T products to reach approval, having demonstrated durable remissions in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia in the pivotal ELIANA trial (22), and CAR-T therapies have since been evaluated economically across a widening range of haematological malignancies. For relapsed or refractory diffuse large B-cell lymphoma, a US analysis found second-line axicabtagene ciloleucel cost-effective at a US$150,000-per-QALY threshold, with an ICER of approximately US$99,000 per QALY, while second-line tisagenlecleucel was dominated by standard care and third-line-or-later tisagenlecleucel yielded an ICER of approximately US$127,000 per QALY (23). In a Chinese healthcare-system analysis, by contrast, CAR-T therapies were not cost-effective at the local willingness-to-pay threshold in any line of therapy, with price reduction identified as the principal lever for achieving value (24). This divergence underscores how cost-effectiveness is contingent on local prices, thresholds, and comparators, rather than an intrinsic property of a technology.

### Haemophilia

The one-time gene therapies valoctocogene roxaparvovec (haemophilia A) and etranacogene dezaparvovec (haemophilia B) displace lifelong prophylactic factor replacement therapy or emicizumab, which are among the most expensive chronic treatments in medicine. A systematic review of published analyses concluded that, despite their high upfront cost, all identified studies modelled the gene therapies as producing lower overall costs and better outcomes than standard care—provided the therapeutic effect remained durable for at least a decade—and recommended outcomes-based agreements to manage the residual durability risk to payers (8).

### Sickle-cell Disease and β-thalassaemia

The gene-edited therapy exagamglogene autotemcel, the first CRISPR-based therapy approved, and the lentiviral therapy lovotibeglogene autotemcel offer potentially transformative benefit in sickle-cell disease (14). A US analysis of exagamglogene autotemcel estimated a substantial survival gain and an ICER of approximately US$16,800 per QALY from the payer perspective, with the therapy dominant from a societal perspective, driven by large reductions in vaso-occlusive events and disease-related costs (25). Yet a Medicaid-focused payment-model analysis showed that, because the annual cost of standard care for sickle-cell disease is relatively modest, achieving budget neutrality over a realistic six-year contract is unlikely even with outcomes-based rebates; such rebates were nonetheless estimated to save on the order of US$260,000-370,000 per patient, illustrating the gap between long-run cost-effectiveness and short-run affordability (3).

### Novel Payment and Access Models

The disjunction between cost-effectiveness and affordability, together with uncertainty about durability, has stimulated a wave of innovation in payment and access mechanisms designed to share financial risk between manufacturers and payers (Table 3). Outcomes-based agreements tie payment to the realisation of pre-specified

**Table 2. Selected cost-effectiveness findings for gene and cell therapies (illustrative; prices approximate list prices)**

| Therapy (indication) | Approx. price | Key economic finding |
|---|---|---|
| Onasemnogene abeparvovec (SMA) | ~US$2.1M | ICER dominant to ~US$31k/QALY vs. nusinersen; NBS dominant (9,17,18) |
| Delandistrogene moxeparvovec (DMD) | >US$3M | ~10.3 discounted evLYs; value-based max ~US$5M at US$500k/evLYG (21) |
| Axicabtagene ciloleucel (2L DLBCL) | ~US$0.4M | ICER ~US$99k/QALY; cost-effective at US$150k threshold (23) |
| Haemophilia A/B gene therapies | ~US$3.5M | Lower lifetime cost + better outcomes if durable ≥10 years (8) |
| Exagamglogene autotemcel (SCD) | ~US$2.2M | ICER ~US$16.8k/QALY (payer); dominant (societal) (25) |

*QALY: Quality-adjusted life-year, ICER: Incremental cost-effectiveness ratio, SMA: Spinal muscular atrophy, NBS: Newborn screening, DMD: Duchenne muscular dystrophy, evLYs: Equal-value life-years, evLYG: Equal-value life-year gained, 2L: Second-line, DLBCL: Diffuse large B-cell lymphoma, SCD: Sickle cell disease*

**Table 3.** Novel payment and access models for one-time therapies

| Model | Mechanism | Rationale |
|---|---|---|
| Outcomes-based agreement | Payment tied to achieved clinical outcomes | Shares durability risk with manufacturer |
| Annuity/instalment | Cost spread over several years | Aligns payment with benefit accrual; eases budget shock |
| Subscription ("Netflix") | Fixed fee for defined population access | Predictable budgeting for payer |
| Coordinated public access model | Standardised outcomes-based purchasing across payers | Equity and negotiating scale (3) |

clinical outcomes over time, so that payers recover value if a therapy fails to deliver durable benefit; such agreements have been proposed and piloted for sickle-cell and haemophilia gene therapies, and are supported by analyses showing meaningful payer savings contingent on therapy performance (3,8). Annuity or instalment models spread the one-time cost over several years, aligning payment with the accrual of benefit and mitigating the single-year budget shock, though they raise practical complications around patient mobility between insurers and accounting treatment (7,26).

Broader systemic approaches have also emerged, including subscription or "Netflix"-style arrangements for defined populations and coordinated public access models. In the United States, a public gene-therapy access model has been developed to standardise outcomes-based purchasing of sickle-cell therapies across state Medicaid programmes, leveraging real-world data to define eligible populations and structure agreements (3). Underpinning several of these proposals is the observation that the value of a durable one-time therapy, appropriately discounted and measured against an expensive chronic comparator, may be greater than intuition suggests—reframing the pricing debate from sticker shock toward risk-sharing and value-based contracting (7). The common thread is a shift from a single upfront transaction toward mechanisms that couple payment to demonstrated durable performance.

### Health Technology Assessment, International Divergence, and Access

The assessment and reimbursement of gene and cell therapies vary markedly across jurisdictions, reflecting differences in willingness-to-pay thresholds, methods for valuing severity and rarity, budget constraints, and appetite for managed-entry agreements. The same therapy may be judged cost-effective in one system and unaffordable in another, and the divergence has real consequences for patient access (19,24). A recent analysis of pricing and reimbursement policies across Europe found that heterogeneous HTA and managed-entry-agreement processes contribute to delayed, unequal, or absent access to cell and gene therapies across member states, exacerbating cross-country health inequalities (27). Several agencies have adapted their processes for ultra-orphan and one-time therapies—through highly specialised technology programmes, elevated thresholds, and confidential commercial arrangements—but no international consensus exists on how to value durable one-time benefit (18).

The fragility of access under these conditions has been demonstrated starkly by market withdrawals. Bluebird bio withdrew its approved gene therapies, including the β-thalassaemia therapy betibeglogene autotemcel (Zynteglo) and the cerebral adrenoleukodystrophy therapy elivaldogene autotemcel (Skysona), from the European market, citing an inability to reach reimbursement agreements with European payers whose frameworks, the company argued, had not evolved to recognise the innovation and expected lifelong benefit of such products (2). These withdrawals illustrate that a therapy can secure regulatory approval yet fail commercially where value-assessment and payment frameworks cannot accommodate its economics, leaving patients without access despite proven efficacy—a cautionary lesson for any health system designing its approach to ATMPs.

### The Turkish Context

In Türkiye, the arrival of gene and cell therapies coincides with an already-strained environment for rare diseases and orphan drugs. Türkiye operates a positive-list reimbursement system in which the Social Security Institution makes coverage decisions, pricing is anchored to an international reference-pricing mechanism, and a mandatory pharmacoeconomic evaluation is required of manufacturers for most products. Orphan drugs, however, have historically been exempted from the formal requirement for pharmacoeconomic analysis, and access to some very-high-cost therapies has been facilitated through mechanisms for importing medicines from abroad. The single-dose, multi-million-dollar economics of gene therapies pose a profound challenge to this system: reference pricing provides little traction for therapies with few or no international comparators; a single cohort of patients can

impose a severe budget shock; and methodological capacity to evaluate durability-dependent lifetime models is still developing.

The international experience reviewed here suggests several priorities for the Turkish setting. Managed-entry agreements and outcomes-based agreements, already available in principle through Türkiye's alternative reimbursement framework, are likely to be indispensable for reconciling access with affordability and managing durability risk. Investment in local real-world data infrastructure would enable the tracking of long-term outcomes on which such agreements depend and reduce reliance on transferred assumptions whose local validity is uncertain. Building HTA capacity to construct and critically appraise lifetime decision-analytic models for one-time therapies and developing explicit, transparent frameworks for valuing severity and rarity would strengthen the legitimacy and consistency of decision-making. As a middle-income country with a large, centralised social-insurance system, Türkiye faces acute affordability pressures, yet possesses institutional structures through which coordinated, value-based purchasing of gene therapies could be organised.

### Challenges and Future Perspectives

Several challenges will shape the evolution of the economics of gene and cell therapies. The foremost remains durability: as long-term follow-up accumulates, the wide uncertainty bands that currently dominate cost-effectiveness estimates should narrow, and analyses will increasingly be able to replace assumption with evidence (5,8). The endpoints problem is equally pressing; the reliance on surrogate markers and single-arm designs, particularly under accelerated approval, means that economic models often rest on incompletely demonstrated clinical benefit, and post-approval evidence generation through registries and real-world data will be central to resolving this (14,20). Methodologically, the field must continue to refine the handling of discounting, perspective, and the valuation of benefit for severe rare disease, ideally converging on transparent, standardised approaches rather than bespoke, therapy-specific rules that invite inconsistency (5,12,15).

The affordability challenge is distinct from and will outlast the cost-effectiveness challenge. Even therapies that are demonstrably cost-effective can overwhelm budgets when their cost is concentrated in time and cohort, and the continued development of payment models—outcomes-based agreements, annuities, and coordinated public purchasing—will be essential to translate favourable value into sustainable access (3,7,26). The market withdrawals seen in Europe are a warning that misalignment between value frameworks and therapy economics harms patients directly (2). Looking forward, as manufacturing costs fall, indications broaden, and competition emerges, prices may moderate and the affordability calculus may ease, but the central analytic task—valuing durable, front-loaded benefit under uncertainty—will remain. Meeting it will require close collaboration among clinical pharmacologists, health economists, regulators, and payers.

## Conclusion

Gene and cell therapies embody one of the most consequential developments in modern medicine and simultaneously represent one of the most challenging problems in pharmacoeconomics. Their single-dose, high-priced structure severs the familiar link between cost and time, concentrating expenditure at a single moment while dispersing benefits—and uncertainty—across a lifetime. The published evidence, spanning SMA, DMD, CAR-T therapies, haemophilia, and the haemoglobinopathies, indicates that these therapies can be cost-saving or exceed conventional cost-effectiveness thresholds substantially, with conclusions depending primarily on durability, the cost of the displaced comparator, discounting, and perspective. Realising the promise of these therapies without destabilising health-system finances will require economic evaluations that are durability-sensitive, transparent about their assumptions, and honest about uncertainty, and payment models that share risk and align payment with demonstrated performance. For Türkiye and comparable systems, the priorities are managed-entry agreements, real-world data infrastructure, and HTA capacity. The single-dose, high-priced paradigm is not a transient anomaly but the leading edge of a durable shift in therapeutics, and the methods used to value it will help determine which patients benefit from it.

### Ethics

**Ethics Committee Approval:** Not required.

**Informed Consent:** Not required.

### Footnotes

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# Randomized, Double-Blind, Controlled Trial of Nebulized Budesonide, Epinephrine and Salbutamol in Infants with Acute Bronchiolitis

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### What is known on this subject?

Acute bronchiolitis remains a leading cause of pediatric lower respiratory tract infections, characterized by a highly variable clinical course. While it is a common diagnosis, the optimal management strategy is still a matter of significant debate. In particular, the clinical utility and therapeutic benefit of bronchodilators remain uncertain, leading to substantial variations in clinical practice.

### What this study adds?

This study establishes that nebulized salbutamol, epinephrine, and budesonide provide no significant therapeutic advantage over normal saline in the management of infants with mild bronchiolitis. Comparative analysis reveals that while long-term outcomes remain unaffected, nebulized salbutamol may offer a modest clinical benefit in achieving short-term symptomatic improvement compared to other nebulized modalities.

## ABSTRACT

**Objective:** Acute bronchiolitis is a leading cause of lower respiratory tract infections, and a wide range of clinical symptoms from mild cough to severe respiratory distress can be seen during the disease course. The optimal treatment for bronchiolitis has been controversial; the role of bronchodilators in the treatment of bronchiolitis is uncertain. The aim of this study was to evaluate the efficacy of nebulized therapies with control groups in the treatment of acute bronchiolitis.

**Material and Methods:** A prospective, randomized, and double blinded study was conducted among the infants diagnosed with acute bronchiolitis in a tertiary children's hospital. Heart rate, respiratory rate (RR), oxygen saturation by pulse oximetry, respiratory distress assessment instrument and side effects were recorded in the follow-up form.

**Results:** A total of 60 infants (66% male) diagnosed with acute bronchiolitis were included into the study. The median age of the patients at admission was 6.5 (3.5-9.5) months, and the median duration time of prodromal symptoms was 5.5 (3-7) days and wheezing symptoms was 3 (2-5) days. The baseline characteristics were similar in all groups ($p>0.05$). The outcome of patients at 120$^{th}$ minute was found to be significantly better than the baseline values ($p<0.05$). However, RR was improved statistically significantly at 30$^{th}$ minute in the salbutamol group ($p=0.031$). No serious side effects were observed in any patient during the follow-up.

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## ABSTRACT

**Conclusion:** The effectiveness of nebulized salbutamol, epinephrine, budesonide and normal saline treatments were not different in infants with mild bronchiolitis; however, nebulized salbutamol was found to be a little bit more effective in short-term improvement.

**Keywords:** Bronchiolitis, budesonide, epinephrine, infants, pediatrics, salbutamol

## Introduction

Acute bronchiolitis is a major cause of lower respiratory tract infection in children under two years of age, with the highest incidence observed during infancy. The disease is characterized by inflammation of the small airways, resulting in airflow limitation due to mucosal edema, increased mucus production, and epithelial cell injury. A distinct seasonal pattern has been described, with case numbers rising predominantly in the winter and early spring months (1,2,3). Viral pathogens account for the majority of cases, with respiratory syncytial virus (RSV) identified as the leading causative agent in infants (3,4).

Bronchiolitis is among the most frequent reasons for presentation to pediatric emergency departments (EDs) due to respiratory distress in this age group (5). Although the clinical course is often self-limiting, some patients may develop severe, potentially life-threatening respiratory compromise. After an initial prodromal phase lasting approximately two to four days and characterized by fever, rhinorrhea, and nasal congestion, affected infants may experience progressive respiratory symptoms, including cough, wheezing, and tachypnea. Current management strategies are primarily supportive and focus on ensuring adequate oxygenation, maintaining hydration, and providing appropriate nutritional support (6,7).

Despite the absence of definitive evidence demonstrating a clear clinical benefit, inhaled pharmacological therapies such as salbutamol, epinephrine, and corticosteroids have been widely used in the treatment of acute bronchiolitis. However, clinical trials and meta-analyses evaluating these interventions have produced inconsistent findings regarding their efficacy and comparative advantages (8).

Although acute bronchiolitis can result in significant morbidity, no therapeutic intervention has been conclusively shown to reduce disease severity, shorten symptom duration, or decrease hospital length of stay. Nevertheless, nebulized treatments remain frequently employed in clinical practice. Accordingly, the present study aimed to compare the clinical effectiveness and potential adverse effects of nebulized salbutamol, epinephrine, and budesonide to those observed in a control group among infants admitted to the pediatric ED with a diagnosis of acute bronchiolitis.

## Material and Methods

### Study Population

This study was conducted in the pediatric ED of Bakırköy Maternity and Children's Diseases Training and Research Hospital, where the participating physicians had previously been employed. That study was a prospective, randomized, double-blind, controlled trial; all patients enrolled in the study had a first or second episode of acute bronchiolitis. Sixty children aged between 1 and 24 months who were diagnosed with acute bronchiolitis were admitted to our pediatric ED and recruited to the study during a two-month period from November to December. The Ethics Committee of Bakırköy Maternity and Children's Training and Research Hospital approved the study (approval number: 147 date: 11.07.2008), and verbal informed consent was obtained from the parents of patients.

### Exclusion Criteria

- >2 attacks of bronchiolitis
- Any prior symptoms or documented history of atopic diseases (atopic dermatitis, asthma)
- Family history of asthma
- Presence of two of the following criteria: Allergic rhinitis, presence of wheezing and cough between attacks (with effort), eosinophilia (4%), specific immunoglobulin E (IgE) positivity and male gender
- Patients with congenital heart disease, chronic lung disease or immunodeficiency
- History of preterm birth
- Presence of cough more than 7 days or pneumonia
- Presence of any of the following criteria: Oxygen saturation by pulse oximetry ($SaO_2$, on admission ≤91%) and/or respiratory rate (RR) >100/minute and/or heart rate (HR) >200/minute and/or fever >38.5 °C (axillary)
- Patients who require mechanical ventilation
- Patients who received nebulizer treatment prior to admission
- Parents who refused to be a participant for the study.

### Study Design

Age, gender, weight, and other demographic information of the patients (duration of prodromal symptoms and wheezing, tobacco exposure, gestational age, presence of prior treatment etc.), and physical examination findings, HR, RR, presence of retraction and wheezing, $SaO_2$, clinical RDAI (respiratory distress assessment instrument) (Table 1) were recorded on the study follow-up form.

The selected patients were randomly assigned to four groups to receive blinded treatment with nebulized budesonide, epinephrine, salbutamol, or 0.9% saline (control group). Randomization of the participants to receive each treatment was performed using a table of random numbers prepared by the ED physician, and codes were assigned to each drug. Both parents and the attending physician were absent during the preparation of the drugs. The attending physician who completed the follow-up forms and assigned the clinical scores was blinded to the patients received to avoid bias.

The ED physician calculated the drug doses for each patient: budesonide 0.5 mg/dose (9), salbutamol 0.15 mg/kg/dose (minimum 1.25 mg/dose) (10), and epinephrine 3 mg/dose (11). All drugs were diluted to a 5 mL dose with normal saline (NS), and the control group received 5 mL/dose of NS. Because all study drugs were colorless and odorless, the study drugs were similar in appearance and smell. The study drugs were prepared by the ED nurse and were administered in two nebulized doses at 30-minute intervals under the supervision of the ED physician.

### Measurements

Viral etiology testing for RSV antigen was performed on nasopharyngeal specimens. Complete blood count and specific IgE tests for cow's milk and egg white were also obtained.

The RDAI scoring system was developed by Lowell et al. (12) (Table 1). The scores range between 0 and 17 and are based on wheezing and respiratory retractions. Patients RDAI scores fewer than 3 were considered clinically mild bronchiolitis, whereas patients RDAI scores greater than 15 were regarded as severe bronchiolitis and excluded from the study (12).

The attending physician examined the infants initially and at 30$^{th}$, 60$^{th}$, and 120$^{th}$ minutes, assessed HR, RR (breaths/minute), $SaO_2$, RDAI score and the presence of side effects (hyperactivity, muscle tremor, vomiting) that may occur during drug administration and recorded at the follow-up form. At the second hour of the study period if the patient's clinical score was ≤3, $SaO_2$ >%95 without supplemental $O_2$ and those without any signs of respiratory distress and feeding difficulty were discharged from the emergency room. Patients who did not meet these criteria continued to receive supportive treatment in the ED, outside the study.

### Statistical Analysis

Statistical analyses were conducted using SPSS® software (version 22.0 for Windows). Descriptive statistics were applied to summarize the data. Continuous variables were presented as mean ± standard deviation for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. Categorical variables were reported as frequencies and percentages with corresponding 95% confidence intervals (95%), and group comparisons were performed using the chi-square test. Univariate analyses were carried out to examine the associations between demographic and clinical variables and clinical outcome scores, using the Mann–Whitney U test with Bonferroni correction, the chi-square test, or the Kruskal–Wallis test, as appropriate. Repeated measurements were analyzed using the Wilcoxon signed-rank test. A p value <0.05 was considered statistically significant.

**Table 1.** **Respiratory distress assessment instrument (12)**

| | 0 | 1 | 2 | 3 | 4 | Maximum points |
|---|---|---|---|---|---|---|
| **Wheezing** | | | | | | |
| Expiration | None | End | 1/2 | 3/4 | All | 4 |
| Inspiration | None | Part | All | - | - | 2 |
| Location | None | Segmental | Diffuse | - | - | 2 |
| **Retractions** | | | | | | |
| Supraclavicular | None | Mild | Moderate | Marked | | 3 |
| Intercostal | None | Mild | Moderate | Marked | - | 3 |
| Subcostal | None | Mild | Moderate | Marked | - | 3 |
| Total | - | - | - | | | 17 |

## Results

### Characteristics of the Study Population

A total of 60 children (66% male) who were diagnosed with acute bronchiolitis were enrolled in the study. The median (IQR) age of the patients at admission was 6.5 (3.5-9.5) months. The median (IQR) durations of the prodromal period and of wheezing symptoms were 5.5 (3-7) and 3 (2-5) days, respectively.

There was no difference among the groups in terms of gender, age, weight, tobacco exposure, previous treatments (symptomatic treatments such as antipyretics and nasal cleansing), RSV positivity, the duration of the prodromal period, and wheezing symptoms ($p>0.05$) at enrollment. The demographic and general characteristics of the patients, with comparisons between groups are depicted in Table 2.

Initial values of RDAI scores, HR, $SaO_2$, and RR on admission are shown in Table 3. There were no significant differences among the groups before the initial nebulized treatment ($p>0.05$), indicating that the treatment groups were similar.

### Time-Dependent Changes in Clinical Scores

The treatment groups were compared with each other to assess time dependent changes in terms of HR, $SaO_2$, RDAI values, and no significant difference was found. The values also did not differ among the groups at 30, 60, and 120 minutes.

When we compared the groups after administration of nebulized salbutamol, epinephrine, budesonide, and NS at the 30$^{th}$, 60$^{th}$, and 120$^{th}$ minutes, RR improved significantly at the 30$^{th}$ minute in the salbutamol group ($p=0.031$). However, there were no statistically significant differences at the 60$^{th}$ and 120$^{th}$ minutes among the study groups (Table 3).

The time-dependent curve of RDAI, HR, $SaO_2$, and RR values among the groups at the beginning, 30$^{th}$ minute, 60$^{th}$ minute, and 120$^{th}$ minute of the treatment is depicted in Figure 1a-d.

The treatment groups were compared with their baseline values and with the values at the 30$^{th}$, 60$^{th}$, and 120$^{th}$ minutes in terms of RDAI scores, HR, and RR. A statistically significant difference was found in the improvement of RDAI scores and RR across all the treatment groups between baseline and 120 minutes after nebulized treatment. In contrast, were no differences between $SaO_2$ and HR values at any time (Table 4).

### Comparison of the Treatment Groups

The treatment groups were compared pairwise with each other and with the placebo group; RR was significantly lower in the salbutamol group than in the placebo group at the 120$^{th}$ minute ($p=0.01$) (Figure 1c). However, there were no statistically significant differences in RDAI scores, HR, or $SaO_2$ at 30, 60, and 120 minutes.

### Side Effects

Patients in the study were also monitored for side effects during the nebulized treatment. No serious side effects were observed in any patient during the follow-up. Oxygen and intravenous (IV) fluid treatment were required for seven patients in the budesonide group, and one patient experienced vomiting. One patient in the salbutamol group also had vomiting. Five patients in the epinephrine group needed supplemental $O_2$ and IV fluid therapy. Supplemental $O_2$ and IV fluid requirements were observed in seven cases in the NS group.

**Table 2. Comparison of the clinical features of nebulized budesonide, salbutamol, epinephrine and control groups**

| | Budesonide (n=16) | Salbutamol (n=15) | Epinephrine (n=15) | Control (n=14) | p |
|---|---|---|---|---|---|
| **Gender (male; n, %)** | 11 (68) | 11 (73) | 8 (54) | 10 (72) | 0.643 |
| **Age, months*** | 6 (3-12) | 8.5 (3-12) | 5.5 (4-11) | 7.5 (3-13) | 0.733 |
| **Weight, kg*** | 7.25 (4-13) | 8 (4.5-10) | 7.5 (4-11) | 7.7 (5-10) | 0.457 |
| **Hospitalization rate** | 8 (50) | 5 (33) | 3 (20) | 5 (35) | 0.378 |
| **Tobacco exposure** | 4 (25) | 6 (40) | 3 (20) | 5 (35) | 0.619 |
| **Duration of prodromal symptoms*** | 5.5 (3-25) | 7 (4-12) | 5 (2-15) | 4.5 (2-15) | 0.662 |
| **Duration of wheezing symptoms*** | 3 (2-6) | 3 (2-6) | 3 (1-7) | 3 (2-7) | 0.701 |
| **Previous treatments** | 5 (30) | 2 (12) | 4 (26) | 3 (21) | 0.678 |
| **Eosinophilia (4%)** | - | - | - | 2 (14) | 0.079 |
| **Specific IgE positivity** | 1 (6) | 2 (13) | 1 (6) | - | 0.347 |
| **RSV positivity** | 5 (31) | 4 (26) | 5 (33) | 1 (7) | 0.349 |
| **WBC** | 9950 (6000-13500) | 9800 (7400-15000) | 12100 (6900-13300) | 8700 (5800-14100) | 0.465 |

**Median (IQR). RSV: Respiratory syncytial virus, WBC: White blood cell, IgE: Immunoglobulin E, IQR: Interquartile range*

**Table 3.** **Comparison of RDAI score, respiratory rate, heart rate and $SaO_2$ among the treatment groups at 0, 30, 60 and 120 minutes**

| | Budesonide (n=16) | Salbutamol (n=15) | Epinephrine (n=15) | Control (n=14) | p |
|---|---|---|---|---|---|
| **RDAI scores** | | | | | |
| 0 min | 10 (9-12) | 12 (9-12) | 11 (9-12) | 11 (8.75-13) | 0.928 |
| 30 min | 10 (8-11.75) | 9 (6-10) | 10 (7-10) | 10 (8.75-12.25) | 0.397 |
| 60 min | 9.5 (6.25-11) | 8 (5-10) | 8 (6-10) | 10 (8.75-12) | 0.146 |
| 120 min | 8 (5.25-9.25) | 7 (3-9) | 6 (3.5-10) | 9 (7.5-10.5) | 0.090 |
| **RR** | | | | | |
| 0 min | 60 (49-67) | 58 (48-60) | 60 (52-60) | 56 (52-61) | 0.351 |
| 30 min | 56 (52-60) | 52 (40-56) | 56 (48-60) | 56 (48-61) | **0.031** |
| 60 min | 52 (49-60) | 50 (40-52) | 56 (44-56) | 54 (44-60) | 0.197 |
| 120 min | 52 (43-56) | 48 (40-50) | 50 (38-56) | 52 (48-56) | 0.100 |
| **HR** | | | | | |
| 0 min | 129 (120-140) | 132 (120-136) | 132 (124-140) | 132 (120-137) | 0.905 |
| 30 min | 132 (124-136) | 132 (120-136) | 132 (128-136) | 132 (124-136) | 0.890 |
| 60 min | 130 (128-136) | 128 (127-140) | 136 (124-140) | 132 (124-136) | 0.805 |
| 120 min | 130 (124-136) | 130 (125-135) | 130 (120-137) | 132 (124-138) | 0.463 |
| **$SaO_2$** | | | | | |
| 0 min | 98 (96-98) | 98 (96-98) | 98 (96-98) | 97 (96-98) | 0.950 |
| 30 min | 97 (96-98) | 98 (96-98) | 97 (96-98) | 97 (96-98) | 0.780 |
| 60 min | 97 (96-98) | 98 (96-98) | 98 (96-98) | 98 (96-98) | 0.840 |
| 120 min | 98 (96-99) | 99 (97-99) | 98 (96-98) | 98 (96-98) | 0.870 |

*Median (IQR). HR: Heart rate, RDAI: Respiratory distress assessment instrument, RR: Respiratory rate, $SaO_2$: Oxygen saturation by pulse oximetry, IQR: Interquartile ranges, min: Minute*

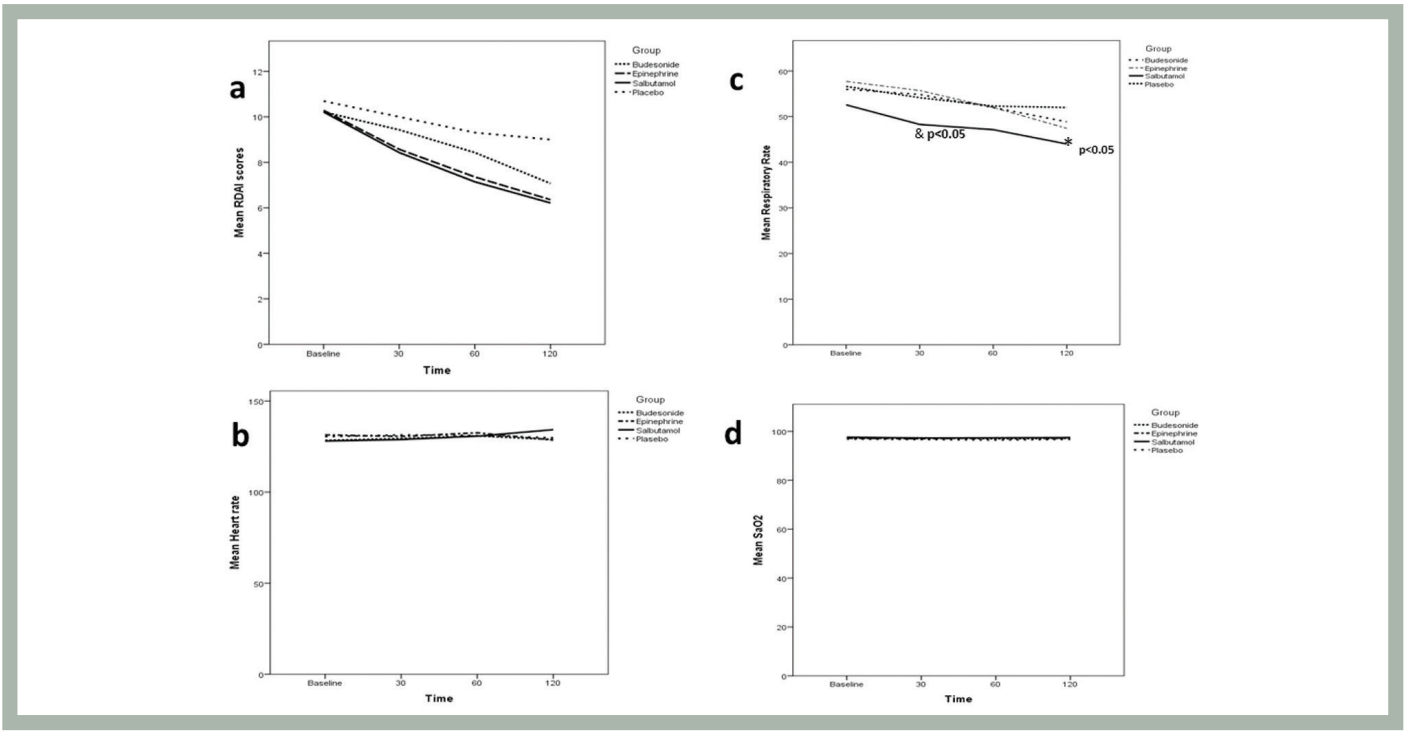


**Figure 1.** (a-d) Comparison of the time dependent changes among the treatment groups in terms of RDAI scores, RR, HR and $SaO_2$. &: p=0.031, *p=0.01

*HR: Heart rate, RDAI: Respiratory distress assessment instrument, RR: Respiratory rate, $SaO_2$: Oxygen saturation by pulse oximetry*

**Table 4.** Comparison of baseline RDAI scores, respiratory rate, heart rate, $SaO_2$ and the values at the second hour

| | Budesonide | | | Salbutamol | | | Epinephrine | | | Control | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | p | Before | After | p | Before | After | p | Before | After | p |
| **RDAI*** | 10 (9-12) | 8 (5.25-9.25) | 0.001 | 12 (9-12) | 7 (3-9) | 0.001 | 11 (9-12) | 6 (3.5-10) | 0.001 | 11 (8.75-13) | 9 (7.5-10.5) | 0.003 |
| **RR*** | 60 (49-67) | 52 (43-56) | 0.005 | 58 (48-60) | 48 (40-50) | 0.001 | 60 (52-60) | 50 (38-56) | 0.002 | 56 (52-61) | 52 (48-56) | 0.003 |
| **HR*** | 129 (120-140) | 130 (124-136) | 0.719 | 132 (120-136) | 130 (125-135) | 0.120 | 132 (124-140) | 130 (120-137) | 0.507 | 132 (120-137) | 132 (124-138) | 0.810 |
| **$SaO_2$*** | 98 (96-98) | 98 (96-99) | 0.859 | 98 (96-98) | 99 (97-99) | 0.608 | 98 (96-98) | 98 (96-98) | 0.891 | 97 (96-98) | 98 (96-98) | 0.660 |

**Median (IQR). HR: Heart rate; RDAI: Respiratory Distress Assessment Instrument; RR: Respiratory rate; $SaO_2$: Oxygen saturation by pulse oximetry*

## Discussion

Acute bronchiolitis is the most common lower respiratory tract infection in children under 2 years of age, often caused by viral agents, and the underlying pathogenesis is mostly inflammatory contractions of small airways (1,2). Several treatment options used during the disease course have been reported. There are controversies about the use of bronchodilator drugs in the treatment; pros and cons have been reported. Although there is a high incidence of bronchiolitis in infants, no consensus has been established on a common effective treatment, yet (5).

We evaluated sixty infants diagnosed with acute bronchiolitis who were followed in the ED. RR and RDAI scores showed significant improvement at the 120$^{th}$ minute compared to baseline in all treatment groups. When comparing RR at baseline and at the 30$^{th}$ minute across all groups, the salbutamol group showed a statistically significant improvement. In addition, the study groups were compared with the control group, and a statistically significant difference in RR at the 120$^{th}$ minute was observed in the salbutamol group.

Despite bronchodilators not being recommended for the treatment of routine bronchiolitis, physicians were found to use them. Salbutamol was the most preferred treatment for bronchodilator treatment (10). There are some studies that demonstrated the effectiveness of salbutamol in terms of $SaO_2$, respiratory distress, and clinical improvement (13,14).

A meta-analysis depicted the ineffectiveness of salbutamol in terms of improvement of $SaO_2$, reducing hospital admission and shortening the duration of hospitalization in the treatment of acute bronchiolitis, also the authors warned for the small sample sizes and lack of standardized treatment groups (15). Moreover, Cai et al. (16) found salbutamol had no effect on bronchiolitis of infants based on the results of their systematic review. They also warned of the side effects of salbutamol treatment particularly on high HR (16). In our study, nebulized salbutamol was found to be slightly more effective for short-term improvement. However, no evidence was found to recommend it for the treatment of bronchiolitis with respect to its long-term effects.

In the current study, we used nebulized epinephrine instead of racemic epinephrine due to its unavailability in our country. However, there are studies reporting that nebulized adrenaline is as effective as the racemic form in the treatment of croup and bronchiolitis (17,18). A significant improvement in RDAI score and RR was observed at the 120$^{th}$ minute compared with baseline in both the epinephrine and control saline groups. Therefore, nebulized epinephrine has not been shown to be a more effective treatment than that in the control group.

Five randomized controlled trials have been published that evaluated the effect of nebulized epinephrine treatment and reported clinical improvement in infants with acute bronchiolitis. In addition, nebulized epinephrine treatment was found to be safe in terms of side effects (17,19,20,21,22). Nevertheless, Anil et al. (23) compared nebulized salbutamol, epinephrine, normal and 3% saline treatments in infants with mild bronchiolitis, and they concluded there were no significant different clinical outcomes among the study groups.

In a clinical trial conducted in children with bronchiolitis requiring admission to the intensive care unit, the combination of repeated doses of systemic steroids and nebulized epinephrine, in addition to standard treatment, has been shown to shorten the duration of positive pressure support, especially in RSV-positive cases. However, the

authors stated that there may be bias due to the design of the study and the lack of blinding (24).

On the other hand, in a systematic review, evaluating the use of nebulized epinephrine for acute bronchiolitis suggested that comparing with placebo no differences were found for length of hospital stay, and emphasized the insufficient evidence to support the use for the treatment of bronchiolitis (25). Considering this information, there is no direct evidence to recommend nebulized epinephrine for the treatment of acute bronchiolitis because clinical outcomes are inconsistent.

Steroids have been used as a maintenance treatment because of their potential effects on inflammation, which underlies the pathogenesis of acute bronchiolitis. There are several studies which evaluate the efficacy of steroids in the treatment of acute bronchiolitis (9,26). In a multicenter, randomized, double-blind, placebo-controlled study in infants who were hospitalized for first-line RSV bronchiolitis, nebulized budesonide was compared to placebo. The result of this study depicted that the use of nebulized corticosteroids during the acute period of RSV bronchiolitis did not provide clinical benefit either in the acute or long-term (27).

Nebulized budesonide was administered at 0.5 mg/dose in this study, and a significant improvement was observed compared with the baseline scores in both RDAI scores and RR at the 120$^{th}$ minute, similar to the control group. There is insufficient evidence that glucocorticoids, whether systemic or nebulized, are beneficial in the treatment of acute bronchiolitis. Therefore, it is not recommended for routine use in bronchiolitis (28).

### Study Limitations

The most important limitation of this study is the lack of long-term results due to the study design.

NS was selected as the placebo in most comparative trials. However, subsequent studies conducted after the completion of our study have suggested that nebulized NS may exert measurable physiological effects and therefore should not be considered an inert placebo (29,30). Additionally, the use of NS in the control group—as well as in other treatment arms for dilution—may have attenuated the observable differences between groups, representing another limitation of our study.

Furthermore, the prospective, randomized, double-blind study design with a control group is a strength of our study.

## Conclusion

In our study, all the nebulized treatment groups showed improvements in RR and RDAI scores at the second hour compared with baseline. However, the salbutamol group was slightly more efficacious for short-term improvement in RR. Also, when we compared the treatment groups with the control group, we observed an improvement in RR during the second hour in the salbutamol group.

Bronchiolitis is an emerging health issue, particularly in infants. Large sample sizes with long-term follow-up and multicenter, placebo-controlled clinical trials are needed to evaluate the efficacy of bronchodilator therapy in the treatment of acute bronchiolitis.

### Acknowledgements

We are very grateful to Suat Bicer, MD, for his contributions to the study and data collection; he unfortunately passed away in 2017. His memory will live on in our hearts.

### Ethics

**Ethics Committee Approval:** The Ethics Committee of Bakırköy Maternity and Children's Training and Research Hospital was approved the study (approval number: 147 date: 11.07.2008).

**Informed Consent:** The informed consent was obtained from the parents of patients.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: B.K., M.A., D.Y.Ö., R.Ş., Concept: M.A., R.Ş., Design: M.A., R.Ş., Data Collection or Processing: B.K., M.A., D.Y.Ö., R.Ş., Analysis or Interpretation: B.K., M.A., D.Y.Ö., Literature Search: B.K., M.A., Writing: B.K., M.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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# Prolonged Jaundice in Term Newborns: Evaluation of Etiological and Clinical Characteristics

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### What is known on this subject?

Prolonged jaundice is common in term newborns and is most frequently associated with late-onset breast milk jaundice. Although usually benign, prolonged jaundice may be the first or only sign of underlying pathological and treatable conditions such as urinary tract infection, blood group incompatibility, or endocrine disorders. Current guidelines recommend systematic evaluation of infants with prolonged jaundice while continuing breastfeeding.

### What this study adds?

In this cohort of term newborns with prolonged jaundice, urinary tract infection was identified as the second most common etiology, with a higher frequency than previously reported. Female sex was significantly more common among infants with breast milk–related prolonged jaundice compared with those with other etiologies, suggesting possible sex-related differences according to underlying cause. Exclusive breastfeeding rates were similar between infants with breast milk–related prolonged jaundice and those with pathological causes, reinforcing recommendations that breastfeeding should not be discontinued during evaluation and follow-up.

## ABSTRACT

**Objective:** Prolonged jaundice is a common reason for neonatal outpatient visits and is usually benign; however, it may occasionally indicate underlying pathological, treatable conditions. This study aimed to evaluate the etiological and clinical characteristics of term newborns presenting with prolonged jaundice.

**Material and Methods:** In this single-center retrospective study, 150 term newborns diagnosed with prolonged jaundice were included between March 2022 and September 2022. Demographic and clinical data were recorded, and laboratory results were evaluated to determine potential underlying causes. All data were analyzed statistically.

**Results:** Among 150 newborns, 54.7% (n=82) were male. The mean gestational age and birth weight were 38.7±1.2 weeks and 3229±396 g, respectively. Late-onset breast milk jaundice was the most common etiology (57.3%), followed by urinary tract infection (22.7%), ABO/Rh incompatibility (14%), sepsis (3.3%), glucose-6-phosphate dehydrogenase deficiency (2%), and congenital hypothyroidism (0.7%). While 46% of the infants presented with jaundice, additional symptoms such as poor feeding (33%), vomiting (11%), and restlessness (5%) were observed in the remainder of the cohort. No significant differences were observed in demographic or laboratory parameters between infants with late-onset breast milk jaundice and those with pathological causes.

**Conclusion:** Late-onset breast milk jaundice is the leading cause of prolonged jaundice in term newborns. Nevertheless, a systematic clinical and laboratory evaluation is warranted in all infants with prolonged jaundice to

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CAM & SAKURA MEDICAL JOURNAL

## ABSTRACT

exclude underlying pathological conditions, even in the absence of additional symptoms. Breastfeeding should be continued during evaluation and follow-up, considering the unique and well-established benefits of breast milk.

**Keywords:** Prolonged jaundice, breastfeeding, urinary tract infection, newborn

## Introduction

Prolonged jaundice is commonly observed in term infants, particularly those who are exclusively breastfed**.** Although the majority of cases follow a benign and self-limiting course, prolonged jaundice may occasionally be the initial or sole manifestation of underlying pathological conditions requiring timely diagnosis and treatment. In term infants, prolonged jaundice is defined as persistence of jaundice beyond the 14$^{th}$ postnatal day, whereas in preterm infants it is defined as persistence beyond the 21$^{st}$ day of life (1). It accounts for one of the most frequent reasons for outpatient referrals and is reported in approximately 2–15% of newborns (1).

While the management of indirect hyperbilirubinemia during the first postnatal week is well established, diagnostic and therapeutic approaches to prolonged jaundice remain less clearly defined (2). A wide spectrum of etiologies, including hematological, infectious, metabolic, genetic, hepatic, and biliary disorders, may underlie prolonged jaundice, warranting thorough clinical assessment and etiological investigation (3). Identifying underlying pathological and treatable conditions is a key component in the management of infants with prolonged jaundice.

Late-onset breast milk jaundice is considered the most common cause of prolonged unconjugated hyperbilirubinemia in healthy term infants (4,5). Despite its benign nature, late-onset breast milk jaundice remains a diagnosis of exclusion, and potentially serious conditions must be ruled out before attributing prolonged jaundice to breastfeeding alone. Failure to identify underlying pathological causes may result in delayed treatment and adverse outcomes.

Therefore, this study aimed to evaluate the etiological and clinical characteristics of term newborns presenting with prolonged jaundice at a tertiary care neonatal outpatient clinic.

## Material and Methods

A single-center, retrospective cross-sectional study was conducted at the Neonatal Outpatient Clinic of an İstanbul Training and Research Hospital. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (decision number: 195, date: June 17, 2022). Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

### Study Population

Newborns born at ≥37 weeks of gestation who were diagnosed with prolonged jaundice were eligible for inclusion. Prolonged jaundice was defined as persistence of total serum bilirubin levels above 5 mg/dL beyond the 14$^{th}$ postnatal day. Direct bilirubin levels were evaluated in all infants. Infants with direct bilirubin levels >1 mg/dL were considered to have possible cholestatic jaundice and were excluded from the study. Late-onset breast milk jaundice was defined as prolonged unconjugated hyperbilirubinemia in otherwise healthy breastfed infants after exclusion of other identifiable causes, such as hemolytic disease, urinary tract infection (UTI), sepsis, endocrine disorders, and metabolic diseases. Sepsis was defined as culture-confirmed sepsis based on a positive blood culture accompanied by compatible clinical and laboratory findings. Newborns with major congenital anomalies, chromosomal abnormalities, or incomplete medical records were excluded from the study.

### Data Collection

Demographic and clinical data were obtained retrospectively from İstanbul Training and Research Hospital medical records. Recorded variables included sex, gestational age, birth weight, length, head circumference, mode of delivery, parity, family history of neonatal jaundice, age at first outpatient admission, age at diagnosis of prolonged jaundice, presenting symptoms, feeding type, and weight changes. Newborns meeting the inclusion criteria were identified retrospectively from İstanbul Training and Research Hospital medical records and included consecutively during the six-month study period.

### Laboratory Evaluation

Laboratory data collected for etiological evaluation included serum total and direct bilirubin levels, complete blood count, liver function tests (alanine aminotransferase

and aspartate aminotransferase), thyroid function tests (thyroid-stimulating hormone and free thyroxine), C-reactive protein levels, glucose-6-phosphate dehydrogenase (G6PD) activity, and serum electrolytes. Urinalysis and urine culture were performed when clinically indicated to evaluate for UTI. Blood group incompatibility was assessed by maternal and neonatal blood group analyses. Urine samples for culture were obtained by sterile urethral catheterization.

### Statistical Analysis

Sample size estimation was performed prior to the study using the equation $n = t^2pq/d^2$. Calculations were based on a 5% type I error rate ($\alpha$=0.05) and 80% statistical power. G*Power (version 3.1.9.2) was used to verify the adequacy of the estimated sample size. The analysis indicated that a minimum of 118 participants would be sufficient. To enhance statistical reliability and compensate for potential data limitations, 150 infants were included in the final dataset.

Data analysis was carried out with IBM SPSS Statistics (version 23.0). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were summarized as mean ± standard deviation or median with range according to distributional characteristics. Group comparisons were conducted using parametric or non-parametric tests depending on whether distributional assumptions were met (independent t-test or Mann–Whitney U test, respectively). Associations between categorical variables were evaluated using the chi-square test. All hypothesis tests were two-sided, and results were considered statistically significant at $p<0.05$.

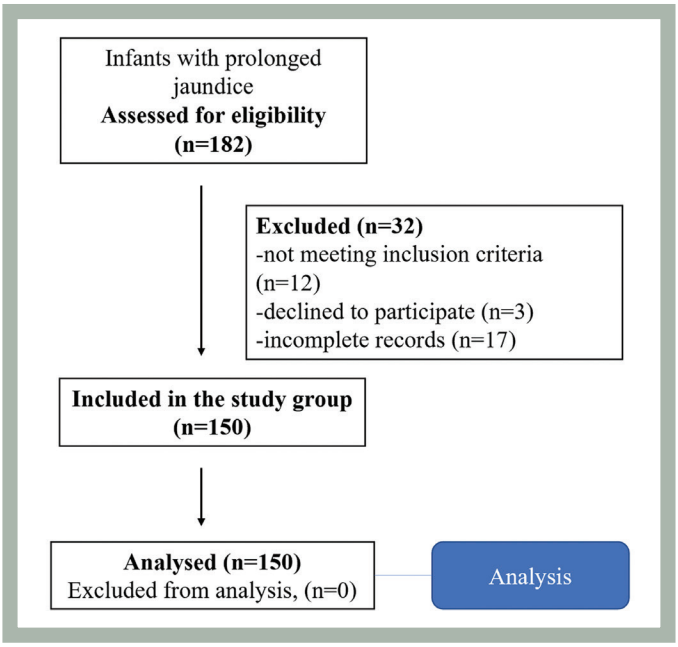


**Figure 1.** Flow diagram of the study population

## Results

A total of 150 term newborns diagnosed with prolonged jaundice were included in the study. The flow diagram of the study is shown in Figure 1. Of the infants, 82 (54.7%) were male and 68 (45.3%) were female. Seventy-six infants (50.7%) were delivered via normal spontaneous vaginal delivery. The mean gestational age was 38.7±1.2 weeks (37-41 weeks). The mean birth weight, length and head circumference were 3229±396 g, 49.39±1.04 cm, and 35.6±0.54 cm, respectively (Table 1). Seventy-three infants (48.7%) were born to primigravid mothers. A positive history of neonatal jaundice in a sibling was reported in 32 infants (21.3%). The mean age at the initial admission to outpatient clinic and the diagnosis of prolonged jaundice was 9.84±6.29 and 15.1±2.28 postnatal days, respectively. Among the infants, 46% presented to the hospital with jaundice as the primary complaint, while the remainder presented with symptoms including poor feeding (33%), vomiting (11%), and restlessness (5%). Caregivers' presenting complaints at admission are shown in Figure 2. Laboratory findings of the study population are summarized in Table 2.

**Table 1. Demographic and clinical characteristics of the study population**

| Variable | | (n)/(%) |
|---|---|---|
| Gender | Female | 68 (45.3%) |
| | Male | 82 (54.7%) |
| | **Mean ± SD** | **Minimum-maximum** |
| Gestational week (w) | 38.7±1.2 | (37-41) |
| Birth weight (g) | 3229±396 | (2510-4000) |
| Length (cm) | 49.39±1.04 | (47-52) |
| Head circumference (cm) | 35.6±0.54 | (34-38) |

*SD: Standard deviation*

The most common causes were in 86 infants (57.3%), followed by UTI in 34 infants (22.7%), ABO incompatibility in 13 infants (8.7%), Rh incompatibility in 8 infants (5.3%), sepsis in 5 infants (3.3%), G6PD deficiency in 3 infants (2%), and congenital hypothyroidism in 1 infant (0.7%) (Figure 3).

When infants with late-onset breast milk jaundice were compared with those with pathological causes of prolonged jaundice, no significant differences were observed in demographic, clinical, or laboratory parameters, except for sex. Male sex was more frequent in infants with late-onset breast-milk jaundice (p=0.046). The formula-feeding rate was 49% in newborns with late-onset breast milk jaundice, while this rate was 53% in newborns diagnosed with prolonged jaundice for other reasons (p=0.205). Type of feeding, serum bilirubin levels, liver enzyme levels, thyroid function tests, and inflammatory markers were similar between the two groups (Table 3).

**Table 2. Laboratory values of the study group**

| | Mean ± SD |
|---|---|
| T. bilirubin (mg/dL) | 13.05±5.03 |
| D. bilirubin (mg/dL) | 0.96±0.60 |
| ALT (U/L) | 18.1±8.9 |
| AST (U/L) | 35.15±11.67 |
| Sodium (mEq/L) | 138.7±3.24 |
| Hemoglobin (g/dL) | 15.12±3.2 |
| Hematocrit (%) | 43.10±9.7 |
| Free T4 (ng/dL) | 1.09±0.32 |
| TSH (mIU/L) | 2.75±2.67 |
| CRP (mg/L) | 10.97±3.32 |

*T. bilirubin: Total bilirubin, D. bilirubin: Direct bilirubin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Free T4: Free thyroxine, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein, SD: Standard deviation.*

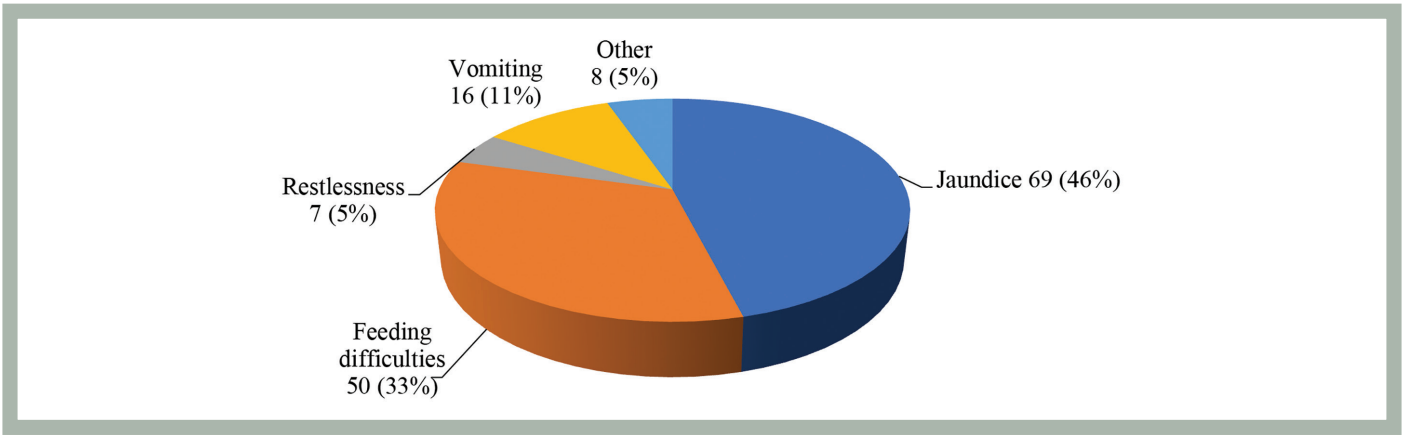


**Figure 2.** Presenting complaints reported by caregivers at the time of hospital admission

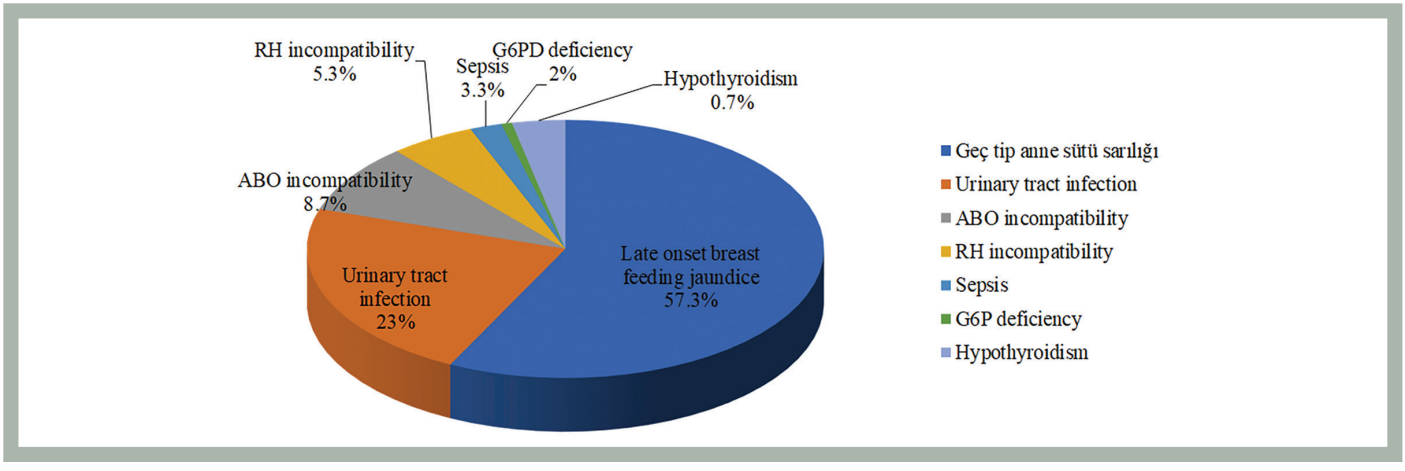


**Figure 3.** Late-onset breast milk jaundice
*G6PD: Glucose-6-phosphate dehydrogenase*

**Table 3.** **Comparison of neonates with prolonged jaundice due to late-onset breast milk jaundice and due to other etiologies**

| | Late-onset breast milk jaundice (n=86) | Other etiologies (n=64) | p |
|---|---|---|---|
| **Demographic and clinical characteristics** | | | |
| First pregnancy (n, %) | 37 (48.1) | 36 (49.3) | 0.877 |
| Gender, female, (n, %) | 40 (51.9) | 28 (38.4) | **0.046** |
| Route of delivery (NSD) | 43 (50.0) | 33 (51.5) | 0.258 |
| Consanguinity | 9 (11.7) | 15 (20.5) | 0.140 |
| Mixed feeding | 49 (63.6) | 53 (72.6) | 0.241 |
| **Laboratory values** | | | |
| Sodium (mEq/L) | 138.19±3.24 | 138.71±3.17 | 0.055 |
| Hgb (g/dL) | 15.29±3.07 | 14.94±3.36 | 0.42 |
| Hct (%) | 43.85±8.97 | 42.28±10.42 | 0.15 |
| ALT (U/L) | 17.89±8.63 | 18.3±9.2 | 0.775 |
| AST (U/L) | 35.2±10.82 | 35.05±13.1 | 0.92 |
| Free T4 (ng/dL) | 1.05±0.36 | 1.14±0.29 | 0.197 |
| TSH (mIU/L) | 2.80±3.05 | 2.69±2.1 | 0.544 |
| CRP (mg/L) | 2.56±2.46 | 3.0±2.74 | 0.310 |
| Bilirubin value at admission (mg/dL) | 13.16±3.07 | 14.26±2.57 | 0.723 |

*NSD: Normal spontaneous delivery, Hgb: Hemoglobin, Hct: Hematocrit, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Free T4: Free thyroxine, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein. A p value <0.05 was considered statistically significant*

## Discussion

In this study, late-onset breast milk jaundice was identified as the most common cause of prolonged jaundice in term newborns, accounting for more than half of the cases. UTI was the second most frequent etiology, followed by blood group incompatibilities, sepsis, G6PD deficiency, and congenital hypothyroidism. These findings highlight the heterogeneous nature of prolonged jaundice and the importance of systematic evaluation.

Consistent with previous reports, male sex was more common among infants with prolonged jaundice. Male predominance has been described as a risk factor for neonatal hyperbilirubinemia (2,6), potentially reflecting sex-related differences in bilirubin metabolism. However, in our cohort, female sex was significantly more common in infants with late-onset breast milk jaundice than in infants with other etiologies. This finding suggests that sex-related differences may vary according to the underlying etiology of prolonged jaundice. However, the clinical significance of this observation remains uncertain, and the finding may reflect sample characteristics rather than a true biological association. Primiparity has also been reported as a risk factor for prolonged neonatal jaundice (7,8). Consistent with previous reports, a high proportion of infants in our cohort were born to primiparous mothers; nevertheless, primiparity rates did not differ between infants with late-onset breast milk jaundice and those with other etiologies. A family history of neonatal jaundice in a sibling has been reported as a risk factor for prolonged jaundice. Brown (9) showed that a history of neonatal jaundice in a sibling increases the likelihood of jaundice in subsequent offspring, while Hansen (10), identified a positive family history as an independent risk factor for severe hyperbilirubinemia. In our study, approximately one in five infants (21.3%) had a sibling with neonatal jaundice requiring phototherapy, underscoring the importance of obtaining a detailed family history when evaluating infants with prolonged jaundice.

Although several studies have evaluated the clinical presentation of infants with neonatal jaundice, data specifically focusing on infants with prolonged jaundice remain limited. In our cohort, jaundice was the most common presenting symptom (46%), followed by poor feeding (33%), vomiting (11%), restlessness (5%), and weight loss or lethargy (5%). Notably, more than half of the infants presented with symptoms beyond isolated jaundice, underscoring the importance of a comprehensive systemic examination when evaluating infants with prolonged jaundice.

A wide range of etiological factors has been implicated in prolonged jaundice. Late-onset breast milk jaundice remains the most common and benign cause of prolonged unconjugated hyperbilirubinemia in healthy term infants (1). Previous studies have consistently reported late-onset breast milk jaundice as the most common cause, accounting for approximately 50-70% of cases (11,12,13). Despite its benign course, late-onset breast milk jaundice should remain a diagnosis of exclusion. Consistent with the literature, late-onset breast milk jaundice was the leading cause in our cohort, accounting for 57.3%. Clinical guidelines and observational studies indicate that prolonged jaundice occurs more frequently in breastfed infants, with longer durations of hyperbilirubinemia reported in breastfed infants than in formula-fed infants. Although a higher rate of exclusive breastfeeding would be expected among infants diagnosed with late-onset breast milk jaundice, the frequency of exclusive breastfeeding was similar between the two groups in our cohort (14). These findings reinforce current recommendations that breastfeeding should be continued in infants with prolonged jaundice, as breast milk provides unique benefits for newborns.

UTI are an important pathological cause of prolonged jaundice in neonates. Previous studies have reported UTI rates ranging between 7% and 15% among infants with prolonged jaundice (11,12,15,16,17,18). In our cohort, UTIs were identified in 34 infants (22.7%), representing the second most common etiology of prolonged jaundice. This rate is higher than rates reported in previous studies and may be related to regional variations, differences in screening practices, or characteristics of the study population. Nevertheless, a UTI may present solely as prolonged jaundice in early infancy; therefore, routine urinalysis and urine culture should be considered in the diagnostic evaluation of infants presenting with prolonged jaundice.

G6PD deficiency is a well-recognized cause of neonatal hyperbilirubinemia and is relatively common in our country. Although G6PD deficiency has been primarily associated with early and severe neonatal jaundice, it may also contribute to prolonged jaundice in some infants (19). In our cohort, G6PD deficiency was identified in a small proportion of cases, which may be related to the limited sample size or to the characteristics of the study population.

Congenital hypothyroidism is a rare but important and treatable cause of prolonged jaundice. Hyperbilirubinemia has been reported in up to 10% of affected newborns (20). The low frequency observed in our study may reflect the effectiveness of national newborn screening programs. Evaluation of infants with prolonged jaundice for congenital hypothyroidism is strongly recommended (21).

### Study Limitations

This single-institution study relied on retrospectively collected data, which should be considered when interpreting the findings, particularly regarding their generalizability. Because this study was conducted in a tertiary care referral center, the study population may include a higher proportion of referred or clinically complex cases, which may limit the generalizability of the findings and may have influenced the observed distribution of etiological factors. However, the relatively large sample size and comprehensive etiological evaluation strengthen the validity of our findings.

## Conclusion

In conclusion, late-onset breast milk jaundice is the most common cause of prolonged jaundice in term newborns. However, a substantial proportion of infants may have underlying pathological conditions, particularly UTIs. Therefore, infants presenting with prolonged jaundice should undergo systematic clinical and laboratory evaluation. Importantly, breastfeeding should be continued during follow-up, given the well-established benefits of breast milk for the newborn.

### Ethics

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (decision number: 195, date: June 17, 2022).

**Informed Consent:** Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

### Footnotes

### Authorship Contributions

Concept: S.Ö., D.A., Design: S.Ö., Z.A.S., D.A., Data Collection or Processing: S.Ö., N.K., Analysis or Interpretation: S.Ö., Y.H., D.A., Literature Search: S.Ö., Z.A.S., S.C., D.A., Writing: S.Ö., Z.A.S., S.C., D.A.

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# Plasmapheresis Activity of a Tertiary Referral Centre Indicating Wide-Spread Interdisciplinary and Safe Use of Therapeutic Plasma Exchange, with an Emphasis on Thrombotic Thrombocytopenic Purpura

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### What is known on this subject?

Therapeutic plasma exchange is an established treatment modality used in a wide range of hematologic, neurologic, renal, and autoimmune disorders. In thrombotic thrombocytopenic purpura (TTP), plasma exchange remains the cornerstone of treatment and has markedly improved survival; contemporary management increasingly incorporates ADAMTS13-guided diagnosis and adjunctive immunosuppressive therapies such as corticosteroids and rituximab.

### What this study adds?

This real-world tertiary-center experience demonstrates broad, interdisciplinary, and safe use of therapeutic apheresis, with favorable outcomes in TTP. The study provides local data on response, relapse, and complications, and highlights the gap between historical practice and current ADAMTS13- and caplacizumab-based management.

## ABSTRACT

**Objective:** This study aimed to evaluate the clinical spectrum, treatment characteristics, and outcomes of therapeutic apheresis (TA) procedures performed at a tertiary care university hospital, with particular emphasis on thrombotic thrombocytopenic purpura (TTP).

**Material and Methods:** In this retrospective cohort study, 303 patients who underwent 2,289 apheresis procedures between 2010 and 2015 were evaluated. Patients were categorized according to the primary procedure performed: therapeutic plasma exchange [(TPE); n=110], therapeutic cytapheresis (n=85), and peripheral blood stem cell collection [(PBSC); n=59]. The remaining 49 patients underwent other apheresis procedures. PBSC cases were excluded from treatment-response analyses. TTP was diagnosed clinically on the basis of thrombocytopenia and microangiopathic haemolytic anaemia, with or without organ involvement, after exclusion of other thrombotic microangiopathies; ADAMTS13 activity testing was not routinely available during the study period.

**Results:** Haematological diseases were the most common indication for apheresis (n=190, 62.7%). TPE was performed in 110 patients, including 22 (20.0%) with TTP. Among 244 patients eligible for outcome analysis, response

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## ABSTRACT

status could be clearly classified for 218 patients: 144 (59.0%) had a complete response, 17 (7.0%) had a partial response, and 57 (23.4%) had no response. The mean number of apheresis sessions per patient was 7.5±3.9. In the TTP subgroup, 17 of 22 patients (77.2%) achieved a clinical response; 7 (31.8%) relapsed during follow-up, and 4 (18.2%) died from refractory disease or underlying critical illness. Procedure-related complications were infrequent; 209 patients (69.0%) had no complications. No deaths were directly attributed to the apheresis procedure.

**Conclusion:** TA was widely used across multiple disciplines and showed an acceptable safety profile in our centre. Haematological disorders, particularly TTP and acute leukaemia, constituted the largest indication group. These findings support the continued role of TPE in routine clinical practice and emergency settings, while highlighting the need for contemporary prospective studies that incorporate ADAMTS13-guided evaluation and assess newer agents such as caplacizumab.

**Keywords:** Therapeutic apheresis, therapeutic plasma exchange, cytapheresis, peripheral blood stem cell collection, thrombotic thrombocytopenic purpura, TTP

## Introduction

Therapeutic apheresis (TA), is the separation of substance from blood. Depending on the type of separated components, TPA is also known as therapeutic cytapheresis. Cytapheresis is the process of separation of the cellular elements in the blood and using the rest for the patient or donor. Therapeutic plasma exchange (TPE) is a procedure in which allogeneic plasma is used as the replacement fluid. The use of Solomon and Fahey in the treatment of Hyperviscosity syndrome in 1960 can be accepted as the beginning of TPE (1). Thrombotic thrombocytopenic purpura (TTP) is a disease characterized by microangiopathic haemolytic anaemia and thrombocytopenia, and may progress to include fever, neurologic findings, and renal failure. The current standard treatment comprises plasma exchange (PEX) and immunosuppressive therapies, such as corticosteroids or rituximab. In 1991, effective treatment of acquired TTP started with documentation of the efficacy of PEX, mortality decreased from 90% to 28% in acute episodes (2). In 1998, acquired TTP was found to be associated *ADAMTS13* gene deficiency due to an inhibitor (3,4) suggesting an autoimmune aetiology thus providing the explanation for corticosteroids in addition to PEX (5). US Food and Drug Administration did not approve rituximab for the treatment of TTP. Since 2002 it has been used off-label with increasing frequency (6,7).

The aim of this study was to evaluate retrospectively patient's demographic characteristics, follow-up clinic, vascular access route, frequency of apheresis application and total number of applications, treatment responses, complications during the procedure, and laboratory, clinical characteristics, response to treatment and TTP patients' response to treatment between 2010 and 2015. With respect to relapse, the data obtained were compared with the world literature and with studies conducted in our country.

## Material and Methods

This retrospective study, conducted at the Department of Haematology, Dicle University Faculty of Medicine, included all adult patients who underwent TA between January 2010 and December 2015. Data were obtained from hospital electronic records and the apheresis unit's registry. The study was approved by the Non-Interventional Research Ethics Committee of Dicle University (decision number: 14, date: 25.12.2015). Due to the retrospective nature of the study, the requirement for informed consent was waived. All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki.

A total of 303 patients were identified and categorized into groups based on their primary indication for apheresis. The classification was as follows:

TTP Group (n=22): Patients who met the clinical and laboratory criteria for TTP and underwent PEX as first-line therapy. Treatment response was defined as follows: a complete response (CR) was defined as normalization of platelet count ($>150 \times 10^9$/L), normalization of lactate dehydrogenase (LDH) levels, and resolution of clinical symptoms. Partial response (PR) was defined as an improvement in platelet count and LDH levels without full normalization. No response (NR) was defined as failure to achieve haematological improvement or as clinical deterioration despite therapy.

Neurological disorders group (n=45): Patients treated with TPE for neurological conditions including Guillain-Barré syndrome, myasthenia gravis, and chronic inflammatory demyelinating polyneuropathy, in accordance with American Society for Apheresis (ASFA) Category I/II indications.

Autoimmune and connective tissue disorders group (n=40): Patients with systemic lupus erythematosus (SLE), vasculitis, or other autoimmune syndromes with organ involvement necessitating apheresis.

Hyperviscosity syndrome group (n=25): Patients presenting with symptomatic hyperviscosity due to Waldenström's macroglobulinemia or multiple myeloma.

Hematologic malignancy group (n=21): Patients with leucocytosis secondary to acute leukaemia or other proliferative disorders who underwent leukapheresis.

Solid organ transplantation group (n=15): Patients who underwent TPE for desensitization or antibody-mediated rejection in renal transplantation.

Hematopoietic stem cell transplantation group (n=111): Donors or patients who underwent peripheral blood stem cell collection (PBSC) using leukapheresis.

Patients with missing essential data, those of paediatric age, or those who underwent apheresis for experimental or unclassified indications were excluded from the analysis.

A total of 303 patients were included. For the primary analysis, patients were classified according to the main apheresis procedure received: TPE (n=110), therapeutic cytapheresis (n=85; leukocytapheresis, thrombocytapheresis, or related cellular procedures), PBSC collection (n=59), and other procedures (n=49; including lipid apheresis, double-filtration plasmapheresis, and bilirubin apheresis). PBSC collection cases were excluded from treatment-response analyses because the procedure was performed for collection rather than for disease-directed therapy.

Clinical response was defined retrospectively based on disease-specific chart documentation. CR indicated the resolution of the main clinical and/or laboratory abnormality that prompted apheresis. A PR indicated a meaningful but incomplete improvement. NR indicates the absence of clinically relevant improvement or progression despite treatment. Because this was a heterogeneous cohort, these definitions were applied in accordance with the underlying indication and the treating team's documented assessment.

TTP was diagnosed clinically on the basis of thrombocytopenia and microangiopathic haemolytic anaemia, with or without neurologic, renal, or febrile manifestations, after exclusion of alternative causes of thrombotic microangiopathy, such as disseminated intravascular coagulation, haemolytic uraemic syndrome, malignant hypertension, sepsis-associated microangiopathy, or pregnancy-related syndromes. ADAMTS13 activity and inhibitor testing were not routinely available during the study period. Cases were categorized as secondary TTP when a clear associated trigger was documented; otherwise, they were considered idiopathic/acquired TTP. Caplacizumab was not available at our centre during the study period. Information regarding the exact timing of rituximab administration was incomplete in the retrospective records and was therefore summarized descriptively.

All apheresis procedures were performed using the Fresenius COM.TEC® continuous-flow cell separator. Acid citrate dextrose-A was used as the primary anticoagulant with a standard blood-to-anticoagulant ratio of 10:1. Venous access was achieved using either peripheral veins or central venous catheters, depending on vein quality and clinical condition. Replacement fluids for PEX included 5% human albumin and fresh frozen plasma (FFP), which were selected according to the underlying indication.

### Statistical Analysis

Data collected included demographic characteristics, primary diagnosis, number of sessions, type of apheresis, venous access route, replacement fluids, and complications. Descriptive statistics were used to summarize the data. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD, and categorical variables were presented as numbers and percentages. Only descriptive statistics were used. Continuous variables are presented as mean ± SD as appropriate. Categorical variables are presented as numbers (percentages). No inferential statistical comparison was performed because the study was primarily descriptive.

## Results

A total of 303 patients who underwent TPA and cytapheresis in the Dicle University Apheresis Unit between 01.01.2010 and 31.12.2015, encompassing 2,289 sessions, were included in the study. Among them, 159 (52.5%) were female and 144 (47.5%) were male. The mean age was 42.76±19.191 (min-max, 10-96) years. The mean number of sessions was 7.69±12.183 (min-max, 1-100). When procedures not requiring replacement fluids (cytapheresis and double filtration plasmapheresis) were excluded, FFP was used as the replacement fluid in all sessions.

Among patients who underwent plasmapheresis, 22 of 110 (20%) were diagnosed with TTP, and among patients who underwent therapeutic cytapheresis, 59 of 85 (69%) had acute leukaemia.

A total of 244 patients who underwent TA were evaluated for treatment response. PBSC collection cases were excluded from outcome assessment. Among the remaining 244

patients, response status could be clearly classified for 218. Overall, 144 patients (59.0%) achieved CR, 17 (7.0%) achieved PR, and 57 (23.4%) had NR. The mean number of sessions per patient was 7.5±3.9.

Overall, most patients were followed up in the haematology unit (Table 1). Temporary central venous catheters were used in 211 patients (69.6%), peripheral catheters in 21 patients (6.9%), and fistulas in 3 patients (1%). The vascular access site was not specified for 68 patients (22.4%) (Table 2).

No complications were observed in 209 patients (69.0%). Reported adverse events included catheter dysfunction in 8 patients (2.6%), allergic reactions in 6 patients (2.0%), hypotension in 1 patient (0.3%), and vomiting in 1 patient (0.3%). One critically ill patient died during treatment; after chart review, this death was attributed to the underlying disease rather than to the apheresis procedure itself (Table 3).

The distribution of patients according to apheresis procedure was as follows: 110 (36.3%) underwent TPE, 73 (24.1%) underwent leukapheresis, 59 (19.5%) underwent peripheral stem cell collection, 31 (10.2%) underwent double filtration plasmapheresis, 16 (5.3%) underwent lipid apheresis, 12 (4%) underwent thrombocytapheresis, and 2 (0.7%) underwent bilirubin apheresis (Table 4).

Among the 110 patients who underwent TPE, 64 (58.2%) responded, 15 (13.6%) had a PR, and 19 (13.4%) did not respond, and 22 (20.0%) were treated for TTP (Table 5). The TTP subgroup comprised 12 males (54.5%) and 10 females (45.5%), with a mean age of 28.2±8.7 years. Twenty patients (90.9%) were considered to have idiopathic/acquired TTP, whereas 2 patients (9.1%) had secondary TTP associated with SLE or clopidogrel exposure. At admission, fever was present in 19 patients (86.4%). Headache was reported in 10 (45.5%) patients, focal neurological abnormalities in 1 (4.5%) patient, confusion in 3 (13.6%) patients, and coma in 3 (13.6%) patients. Among the 20 patients with neurological involvement (91%), 7 (31.8%) had severe, and 13 (59.1%) had mild neurological symptoms, including seizures. Petechiae were detected in 11 (50%) patients at admission. Fatigue was reported in 21 (95.5%) participants. Petechiae were present in 14 (63.6%) patients,

**Table 1. Referring departments of patients undergoing therapeutic apheresis**

| Department | Patients, n (%) |
|---|---|
| Hematology | 190 (62.7) |
| Neurology | 46 (15.2) |
| Nephrology | 27 (8.9) |
| Intensive care unit | 15 (5.0) |
| Endocrinology | 15 (5.0) |

**Table 2. Baseline characteristics of the overall cohort**

| Total number of patient n (%) | 303 | |
|---|---|---|
| Female | 159 | 52.5% |
| Male | 144 | 47.5% |
| Total number of procedure | 2289 | |
| Age: mean (min-max) | 42.76±19,191 | (10–96) |
| Number of procedure (min-max) | 7.69±12.183 | (1–100) |
| Venous access, n (%) | | |
| Central venous catheter | 211 | 69.6% |
| Peripheral vein | 21 | 6.9% |
| Arterio-venous fistula | 3 | 1% |
| Five most indications, n (%) | | |
| Acute leukaemia | 59 | 19.5% |
| Multiple myeloma | 41 | 13.5% |
| TTP | 22 | 7.3% |
| Sepsis | 17 | 5.6% |
| HUS | 14 | 4.6% |
| Department, n (%) | | |
| Haematology | 190 | 62.7% |
| Neurology | 46 | 15.2% |
| Nephrology | 27 | 8.9% |
| Intensive care unit | 15 | 5.0% |
| Endocrinology | 15 | 5.0% |
| Procedure type, n (%) | | |
| Bilirubin apheresis | 2 | 0.7% |
| Double filtration apheresis | 31 | 10.2% |
| Lipid apheresis | 16 | 5.3% |
| Leukocytapheresis | 73 | 24.1% |
| Stem cell collection | 59 | 19.5% |
| Therapeutic plasma exchange | 110 | 36.3% |
| Thrombocyte apheresis | 12 | 4.0% |

*TTP: Thrombotic thrombocytopenic purpura, HUS: Hemolytic uremic syndrome, min: Minimum, max: Maximum*

**Table 3. Procedure related adverse events n (%)**

| Adverse event | Patients, n (%) |
|---|---|
| No complication | 209 (69.0) |
| Catheter dysfunction | 8 (2.6) |
| Allergic reaction | 6 (2.0) |
| Hypotension | 1 (0.3) |
| Vomiting | 1 (0.3) |
| Death during treatment* | 1 (0.3) |

**After chart review, this event was judged to be related to the underlying disease rather than to the apheresis procedure itself*

**Table 4.** Distribution of procedure types

| Procedure type | Patients, n (%) |
|---|---|
| Therapeutic plasma exchange | 110 (36.3) |
| Leukocytapheresis | 73 (24.1) |
| Peripheral blood stem cell collection | 59 (19.5) |
| Double–filtration plasmapheresis | 31 (10.2) |
| Lipid apheresis | 16 (5.3) |
| Thrombocytapheresis | 12 (4.0) |
| Bilirubin apheresis | 2 (0.7) |

and haematuria was present in 1 (4.5%) patient. Five patients (22.7%) had no bleeding. Chest pain was present in 4 patients (18.2%) and absent in 12 patients (54.5%). Gastrointestinal complaints were noted in 17 patients (87.3%), including nausea in 7 (31.8%), diarrhoea in 2 (9.1%), abdominal pain in 5 (22.7%), and vomiting in 3 (13.6%). Five patients (22.7%) had no gastrointestinal symptoms. Acute renal failure was present in 11 patients (50%).

Seventeen patients (77.2%) achieved a clinical response. Seven patients (31.8%) relapsed during follow-up, and four patients (18.2%) died from refractory TTP or severe concomitant illness (Table 6). Regarding treatment modalities, 9 patients (40.9%) received only TPE; 6 (27.2%) received TPE and steroids; 3 (13.6%) received TPE, steroids, and vincristine; 2 (9.1%) received TPE, steroids, and rituximab; 1 (4.5%) received TPE, steroids, rituximab, and vincristine; and 1 (4.5%) received TPE and vincristine. Treatment response was not specified for 1 patient (4.5%) who left the hospital during follow-up.

Regimens containing rituximab and/or vincristine were used in selected refractory cases, but the exact timing of rituximab administration was not consistently documented.

## Discussion

In our study, the treatment response rate among TTP patients who underwent plasmapheresis was 77.2%, which aligns with both national data and international literature. During the six-year evaluation period at our centre's TA unit, most patients were referred from the haematology clinic. The relatively low number of patients from other departments may be attributed to limited awareness or to fewer TA indications outside haematology.

The most frequently performed procedure was TPE, predominantly indicated for TTP. According to guidelines published by the ASFA and the American Association of Blood Banks, TPE is a first-line treatment for TTP. In our cohort, 22 (20%) of the 110 patients who underwent TPE were diagnosed with TTP after referral to internal medicine. Therapeutic cytapheresis was performed in 85 patients, the majority (59 patients, 69%) of whom had acute leukaemia and were treated for hyperleukocytosis. These findings are consistent with previous reports in the literature (8,9,10,11,12).

In all TTP cases in our study, FFP was used as the replacement fluid, in line with the standard recommendation for this indication (8,9,10,11,12).

Apheresis can also be used in cases of poisoning. Current literature suggests that the number of sessions should be determined by clinical response rather than by a predetermined number (13,14,15,16). In our study, one patient with levothyroxine intoxication showed complete clinical recovery after three sessions of TPE.

For patients with hypertriglyceridemia-induced pancreatitis, apheresis has been shown to be effective. One study reported a 76.5% response rate among 17 such patients (17). In our series, 4 of 6 patients (66.7%) responded to treatment, and 1 (16.7%) achieved a PR, supporting previously reported findings.

Kadikoylu et al. (18) reported the use of FFP in 88% of TPE cases, while 12% used albumin as the replacement fluid. In contrast, our study utilized TDP (thawed plasma) in 100% of sessions, mainly due to reimbursement restrictions, limited availability of albumin, and greater accessibility of TDP. The estimated cost of a single TPE session in Türkiye is approximately $520 with FFP and $800 with albumin (19).

Complications related to TPE procedures are typically categorized as mild, moderate, severe, or fatal (20). Mortality rates range between 0.03–0.05% per session (20,21). In our study, 209 (69%) of 303 patients experienced no complications, and only 1 death occurred during 1,823 TPE sessions, corresponding to a mortality rate of 0.05%. Reported complications included allergic reactions (6 patients, 2%), hypotension (1 patient, 0.3%), vomiting (1 patient, 0.3%), and catheter-related issues (8 patients, 2.6%). Another study reported higher complication rates: nausea/vomiting in 4%, hypotension in 3%, itching in 1.7%, and catheter-related complications in 3.6% of procedures (18). The relatively low rate in our centre may be attributed to the presence of experienced apheresis personnel.

Citrate-induced hypocalcaemia is a known side effect of TPE. While some centres opt for calcium supplementation only when symptoms arise, others use routine prophylactic replacement. Studies show that without prophylaxis, hypercalcaemic symptoms occur in 9% of patients, whereas this drops to 1% with prophylaxis (22). In our centre, all 1,823 sessions included routine calcium supplementation, and no hypercalcaemic symptoms were observed. A study

**Table 5. The indications and procedure burden**

| | Number of patient (%) | Procedure type | Number of procedure (%) | CR | PR | No response | ASFA 2016 category |
|---|---|---|---|---|---|---|---|
| Hematologic diseases | | | | | | | |
| Acute leukaemia | 59 (19.5%) | Leukocytapheresis | 122 (5.24%) | 29 (55.7%) | | 23 (44.3%) | II |
| Cryoglobulinemia | 1(0.3%) | TPE | 2 (0.08%) | 1 (100%) | | | I |
| Multiple myeloma | 41(13.5%) | TPE | 42 (1.83%) | 1 (100%) | | | I |
| Cold agglutinin disease | 1(0.3%) | TPE | 4 (0.17%) | 1 (100%) | | | II |
| TTP | 28 (9.2%) | TPE | 843 (36.8%) | 25 (89.3%) | | 3 (10.7%) | I |
| Pregnancy-associated diseases | | | | | | | |
| Pregnancy-associated TMA | 2 (0.7%) | TPE | 35 (1.52%) | 2 (100%) | | | I |
| HELLP syndrome | 2 (0.7%) | TPE | 46 (2%) | 1 (50%) | 1 (50%) | | II |
| Neurological diseases | | | | | | | |
| Chronic inflammatory demyelinating polyradiculoneuropathy | 2 (0.7%) | TPE | 14 (0.61%) | | | 1 (50%) | I |
| Guillain-Barré syndrome | 13 (4.3%) | TPE | 68 (2.97%) | 7 (53.8%) | 1 (7.7%) | 3 (23.1%) | I |
| Myastenia gravis | 7 (2.3%) | TPE | 39 (1.7%) | 6 (75%) | | 1 (12.5%) | I |
| Neuromyelitis optica | 6 (2.0%) | TPE | 38 (1.66%) | 4 (66.7%) | 1 (16.7%) | | II |
| Renal diseases | | | | | | | |
| Glomerulonephritis | 3 (1.0%) | TPE | 39 (1.7%) | 2 (66.7%) | | 1(33.3%) | II |
| Renal transplantation, ABO compatible Graft rejection | 3 (1.0%) | TPE | 20 (0.87%) | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) | I |
| MPGN | 1 (0.3%) | TPE | 3 (0.13%) | | 1 (100%) | | II |
| RPGN | 1 (0.3%) | TPE | 14 (0.61%) | 1 (100%) | | | II |
| Critical illness | | | | | | | |
| Levothyroxine intoxication | 1(0.3%) | TPE | 3 (0.13%) | 1 (100%) | | | II |
| Sepsis | 17 (5.6%) | TPE | 269 (11.75%) | 7 (41.2%) | 2 (11.8%) | 4 (23.5%) | III |
| Endocrine diseases | | | | | | | |
| Hyperlipidaemia | 10 (3.3%) | Lipid apheresis | 15 (0.65%) | 8 (80%) | | 1 (10%) | I |
| Hyper triglyceridemic Pancreatitis | 6 (2.0%) | Lipid apheresis | 9 (0.39%) | 4 (66.7%) | 1 (16.7%) | | I |
| Rheumatic diseases | | | | | | | |
| SLE | 1 (0.3%) | TPE | 31(1.35%) | | | 1 (100%) | II |
| Vasculitis | 1 (0.3%) | TPE | 1 (0.04%) | 1 (100%) | | | II |

*CR: Complete response, PR: Partial response, ASFA: American Society for Apheresis, TPE: Therapeutic plasma exchange, TMA: Thrombotic microangiopathy, MPGN: Membranoproliferative glomerulonephritis, RPGN: Rapidly progressive glomerulonephritis, SLE: Systemic lupus erythematosus, TTP: Thrombotic thrombocytopenic purpura*

by Korkmaz et al. (23) also highlighted hypocalcaemia as the most common adverse event (19), noting that calcium and magnesium prophylaxis is not routinely practiced in many centres in Türkiye. However, our centre consistently employed this measure.

Regarding neurological indications, our findings were also consistent with existing data. Among patients with Guillain-Barré syndrome, 7 (53.8%) responded to therapy, 1 (7.7%) had a PR, and 3 (23.1%) did not respond to therapy. In myasthenia gravis, 6 of 8 patients (75%) showed favourable outcomes, while 1 patient (12.5%) had NR (23).

**Table 6. Clinical characteristics and outcomes of the TTP subgroup**

| Variable | Value |
|---|---|
| Patients, n | 22 |
| Age, mean ± SD, years | 28.2±8.7 |
| Male sex, n (%) | 12 (54.5) |
| Female sex, n (%) | 10 (45.5) |
| Idiopathic/acquired TTP, n (%) | 20 (90.9) |
| Secondary TTP, n (%) | 2 (9.1) |
| Clinical response, n (%) | 17 (77.2) |
| Relapse during follow-up, n (%) | 7 (31.8) |
| Death, n (%) | 4 (18.2) |
| Received rituximab-containing therapy, n | 3 |
| Received vincristine-containing therapy, n | 5 |

*TTP, Thrombotic thrombocytopenic purpura, SD: Standard deviation*

The classic TTP pentad is seen in only 5% of patients (24), whereas 50% (11 patients) of our cohort presented with the full pentad at diagnosis. One patient developed TTP following clopidogrel use, and another had secondary TTP due to SLE, findings that echo earlier reports (25).

Rituximab is recommended for refractory or relapsing TTP cases and is administered weekly at 375 mg/m² for four weeks when response to TPE and corticosteroids is inadequate within 4-7 days (6,8,11,26). In our study, 7 of 8 refractory patients responded favourably to immunosuppressive therapy with rituximab.

The TTP subgroup was a principal focus of the study. Our response rate of 77.2% is comparable to previously published real-world cohorts, although direct comparison is limited by differences in case definitions, disease severity, and treatment era. During the 2010-2015 study period, ADAMTS13 activity testing was not routinely available in our institution. Consequently, the diagnosis was based on clinical and laboratory findings after exclusion of other thrombotic microangiopathies. We have clarified this point because it is important for the interpretation of the TTP results.

Current management of immune-mediated TTP has evolved substantially. Contemporary practice emphasizes early confirmation with ADAMTS13 testing, close monitoring of ADAMTS13 activity during remission, and adjunctive therapy with corticosteroids, rituximab, and caplacizumab in appropriate patients. Caplacizumab was not available in our centre during the study years, and this should be considered when interpreting outcomes. Although rituximab was used in selected refractory or relapsing cases, the retrospective records did not allow for a uniform analysis of treatment timing.

The complication profile in our cohort was favourable. Nearly seven in ten patients had no recorded complications, and most adverse events were mild and manageable. The single death observed during treatment occurred in a critically ill patient and was not considered procedure-related after chart review. This finding is consistent with published evidence showing that severe apheresis-related mortality is uncommon in experienced centres.

### Study Limitations

This study has several limitations. First, its retrospective single-center design limits control over confounding factors and introduces the potential for selection and information bias. Second, data were obtained from electronic medical records, and missing or incomplete documentation may have affected the assessment of clinical response and other outcomes. Third, several key variables, including specific laboratory parameters, immunological markers, detailed treatment timing, and standardized long-term follow-up data, were not uniformly available. In addition, clinical response was determined primarily from physicians' documentation, which may have introduced subjectivity. Finally, no formal sample size calculation was performed because all eligible patients within the study period were included.

## Conclusion

TA remains an important treatment option across a wide range of clinical indications. At our tertiary center, the procedure was used safely and most frequently for hematologic disorders, particularly TTP and acute leukemia. The present data support the continued use of TPE in multidisciplinary practice, while underscoring the need for contemporary prospective studies in the era of ADAMTS13-guided diagnosis and caplacizumab-based therapy.

### Ethics

**Ethics Committee Approval:** The study was approved by the Non-Interventional Research Ethics Committee of Dicle University (decision number:14, date:25.12.2015).

**Informed Consent:** Due to the retrospective nature of the study, the requirement for informed consent was waived. All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: B.B., V.D., A.K., B.G., O.A., Concept: B.B., O.A., Design: B.B., O.A., Data Collection or

Processing: B.B., V.D., A.K., B.G., Analysis or Interpretation: B.B., O.A., Literature Search: B.B., Writing: B.B.

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# The Impact of Weight and Circumcision on Penile Measurements and Micropenis Evaluation in Pediatric Patients

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### What is known on this subject?

Penile measurements in pediatric patients are highly sensitive to external clinical factors, and current evaluation methods can yield inconsistent outcomes depending on individual physical characteristics. Circumcision status and body weight percentile are known to substantially influence both flaccid and stretched penile length (SPL) measurements, often complicating clinical assessments. Confounding factors—such as increased suprapubic fat or post-operative tissue changes—frequently create measurement-related variability that can obscure true anatomical dimensions, directly impacting the accuracy of micropenis screening and pediatric clinical decision-making.

### What this study adds?

This study of 540 patients demonstrates a paradoxical decrease in SPL following circumcision in overweight children, highlighting measurement variability over true anatomical change. The findings emphasize that incorporating weight percentile and circumcision status into normative reference charts is necessary for refining pediatric micropenis diagnosis.

## ABSTRACT

**Objective:** Penile measurements are critical in the evaluation of micropenis, yet the potential effects of circumcision and higher body weight percentiles remain underexplored. This study aimed to assess how circumcision status and weight percentiles (specifically comparing <75$^{th}$ and ≥75$^{th}$ percentiles) influence penile length measurements and glans diameter (GD) in children aged 0-10 years.

**Material and Methods:** This retrospective study included 540 boys who underwent circumcision between 2022 and 2024. Age, weight, and weight percentile were recorded along with penile measurements. Baseline (flaccid) penile length (BPL) and stretched penile length (SPL) were measured before circumcision; BPL, SPL, and GD were reassessed postoperatively. Patients were categorized as <75$^{th}$ or ≥75$^{th}$ percentile for weight. Comparative and correlational analyses were conducted to evaluate associations between weight status and penile measurements.

**Results:** In infants, SPL was significantly lower in children in the ≥75$^{th}$ percentile group compared to those in the <75$^{th}$ percentile group. Across all age groups, BPL was significantly lower in children with higher weight percentiles. GD was larger only among infants in the ≥75$^{th}$ percentile group. While SPL generally increased following circumcision, a paradoxical decrease was noted in children with higher weight percentiles (≥75$^{th}$ percentile), likely reflecting differences in measurement conditions rather than true anatomical shortening.

**Conclusion:** Circumcision status and weight percentile may significantly influence penile measurements among children. Current normative data may not fully represent circumcised children and those with higher weight percentiles, potentially affecting clinical interpretation. These findings should be interpreted as reflecting measurement-related variability rather than true anatomical changes in penile length. Updated population-specific reference standards incorporating circumcision status and body weight percentiles may improve diagnostic accuracy and clinical decision-making.

**Keywords:** Micropenis, circumcision, body weight percentiles, penile length measurements, children, concealed penis

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## Introduction

Circumcision has been practiced mostly on boys since ancient times for religious, cultural, and personal reasons. Almost 40% of adult men worldwide are circumcised, with approximately 80% in the United States and 99% in Islamic countries such as Türkiye (1). Male circumcision involves excision of the prepuce covering the glans. Despite its prevalence, few studies have examined the impact of circumcision on penile measurements, particularly in children. The penile length and glans diameter (GD) are key parameters for evaluating normal penile development. Understanding how these measurements change before and after circumcision is crucial for assessing the effects of the procedure, identifying potential complications (such as an inconspicuous penis or other penile disorders), and evaluating a diagnosis of micropenis.

A micropenis is defined as a penis size that is significantly shorter due to hormonal or genetic reasons (2). Specifically, a penis length below 2.5 SDs is generally accepted as the criterion for diagnosing a micropenis. Being below 2.5 SDs corresponds to falling below the measurements of 99.4% of the normal population. The evaluations also considered pubertal stage and age. The diagnosis of micropenis is established by physical examination, the most important component of which is measurement of penile length. During measurement of penile length, the penis was stretched maximally toward the pubis, and the stretched penile length (SPL) was measured. These evaluations and diagnoses were based on overall averages.

According to the 2022 World Obesity Atlas, more than 100 million children aged 5-9 and over 150 million children aged 10-19 years will be affected by obesity worldwide by 2030 (3). In pediatric clinical practice, analyzing how variations in body weight percentiles interact with anatomical assessments is essential, as increased suprapubic fat pad thickness can potentially confound physical examination findings, including penile measurements (4,5).

The primary objective of this study was to evaluate the combined impact of circumcision status and body weight percentiles ($<75^{th}$ vs. $\geq75^{th}$ percentile) on penile length measurements and GD during micropenis assessment in children aged 0-10 years.

Although previous literature has occasionally addressed penile sizes before and after surgery, the specific interaction between circumcision status and body weight percentiles has received limited attention in the pediatric literature.

By comparing these measurements, this study seeks to provide a better understanding of the effects of circumcision and weight status on penile assessment and to contribute to the existing knowledge on pediatric urology.

## Material and Methods

### Study Design

This retrospective study included data from 540 patients aged 0-10 years who underwent circumcision at the Pediatric Surgery Department of the Ordu University Faculty of Medicine Training and Research Hospital between 2022 and 2024. In our clinic, penile measurements are performed routinely and in a standardized manner as part of the preoperative and intraoperative clinical assessment under anesthesia for all children undergoing urological procedures, and these data are systematically recorded in patient charts.

In this study, participants were divided into five main age groups: infants (0-2 years), 3-4-year-olds, 5-6-year-olds, 7-8-year-olds, and 9-10-year-olds. The patients' weight percentiles were evaluated using the Centers for Disease Control and Prevention growth charts and the World Health Organization weight-for-age standards for boys. Patients with weight above the $75^{th}$ percentile were categorized separately (6,7). This classification aimed to enable a comparison between children in the higher weight percentile group ($\geq75^{th}$ percentile) and those in the lower weight percentile group ($<75^{th}$ percentile), to test the study hypothesis.

Ethical approval for this study was obtained from the Ordu University Non-Interventional Scientific Research Ethics Committee on September 13, 2024 (approval number: 2024/116). Because this study utilizes a retrospective design based on historical patient records and contains absolutely no patient-identifying personal data, the requirement for written informed consent was evaluated and waived by the institutional review board.

### Inclusion and Exclusion Criteria

Inclusion criteria: Male children aged 0-10 years who underwent circumcision at our clinic and had penile measurements recorded both before and after the procedure (while under anesthesia) were included in the study.

Exclusion criteria: Children were excluded if they had congenital penile anomalies such as hypospadias, penile chordee, or buried penis; acquired penile deformities resulting from circumcision complications; chronic diseases affecting physical development (e.g., hemiplegia, Grade 3-5 cerebral palsy, severe congenital heart defects); or scrotal pathologies causing swelling, such as hydrocele.

### Data Collection

Demographic data, including age, weight, weight percentile, and penile measurements, were recorded for each patient. Penile measurements included:

Before circumcision (under anesthesia): Baseline (flaccid) penile length (BPL) and SPL.

After circumcision (under anesthesia): BPL, SPL, and GD.

All measurements were performed under anesthesia by the same two surgeons using a standardized technique to minimize inter-observer variability. To achieve strict standardization, all measurements were conducted in an operating room maintained at a constant ambient temperature (22 °C), with the patient in a supine position under general anesthesia, ensuring total muscle relaxation. Penile length was measured dorsally at a 90-degree angle using a single-use, rigid cardboard ruler calibrated in millimeters, which was chosen to ensure strict cross-infection control for each patient. For the SPL measurement, the surgeon firmly compressed the suprapubic adipose tissue vertically at the base of the penis until the rigid edge of the ruler directly abutted the underlying pubic bone, fully displacing the fat pad. Simultaneously, the glans penis was grasped and stretched dorsally along its longitudinal axis with a steady, uniform force until definitive physical tissue resistance (maximum non-elastic extension) was reached; the distance to the tip of the glans was then recorded. GD was measured at the coronal sulcus after circumcision (Figure 1).

### Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Descriptive analyses were presented using the mean, standard deviation (SD), median, and min-max values. Non-parametric variables were compared between two groups using the Mann-Whitney U test. Changes in measured values between groups were evaluated using repeated measures analysis. p values below 0.05 were considered statistically significant.

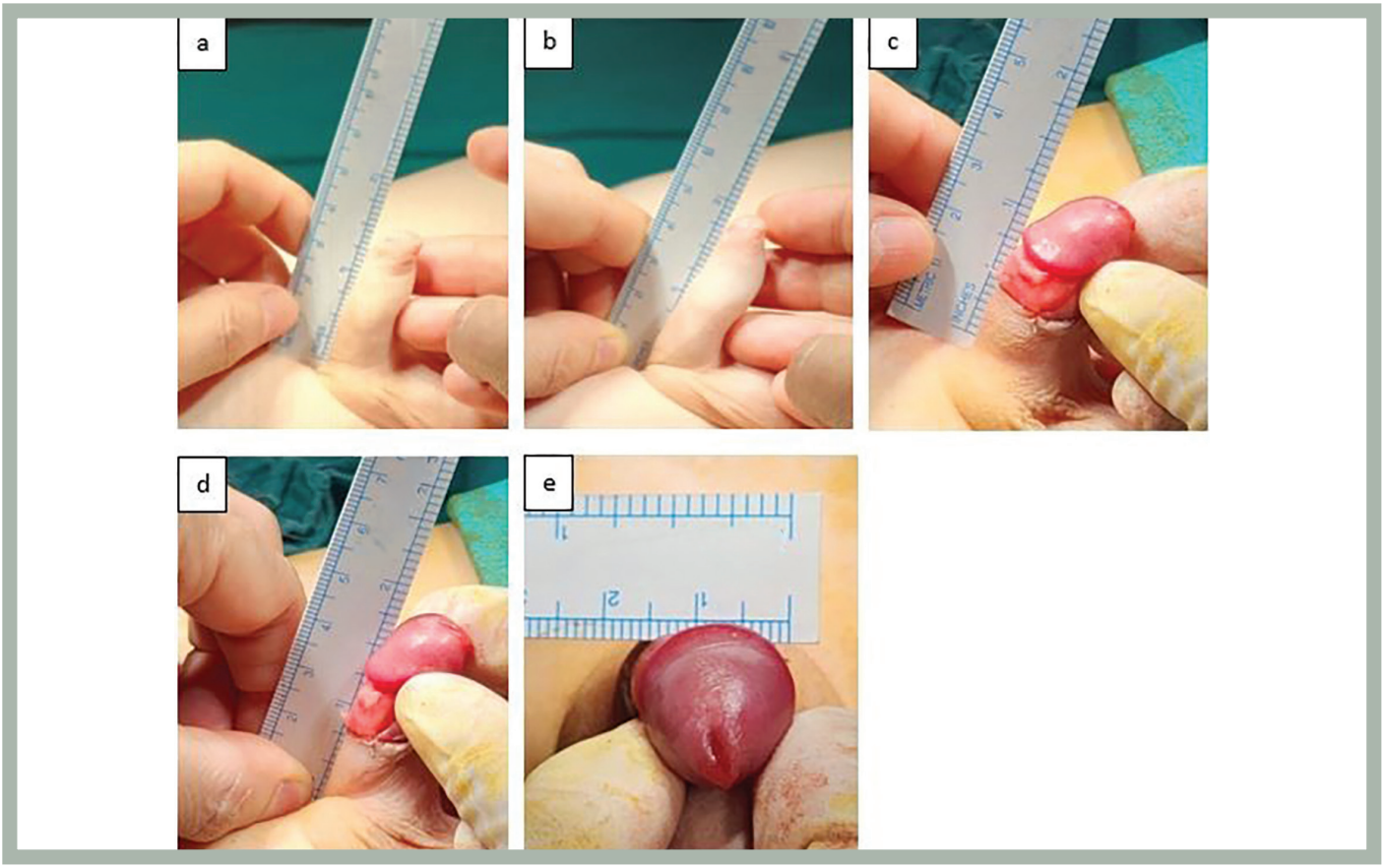


**Figure 1.** The measurements taken sequentially on the same patient have been photographed. a) Before circumcision, under anesthesia BPL. b) Before circumcision, under anesthesia SPL. c) After circumcision, under anesthesia BPL. d) After circumcision, under anesthesia SPL. e) Glans diameter measurement

*BPL: Baseline (flaccid) penile length, SPL: Stretched penile length*

## Results

### Patients Demographics

A total of 540 patients were included in the study. The demographic characteristics of the patients are detailed in the table below. The age ranges from 17 to 117 months (minimum-maximum: 5-120 months). Weight percentile values were categorized as <75$^{th}$ percentile (P) and <75$^{th}$ percentile (Figure 2). Specifically, in the 3-4-year age group, circumcision in Ordu University Training and Research Hospital is not typically performed on children aged 3-5 years due to the psychosexual development phase. Therefore, the sample size for this group is insufficient (Table 1).

### Penile Measurements

### Baseline (Flaccid) Penile Length

The change in BPL was compared separately for each age group between those below the <75$^{th}$ percentile (<75 P) and those at or above the <75$^{th}$ percentile (≥75 P). In the infant group, the BPL value decreased more in those with ≥75 P compared to those with <75 P. No significant change was found in other age groups. When looking at the change in BPL within the groups, a significant decrease was observed in the 5-6 and 7-8 age groups for those with <75 P, and in the infant, 5-6, and 7-8 age groups for those with ≥75 P (Table 2).

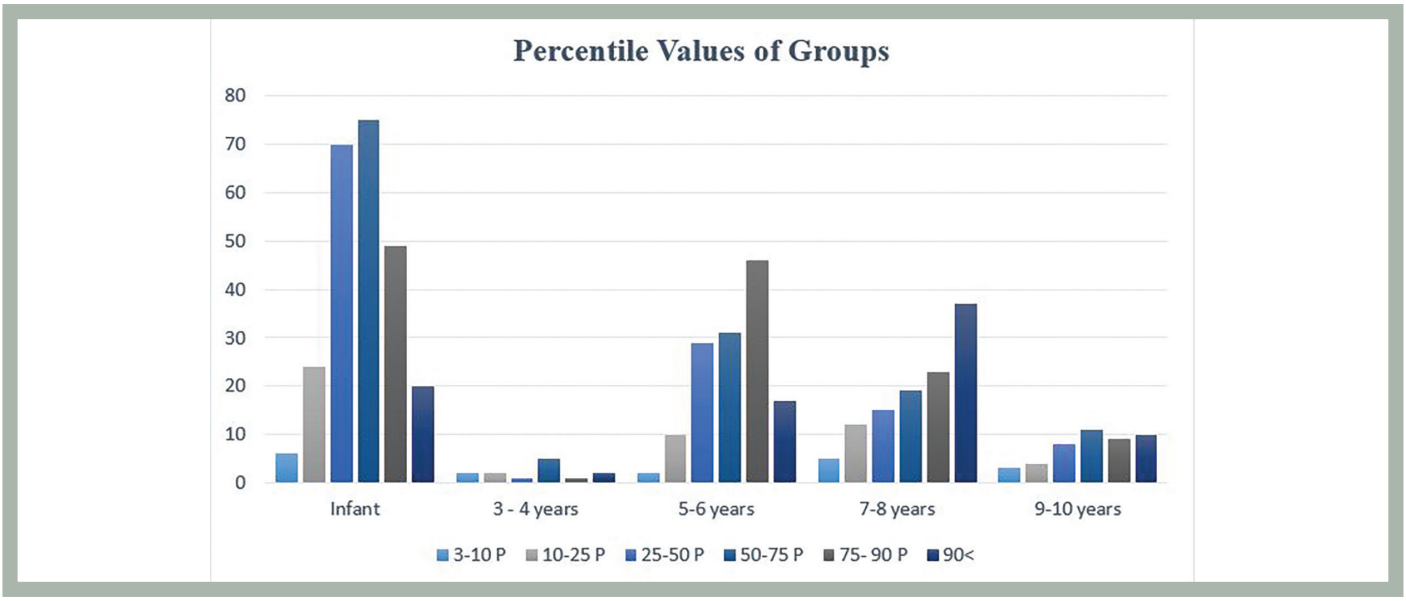


**Figure 2.** Weight percentile values of groups

**Table 1.** Patient demographics and penile measurements

| <75$^{th}$ P | n | Age (months) | Weight (kg) | BPL (mm) | SPL (mm) | GL (mm) | PC-BPL (mm) | PC-SPL (mm) |
|---|---|---|---|---|---|---|---|---|
| Infant | 161 | 18.84 | 11.16 | 27.71 | 38.34 | 16.19 | 27.41 | 38.31 |
| 3-4 | 9 | 42.67 | 14.28 | 33.00 | 42.67 | 17.89 | 31.33 | 43.00 |
| 5-6 | 64 | 68.34 | 19.31 | 35.70 | 44.52 | 18.17 | 32.92 | 43.14 |
| 7-8 | 52 | 89.42 | 23.20 | 35.75 | 44.85 | 19.02 | 32.69 | 42.50 |
| 9-10 | 19 | 112.74 | 28.24 | 36.21 | 46.32 | 19.32 | 33.89 | 44.84 |
| ≥75$^{th}$ P | | | | | | | | |
| Infant | 83 | 17.64 | 13.51 | 30.75 | 42.78 | 19.10 | 28.52 | 41.53 |
| 3-4 | 7 | 41.14 | 18.14 | 27.00 | 37.00 | 17.86 | 29.00 | 34.14 |
| 5-6 | 71 | 71.49 | 25.10 | 31.41 | 43.25 | 18.46 | 30.07 | 41.80 |
| 7-8 | 58 | 90.31 | 33.34 | 32.20 | 43.75 | 19.15 | 29.85 | 42.51 |
| 9-10 | 16 | 117.38 | 41.69 | 32.56 | 46.00 | 18.75 | 29.75 | 44.81 |

*BPL: Baseline (flaccid) penile length, SPL: Stretched penile length, GL: Glans Lenght, PC: Post-circumcision*

### Stretched Penile Length

For each age group, change in SPL was compared between those below the <75th percentile and those at or above the <75th percentile. In the infant group, the SPL value decreased more in those with ≥75 P compared to those with <75 P. The decrease in SPL value by percentile in other age groups was not found to be significant. When looking at the change in SPL within the groups, a significant decrease was observed in the 5-6 and 7-8 age groups for those with <75 P, and in the infant and 7-8 age groups for those with ≥75 P (Table 3).

**Table 2.** The change in BPL was compared separately for each age group between <75 P and ≥75 P

| | | <75 P | | ≥75 P | | p[1] |
|---|---|---|---|---|---|---|
| | | Mean ± SD (mm) | Median (min-max) (mm) | Mean ± SD (mm) | Median (min-max) (mm) | |
| Infant | BPL | 27.71±5.18 | 27 (15-50) | 30.75±7.08 | 30 (20-47) | **0.002** |
| | PC-BPL | 27.41±5.33 | 26 (15-45) | 28.52±6.35 | 28 (10-50) | |
| p[2] | | 0.398 | | **0.001** | | |
| 3-4 | BPL | 33±6.46 | 33 (22-40) | 27±6.81 | 27 (20-35) | 0.177 |
| | PC-BPL | 31.33±6.44 | 30 (22-40) | 29±5.66 | 32 (20-35) | |
| p[2] | | 0.196 | | 0.610 | | |
| 5-6 | BPL | 35.7±6.63 | 35 (20-50) | 31.41±6.61 | 30 (20-47) | 0.113 |
| | PC-BPL | 32.92±6.6 | 32.5 (20-50) | 30.07±7.03 | 30 (18-50) | |
| p[2] | | **<0.001** | | **0.037** | | |
| 7-8 | BPL | 35.75±6.75 | 35 (25-50) | 32.2±7.93 | 30 (17-55) | 0.515 |
| | PC-BPL | 32.69±5.36 | 32 (23-45) | 29.85±6.33 | 30 (20-53) | |
| p[2] | | **0.001** | | **0.003** | | |
| 9-10 | BPL | 36.21±5.44 | 35 (30-50) | 32.56±6.43 | 31 (25-45) | 0.792 |
| | PC-BPL | 33.89±5.1 | 32 (25-42) | 29.75±7.7 | 30 (20-50) | |
| p[2] | | 0.115 | | 0.051 | | |

*[1]Repeated measures analysis, [2]Wilcoxon test. SD: Standard deviation, BPL: Baseline (flaccid) penile length, PC: Post-circumcision, min-max: Minimum-maximum*

**Table 3.** The change in SPL was compared separately for each age group between <75 P and ≥75 P

| | | <75 P | | ≥75 P | | p |
|---|---|---|---|---|---|---|
| | | Mean ± SD (mm) | Median (min-max) (mm) | Mean ± SD (mm) | Median (min-max) (mm) | |
| Infant | SPL | 38.34±6.4 | 40 (21-60) | 42.78±8.59 | 45 (26-65) | **0.047** |
| | PC-SPL | 38.31±5.87 | 37 (24-53) | 41.53±6.94 | 40 (28-60) | |
| p[2] | | 0.695 | | **0.037** | | |
| 3-4 | SPL | 42.67±5.52 | 43 (35-50) | 37±6.08 | 40 (28-45) | 0.113 |
| | PC-SPL | 43±6.12 | 44 (35-55) | 34.14±9.15 | 37 (15-40) | |
| p[2] | | 0.892 | | 0.144 | | |
| 5-6 | SPL | 44.52±6.44 | 45 (33-60) | 43.25±7.43 | 42 (30-60) | 0.936 |
| | PC-SPL | 43.14±6.13 | 43,5 (32-55) | 41.8±6.73 | 41 (25-60) | |
| p[2] | | **0.022** | | 0.085 | | |
| 7-8 | SPL | 44.85±7.99 | 45 (30-60) | 43.75±7.06 | 45 (25-60) | 0.257 |
| | PC-SPL | 42.5±6.34 | 42 (30-60) | 42.51±6.77 | 42 (28-65) | |
| p[2] | | **0.008** | | **0.043** | | |
| 9-10 | SPL | 46.32±8.71 | 45 (35-65) | 46±11.37 | 45.5 (30-80) | 0.884 |
| | PC-SPL | 44.84±7.46 | 45 (35-65) | 44.81±12.68 | 45 (25-85) | |
| p[2] | | 0.409 | | 0.202 | | |

*[1]Repeated measures analysis, [2]Wilcoxon test. SD: Standard deviation, SPL: Stretched penile length, PC: Post-circumcision, min-max: Minimum-maximum*

In the infant group, the average SPL value before and after circumcision post-circumcision (PC-SPL) varied by percentile, with a more pronounced postoperative decrease observed in the higher-percentile group. When micropenis was evaluated using individual patient data, it was detected in 5.6% (n=12) of the infant group before circumcision. This rate decreased to 3% (n=7) after circumcision; however, when evaluated individually, the presence or absence of micropenis differed in 13 patients between pre- and PC assessments.

In the 5–6-year age group, micropenis was detected in 13% (n=18) of patients before circumcision and in 14% (n=19) after circumcision. When these data were examined individually, 15 patients showed a change in the presence or absence of micropenis before vs. after circumcision.

### Glans Diameter

As a result of comparing GD values between percentile groups for each age group separately, it was observed that in the infant group, those with ≥75 P had higher GD values compared to those with < 75P. In other groups, no significant difference in GD measurements was found between percentiles above and below the 75$^{th}$ (Table 4).

As shown in Table 4, the standard mean values among children below the 75$^{th}$ percentile increase proportionally with age. However, age-independent changes have been observed in children above the 75$^{th}$ percentile, unlike in those below the 75$^{th}$ percentile.

## Discussion

Penile shortening is a condition that may raise concerns among both parents and children, leading to significant psychosocial consequences, including impaired self-confidence and disruption of sexual identity development. Early diagnosis and the continuous updating of treatment and follow-up protocols are critical in the management of micropenis. It is recommended that follow-up, extending from the neonatal period through adolescence, be conducted via a multidisciplinary approach involving pediatric urology, pediatric endocrinology, and pediatric psychiatry (6).

Micropenis is defined, based on normative data adjusted for ethnicity and geographic region, as a SPL below -2.5 SDs. According to national standards, Cinaz et al. (7) reported a mean SPL of 5.4 cm for the infant group in Türkiye, with a corresponding -2.5 SD threshold of 3.8 cm. In contrast, the widely referenced study by Custer and Rau (9) reported a mean SPL of 4.7 cm for the infant group, with the -2.5 SD value at 2.6 cm (8)

In our study, the mean SPL in the ≥75$^{th}$ percentile weight group was 4.2 cm (minimum 2.6 cm), while in the <75$^{th}$ percentile group, it was 3.8 cm (minimum 2.1 cm) for infants (Table 5). Similarly, in the 5-6-year age group, which included the second-largest number of patients, SPL measurements obtained before circumcision were below the micropenis threshold according to both reference standards.

**Table 4.** GD values between percentile groups

| GD | <75 P | | ≥75 P | | p |
|---|---|---|---|---|---|
| | Mean ± SD | Median (min-max) | Mean ± SD | Median (min-max) | |
| Infant | 16.19±1.82 | 16 (12-20) | 19.1±2.47 | 20 (15-26) | **<0.001** |
| 3-4 | 17.89±2.52 | 18 (13-20) | 17.86±2.12 | 17 (15-20) | 0.824 |
| 5-6 | 18.17±2.39 | 18 (10-25) | 18.46±2.43 | 18 (13-23) | 0.426 |
| 7-8 | 19.02±2.11 | 20 (15-25) | 19.15±3.48 | 19 (12-32) | 0.909 |
| 9-10 | 19.32±3.16 | 20 (15-27) | 18.75±6.09 | 17.5 (15-30) | 0.652 |

*Mann-Whitney U test. GD: Glans diameter, SD: Standard deviation, min-max: Minimum-maximum*

**Table 5.** SPL values of the infant and 5-6 age groups: standard references and measurements from this study

| | Age groups | Mean (cm) | -2.5 SD (cm) |
|---|---|---|---|
| Custer and Rau (9) | Infant | 4.7 | 2.6 |
| Cinaz et al. (7) | Infant | 5.4 | 3.8 |
| **This study (PC-SPL)** | **Infant (<75 P≥75 P)** | **3.8-4.1** | **2.4-2.8** |
| Custer and Rau (9) | 5-6 | 6.0 | 3.8 |
| Cinaz et al. (7) | 5-6 | 6.3 | 4.45 |
| **This study (PC-SPL)** | **5-6 (<75 P≥75 P)** | **4.3-4.1** | **3.2-2.5** |

*PC-SPL: Post-circumcision-stretched penile length, SD: Standard deviation*

When infants were individually assessed, micropenis was identified in 5.6% prior to circumcision, decreasing to 3% postoperatively. In the 5-6-year age group, the prevalence of micropenis slightly increased from 13% preoperatively to 14% postoperatively. These findings suggest that both body weight percentiles and circumcision status may significantly influence the clinical evaluation and diagnosis of micropenis. However, circumcision does not alter the anatomical length of the penile shaft; the observed differences most likely reflect measurement-related variability, such as suprapubic fat compression, traction applied during SPL measurement, and absence of the prepuce as a reference landmark after circumcision. Therefore, the detected variations should be interpreted as measurement-related changes rather than true morphological alterations.

Akyüz (10) were among the first to investigate differences in SPL between circumcised and uncircumcised children, reporting significantly higher SPL values in circumcised patients. Their findings demonstrated that penile length measurements taken after circumcision were significantly longer than those taken before the procedure (10). These results support the findings of the current study, indicating that circumcision can influence penile measurements without affecting anatomical penile length.

Because the diagnosis of micropenis is based exclusively on SPL measurements, methodological differences in SPL measurements before and after circumcision may lead to false-positive or false-negative diagnoses. Clinicians should therefore interpret SPL values cautiously, particularly in recently circumcised patients and when evaluating micropenis based solely on SPL measurements.

With growing concerns about variations in pediatric body weight and their effects on general health, understanding the relationship between weight percentiles and penile dimensions may provide valuable insights for clinical assessment and surgical planning. Such knowledge is essential for improving the accuracy of diagnoses and optimizing patient outcomes.

A study by Mancini et al. (11) found that penile length in children with higher weight percentiles was approximately 10% shorter compared to children with normal weight. The authors also proposed a modified technique to enhance the accuracy of penile measurements in both normal-weight and higher-weight boys. Similarly, a study by Lee et al. (12) reported that body mass index (BMI) had a measurable impact on penile size assessments, with children in the normal BMI range having significantly longer BPL and SPL values than their higher-weight counterparts (12).

In our study, penile measurements in children with higher weight percentiles (≥75$^{th}$ percentile) were compared to those of children with normal or below-normal weight (<75$^{th}$ percentile). The results showed age-dependent differences: in the infant group, SPL values were significantly higher in the ≥75 P group compared to the <75 P group. However, repeated measurements in the ≥75 P group before and after circumcision revealed a significant decrease in SPL following the procedure. This reduction likely reflects technical measurement conditions and the presence of a prominent suprapubic fat pad PC, rather than an actual decrease in penile tissue length.

Conversely, in the 5-6 years age group, children in the ≥75 P group had significantly shorter SPL values than those in the <75 P group. Additionally, both percentile groups within this age range demonstrated significant reductions in SPL after circumcision. Among infants, these findings suggest that higher weight percentiles are associated with greater measured penile length. However, among children in higher percentiles, particularly in the 5-6-year group, pre-circumcision measurements may appear shorter, and the circumcision procedure may introduce further measurement-related variability that reduces the penile length measured on physical examination. Therefore, circumcision and weight percentile should be considered solely confounding factors when evaluating penile size, especially in the context of micropenis assessment, as they do not alter the underlying penile morphology.

Previous longitudinal studies have demonstrated that a proportion of children diagnosed with micropenis or constitutional small penis in the prepubertal period may reach normal penile dimensions during puberty, emphasizing the need for cautious interpretation of early diagnoses (13,14).

When evaluating glans size, GD was measured as the width rather than as the penile circumference. This measurement method is commonly used in the surgical assessment of patients with hypospadias. As expected, anthropometric measurements, such as GD, increase proportionally with age across all percentile groups. In our study, GD measurements increased proportionally with age in children below the 75$^{th}$ percentile (<75 P). However, in children at or above the 75$^{th}$ percentile (≥75 P), this pattern was not observed, and the results varied independently of age.

When subgroup analyses were performed, a statistically significant increase in GD was found only in infants in the ≥75 P group compared to those in the <75 P group. In all other age groups, the weight percentile did not appear to influence GD.

Bush et al. (15) reported that a smaller glans size is associated with a higher risk of urethroplasty complications. Based on our findings, weight percentile did not appear to influence GD in children older than two years with hypospadias. However, in the infant group, the observed proportional increase in GD among children in higher percentiles is a notable clinical finding that warrants further investigation of its anatomical permanence, and it may have a beneficial effect on surgical outcomes of procedures such as urethroplasty.

### Study Limitations

This single-center, retrospective study has limited generalizability. Secondly, due to the retrospective design of our study, a formal post-hoc statistical analysis for inter-observer agreement could not be performed. Although all measurements follow a strict, deeply embedded institutional standardization protocol using identical anatomical landmarks across all urological procedures, minor variations arising during handovers or from differences in individual technique between the two senior surgeons cannot be entirely ruled out. Furthermore, using the 75$^{th}$-percentile weight cut-off rather than the stricter 95$^{th}$-percentile definition of obesity limits direct comparison with the pediatric obesity literature and constitutes another methodological limitation.

The use of manual measurement tools may have introduced minor inaccuracies; potential confounding factors, such as hormonal or genetic influences, were not assessed. Postoperative conditions such as partial penile entrapment or trapped penis, which may influence perceived penile length, were not systematically evaluated and should be considered in future prospective studies. Furthermore, utilizing the 75$^{th}$ percentile weight cut-off rather than the standard percentile thresholds for overweight or obesity limits direct comparison with broader pediatric weight-status literature, which is another methodological limitation.

## Conclusion

This study demonstrates that circumcision status and body weight percentile can substantially influence penile measurement outcomes in pediatric patients, highlighting the importance of standardized measurement techniques in clinical evaluation. Importantly, the observed PC differences most likely reflect measurement-related variability rather than true anatomical alterations. Incorporating circumcision status and weight percentile into future normative reference data may improve the accuracy of micropenis diagnosis and enhance clinical decision-making in pediatric practice.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from the Ordu University Non-Interventional Scientific Research Ethics Committee on September 13, 2024 (approval number: 2024/116).

**Informed Consent:** Because this study utilizes a retrospective design based on historical patient records and contains absolutely no patient-identifying personal data, the requirement for written informed consent was evaluated and waived by the institutional review board.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: A.K.A., O.Y., Concept: A.K.A., Design: A.K.A., Data Collection or Processing: A.K.A., O.Y., Analysis or Interpretation: A.K.A., Literature Search: A.K.A., Writing: A.K.A., O.Y.

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CASE REPORT

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# Chylomicronemia-Induced Necrotizing Pancreatitis Treated with Therapeutic Plasma Exchange: A Case Report

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### What is known on this subject?

Severe hypertriglyceridemia (HTG) is a well-established but relatively uncommon cause of acute pancreatitis, particularly in patients with underlying familial hyperlipidemia or chylomicronemia. HTG-induced pancreatitis may follow a severe course, with an increased risk of necrotizing disease, organ failure, and intensive care unit admission. Rapid reduction of triglyceride (TG) levels is considered a key component of management in severe and complicated cases.

### What this study adds?

This case demonstrates that early therapeutic lipoprotein apheresis can provide rapid biochemical improvement and clinical stabilization in severe necrotizing pancreatitis secondary to chylomicronemia. It highlights the potential role of lipoprotein apheresis as an effective adjunct to standard medical therapy in selected high-risk patients with familial hyperlipidemia. The report emphasizes the importance of early recognition and aggressive TG-lowering strategies in the intensive care management of HTG-induced pancreatitis.

## ABSTRACT

Acute pancreatitis associated with severe hypertriglyceridemia, especially when it develops in the context of familial hyperlipidemia and chylomicronemia syndrome, is characterized by rapid clinical deterioration, a necrotizing course, and multiple organ dysfunction. Therapeutic plasma exchange (TPE) may be considered a treatment option in severe cases due to its rapid triglyceride (TG)-lowering effect. In our patient, TG levels above 2000 mg/dL, together with necrotizing pancreatitis, metabolic acidosis, and acute kidney injury, indicated rapid clinical deterioration. The observed reduction in TG levels and the clinical improvement in this patient suggest that TPE could be considered in selected severe cases. Early use of TPE in intensive care settings may be an option in selected cases; however, further studies are required.

**Keywords:** Critical care medicine, therapeutic plasma exchange, acute necrotizing pancreatitis, hypertriglyceridemia, chylomicronemia

## Introduction

Acute pancreatitis (AP) associated with severe hypertriglyceridemia (HTG) can progress rapidly with multiple organ dysfunction, particularly when it develops in the context of familial hyperlipidemia and chylomicronemia syndrome (1). HTG-AP develops from lipotoxicity resulting from disruption of the pancreatic microcirculation by triglyceride (TG)-rich lipoproteins, particularly chylomicrons, which circulate in the bloodstream and are hydrolyzed by pancreatic lipase into free fatty acids (FFAs). These mechanisms lead to pancreatic ischemia, inflammation, and necrosis, resulting in a severe course of the disease (2). Recurrent pancreatitis attacks and the need

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for intensive care unit (ICU) follow-up are more frequently reported in patients with hereditary lipoprotein metabolism disorders (3,4).

The treatment of hypertriglyceridemic pancreatitis essentially involves the standard approach to AP; however, rapidly lowering TG levels is critically important in the course of the disease. In addition to medical treatment, TPE has been proposed as a potential treatment option for the rapid control of TG levels in these patients (2).

In this report, we present the management and clinical course of severe hypertriglyceridemic necrotizing pancreatitis developing on the basis of chylomicronemia associated with familial hyperlipidemia in patients treated with TPE in the ICU.

## Case Report

A 25-year-old male patient with known type 1 diabetes mellitus and familial hyperlipidemia presented to the emergency department with complaints of abdominal pain, nausea, and vomiting. Blood samples drawn in the emergency department yielded lipemic serum. The patient's tests revealed an amylase level of 1741 U/L and a lipase level of 1424 U/L; contrast-enhanced computed tomography showed acute necrotic pancreatitis, and the patient was admitted to the ICU. The patient's history was notable for recurrent episodes of pancreatitis and one prior episode of TPE. Tests performed in the ICU revealed metabolic acidosis (pH 7.273, bicarbonate 14.8), a TG level of 2786 mg/dL, a urea level of 61.4 mg/dL, a creatinine level of 2.75 mg/dL, and a glomerular filtration rate of 31. The patient was diagnosed with acute necrotizing pancreatitis due to chylomicronemia. In the ICU, in addition to intravenous hydration, fibrate therapy for HTG, omega-3 supplementation, and insulin infusion therapy, TPE was performed. Therapeutic plasma exchange was initiated 24 hours after ICU admission and on day 3. The procedure was performed using a centrifugal technique. Each session lasted approximately 1.5 hours. Two sessions were conducted. No procedure-related complications were observed. TG levels were monitored. During follow-up, the patient's TG level decreased to 482 mg/dL and did not increase thereafter. The percentage reduction and temporal changes in TG levels are summarized in Figure 1. After a 9-day stay in the ICU, the patient was transferred to the internal medicine ward upon achieving clinical stabilization and improvement.

Written informed consent was obtained from the patient for publication of clinical data and accompanying images.

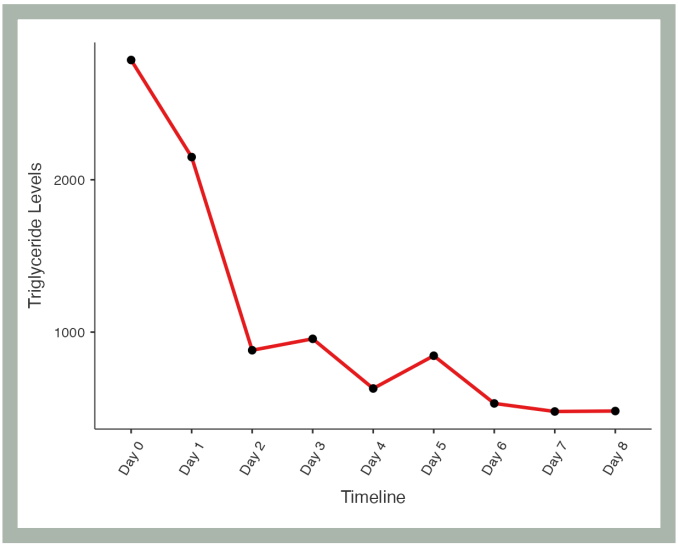


**Figure 1.** Trend of serum triglyceride levels during intensive care follow-up and after therapeutic plasma exchange

## Discussion

AP associated with HTG is a well-defined clinical entity that is often subject to diagnostic delay in clinical practice and can be severe, particularly when it occurs in the context of a genetic predisposition. According to the Endocrine Society guidelines, TG levels above 1000 mg/dL significantly increase the risk of AP, and this risk becomes even more pronounced at levels above 2000 mg/dL (1). A TG level of 2786 mg/dL was the biochemical basis for the development of necrotizing pancreatitis.

The pathophysiology of HTG-AP is related to lipotoxicity resulting from disruption of the pancreatic microcirculation by chylomicron-rich lipoproteins and from hydrolysis of TG into FFAs via pancreatic lipase. Unbound FFAs trigger acinar cell necrosis by causing local acidosis, endothelial dysfunction, and mitochondrial damage (2). These mechanisms biologically explain why HTG-AP is associated with a more frequent necrotizing course, organ failure, and ICU requirements (3). The presence of metabolic acidosis and acute kidney injury in this case can be considered a clinical manifestation of these systemic effects.

An important clinical pitfall in the diagnosis of HTG-AP is that TG levels can decrease rapidly in the acute phase, and the etiology may be overlooked in later measurements (5). Findings reported in the literature suggest that measuring serum TG levels early may be useful in clinical practice for patients evaluated for idiopathic pancreatitis.

The primary approach for the treatment of HTG-AP involves rapid reduction of TG levels, as reducing the TG

load during the acute phase, in conjunction with standard AP management, may limit pancreatitis and the systemic inflammatory response associated with lipotoxicity (6). For this purpose, intravenous insulin infusion is commonly used and may facilitate TG reduction (7). Additionally, fibrate therapy, which suppresses hepatic TG production, and omega-3 fatty acids, which reduce TG synthesis, contribute to long-term TG control (1). To our patient, intravenous insulin infusion, fibrate therapy, and omega-3 fatty acid therapy were administered in addition to standard intensive care.

TPE has been reported to produce rapid biochemical improvement in patients with HTG-AP by removing circulating chylomicrons and TGs. However, its superiority in terms of mortality and long-term clinical outcomes is unclear (8). According to the American Society for Apheresis guidelines, TPE may be considered in selected severe cases (9). Because of the clinical characteristics of our patient, TPE was performed, and clinical stabilization was achieved, with TG levels falling below 500 mg/dL within a short period.

## Conclusion

AP associated with HTG can be severe, particularly when it occurs in the setting of chylomicronemia. Our patient had a history of recurrent pancreatitis characterized by high TG levels, and TPE was followed by a rapid reduction in TG levels and clinical improvement. This case suggests that TPE may be considered an adjunctive option for selected patients with severe HTG-AP. Further studies are required to clarify its clinical impact.

### Ethics

**Informed Consent:** Written informed consent was obtained from the patient for publication of clinical data and accompanying images.

### Footnotes

### Authorship Contributions

Concept: M.D., G.H.A., Design: M.D., K.U., Data Collection: M.D., Literature Search: M.D., K.U., Writing: M.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Severe Orthostatic Hypotension and Weight Loss After Bortezomib, Lenalidomide, and Dexamethasone Therapy

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**Keywords:** VRD therapy, multiple myeloma, orthostatic hypotension, weight loss

**To the Editor,**

Peripheral neuropathy is common in patients with multiple myeloma (MM), whereas severe treatment-related orthostatic hypotension, syncope, and weight loss are rarely reported. We describe a patient who developed severe orthostatic hypotension and marked weight loss during VRD therapy (bortezomib, lenalidomide, dexamethasone).

A 55-year-old man presented with dizziness, blurred vision, and shortness of breath for 1-2 weeks. He had a history of coronary artery disease and hypertension, and he was diagnosed with immunoglobulin G lambda MM. The disease was stage II according to both the International Staging System (ISS) and the revised ISS. Because of findings of hyperviscosity, three sessions of plasmapheresis were performed, and VRD therapy (bortezomib 1.3 mg/m$^2$, lenalidomide 25 mg/day, dexamethasone 40 mg/week) was initiated.

On day 8 of the second treatment cycle, the patient developed anorexia, nausea, and dizziness upon standing. Laboratory tests showed: Na 133 mmol/L, creatinine 1.5 mg/dL, hemoglobin 10 g/dL, platelets 350,000/mm$^3$, and white blood cells 5,000/mm$^3$. Blood pressure was monitored. Within 1 minute of standing, a 30 mmHg drop in systolic blood pressure and a 20 bpm increase in heart rate confirm orthostatic hypotension. Intravenous saline replacement was administered. Doxazosin was discontinued, and the lercanidipine dose was reduced.

After the third cycle, the patient developed persistent anorexia, presyncope, orthostatic hypotension, and marked weight loss (approximately 30% of body weight). Lercanidipine was discontinued. Echocardiography showed a normal ejection fraction without valvular pathology. Endoscopy and colonoscopy with biopsy revealed no evidence of amyloidosis.

Following the fourth cycle, the patient experienced recurrent presyncope upon standing. A brain magnetic resonance imaging was performed to rule out neurological disorders, but no pathological findings were observed. Echocardiography was repeated and rhythm and blood pressure were monitored with a Holter monitor. Carotid Doppler ultrasonography was performed. No stenosis was observed. VRD therapy was discontinued. Response evaluation after the fourth cycle demonstrated a complete response, and the patient subsequently underwent

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autologous hematopoietic stem cell transplantation with high-dose melphalan (200 mg).

During hospitalization, he received intensive hydration until engraftment and experienced no syncope. However, two days after discharge, he was readmitted due to recurrent syncope when standing. He was unable to perform daily activities and reported severe dizziness even while sitting, along with persistent anorexia. Neurology and cardiology evaluations revealed no pathology other than orthostatic hypotension.

Compression stockings, increased oral hydration, and midodrine (5 mg twice daily) were initiated. Because recurrent syncope caused anxiety, escitalopram was started and oral nutritional support was provided. After initiation of midodrine, syncope did not recur, and the patient gradually returned to normal physical activity. Midodrine was tapered during follow-up. Weight loss stabilized after discontinuation of VRD therapy.

Peripheral neuropathy occurs in approximately 35% of MM patients and is more common in those who have previously received neurotoxic treatment or have pre-existing neuropathy (1). Bortezomib-associated neuropathy is predominantly sensory, and postural hypotension has been reported in approximately 10% of patients; this condition is likely related to dehydration, concomitant antihypertensive treatment, or autonomic dysfunction (2). A clear association between lenalidomide and orthostatic hypotension has not been reported. In our case, VRD treatment was associated with progressive orthostatic hypotension, leading to syncope and significant impairment of daily activities. Discontinuation of antihypertensive drugs and administration of intravenous hydration initially improved symptoms, but the improvement was insufficient in subsequent treatment cycles. It was controlled with compression stockings and midodrine. Pregabalin (3) improved bortezomib-associated orthostatic hypotension in a previously reported case. Shishkina et al. (4) reported postural hypotension and weight loss in a case series of patients receiving VRD treatment. Patients were treated with fludrocortisone or midodrine, and appetite stimulants were used to control weight loss. In this case, tests necessary to differentiate neurogenic orthostatic hypotension, such as the tilt-table test and Valsalva maneuver, could not be performed. Bortezomib-associated autonomic dysfunction was considered the most likely cause given the significant neuropathic effects; however, the contribution of lenalidomide could not be ruled out. We believe that classifying orthostatic hypotension in this patient group will guide drug selection.

Clinicians should be aware that severe orthostatic hypotension, accompanied by syncope and weight loss, may occur during VRD therapy. Management may include hydration, compression stockings, discontinuation of antihypertensive medications, and pharmacological agents such as midodrine.

### Ethics

**Informed Consent:** Written informed consent for publication of this case was obtained from the patient.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: B.T.T., E.K., Concept: B.T.T., Design: B.T.T., Data Collection or Processing: B.T.T., E.K., Analysis or Interpretation: B.T.T., Literature Search: B.T.T., Writing: B.T.T.

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