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UPSTREAM VS. DOWNSTREAM: COMPLEMENT INHIBITION STRATEGIES FOR PEDIATRIC C3G AND AHUS—EFFICACY, SAFETY, AND LONG-TERM KIDNEY OUTCOMES

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Abstract
Complement dysregulation drives C3 glomerulopathy (C3G) and atypical hemolytic uremic syndrome (aHUS), two rare pediatric kidney diseases with substantial risks for chronic kidney disease, dialysis, and transplant complications. Therapeutic strategies target either upstream complement nodes or the downstream terminal pathway at C5.
For pediatric aHUS, C5 blockade with eculizumab and ravulizumab demonstrates consistent clinical benefit with acceptable safety in trials and registries, though meningococcal disease prevention is mandatory. For pediatric C3G, upstream approaches—especially factor B inhibition with iptacopan—show early signals of proteinuria reduction and kidney function stabilization, but pediatric-specific data remain limited within broader mixed-age cohorts. Across both conditions, longer-term renal trajectories, relapse rates after stopping therapy, and transplant outcomes in children are incompletely documented. Until robust pediatric trials arrive, C5 blockade anchors aHUS care, while upstream strategies in C3G require case-by-case consideration based on phenotype, access, and transparent discussion of evidence gaps.

Keywords: pediatric; C3 glomerulopathy; atypical hemolytic uremic syndrome; complement inhibition; C5 blockade; alternative pathway

Introduction

Complement activation drives the pathogenesis of C3 glomerulopathy (C3G) and atypical hemolytic uremic syndrome (aHUS). In children, both conditions can progress rapidly and cause long-term kidney damage. Therapeutic strategies fall into upstream control of C3/convertase or alternative/lectin pathway factors, and downstream terminal pathway inhibition at C5. The attached pediatric literature on aHUS robustly supports C5 blockade with eculizumab or the long-acting ravulizumab [1–7]. Pediatric-specific evidence for upstream inhibition in C3G is emerging, with iptacopan (factor B inhibition) reports and mechanism-focused studies of factor D and other targets, though much of the evidence mixes adult and pediatric data or does not separate them clearly [8–13].
This review uses only the attached sources to compare upstream and downstream strategies for children with C3G and aHUS, focusing on efficacy, safety (especially meningococcal risk), and longer-term kidney outcomes.

Mechanistic overview: upstream vs. downstream targets

Upstream targets reduce formation or activity of the C3/C3-convertase and alternative/lectin pathway amplification. In the attachments, upstream strategies include **factor B inhibition (iptacopan)** with signals of proteinuria reduction and renal stabilization in C3G cohorts, and **factor D inhibition** blocking alternative pathway activation induced by C3 nephritic factors in experimental and translational contexts. Pediatric-specific upstream data exist but remain limited compared with adult-rich datasets in several PDFs (not always separable). **Lectin-pathway/MASP-2** targeting is conceptually upstream; pediatric data are absent from the attachments.

Downstream C5 inhibition (eculizumab, ravulizumab) blocks terminal pathway activation and membrane attack complex formation. For pediatric aHUS, the attachments include trials, registries, and multicenter reports that demonstrate clinical response and renal recovery patterns with eculizumab and similar efficacy with less frequent dosing for ravulizumab. For C3G, clinicians have used downstream inhibition in selected cases; pediatric subgroup outcomes appear in some reports, often mixed with adults. Upstream strategies block complement amplification earlier in the cascade, while downstream C5 blockade stops terminal pathway damage regardless of upstream driver.

Pediatric evidence—C3 glomerulopathy (C3G)

Upstream approaches

Factor B inhibition (iptacopan). Reports describe proteinuria reduction and kidney function stabilization in C3G cohorts that include or comment on pediatric cases, though pediatric-only data remain limited and sometimes embedded within mixed-age analyses [8–10].

Factor D inhibition. Early translational evidence supports factor D inhibition reducing alternative pathway activation induced by C3 nephritic factors in experimental and C3G-like settings, though clinical pediatric outcome data remain limited to high-level mentions [11–13].

Lectin pathway (MASP-2) inhibition. Pediatric data for MASP-2 targeting are absent from the attachments. Across upstream agents, pediatric-only numerics (numerators/denominators, eGFR slopes, remission rates) are not reported in attached sources [8–13].

Downstream approaches

C5 inhibition (eculizumab, ravulizumab). Many reports focus on aHUS or adult C3G [4–6]; where pediatric C3G appears, detailed pediatric-only renal efficacy (e.g., eGFR slope) is not reported in attached sources [4–6].

Durability, remission, and relapse

Sustained remission, relapse after weaning, and ≥12-month pediatric outcomes in C3G are inconsistently documented across the attachments. For iptacopan-treated cohorts, longer-term pediatric-only durability signals are not reported in attached sources [8–10].

Transplant C3G

Pediatric transplant recurrence and graft outcomes under upstream or downstream inhibition are not reported in attached sources where not explicitly stated.

Clinical implications

Upstream factor B inhibition (iptacopan) shows signals relevant to C3G, with pediatric-specific detail limited [8–10]. Factor D evidence remains mechanistic or early-stage [11–13]. C5 blockade evidence in pediatric C3G is sparse [4–6]. Clinicians must individualize choice of upstream versus downstream therapy in a child with C3G pending dedicated pediatric trials.

Pediatric evidence—aHUS

Downstream C5 inhibition (anchor therapy)

Multiple pediatric studies and multicenter experiences support C5 blockade in aHUS. A pediatric ravulizumab trial in treatment-naïve patients reports N=21 in the safety analysis set, with follow-up

to week 50 and improvements in hematologic and quality-of-life measures [1]. A cohort of N=10 pediatric patients previously treated with eculizumab and switched to ravulizumab showed stable kidney and hematologic parameters through 50 weeks, with dosing every 4–8 weeks [3].
Eculizumab data span longer-term experience and registries with improvement in TMA markers and renal recovery; pediatric cohorts and mixed-age analyses appear in multiple attachments [4–7]. Where precise pediatric numerics (e.g., platelet normalization time, dialysis discontinuation rates) are not clearly extractable from the PDFs, those specifics are not reported in attached sources [4–7].

Upstream inhibition in pediatric aHUS
The attachments do not present pediatric aHUS outcome data with upstream agents. Mechanistic plausibility exists for alternative pathway control, but clinical pediatric-only results are not reported in attached sources [11–13].

Genetics and response
aHUS genetics (complement gene variants, autoantibodies) shape disease and may influence therapy duration. Attached genetic reviews provide background but do not consistently link specific pediatric genotypes to differential responses to upstream versus downstream therapy in extractable tables [14–16]. Where explicit pediatric genotype-response data are absent, this is not reported in attached sources [14–16].

Table 1. Targets and agents (Upstream vs Downstream)

Pathway position	Target	Agent	Population in attachments	Evidence type	Pediatric notes
Upstream	Factor B (alternative pathway)	Iptacopan	Mixed C3G cohorts; pediatric subset referenced/embedded [8–10]	Trials/clinical reports	Proteinuria reduction and kidney stabilization reported; pediatric-only numerics not reported in attached sources [8–10]
Upstream	Factor D (alternative pathway)	Factor D inhibitors	Translational/early clinical contexts [11–13]	Experimental/translational	Pediatric clinical outcomes not reported in attached sources [11–13]
Upstream	Lectin pathway	MASP-2 inhibitors	Not reported in attached sources	—	Not reported in attached sources
Downstream	C5	Eculizumab	Pediatric aHUS cohorts/registries [4–7]	Trials/registries	Consistent clinical benefit; meningococcal prevention required [17]
Downstream	C5	Ravulizumab	Pediatric aHUS (naïve and switch cohorts) [1,3]	Trials/multicenter	Similar efficacy with extended dosing interval in children [1,3]

Table 2. Pediatric efficacy by disease & agent

Disease	Agent	N (pediatric)	Follow-up (months)	Primary signal	Relapse/Failure	Transplant outcomes
aHUS	Ravulizumab (naïve) [1]	21	11.5 (week 50)	Hematologic response over time; QoL improvement	—	—
aHUS	Ravulizumab (switch from eculizumab) [3]	10	11.5 (week 50)	Stable kidney and hematologic parameters; dosing every 4–8 weeks	—	—
aHUS	Eculizumab [4–7]	—	—	Resolution of TMA markers and renal recovery described	—	—
C3G	Iptacopan (factor B) [8–10]	—	—	Proteinuria reduction; kidney stabilization in cohorts with pediatric inclusion	—	—
C3G	Factor D inhibitors [11–13]	—	—	Translational AP blockade; clinical pediatric signals not reported	—	—

Note: Values shown only when present in the manuscript. Em dashes (—) indicate data not reported in attached sources.

Table 3. Safety & monitoring in children

Agent	Serious infections (incl. meningococcus)	Discontinuations due to AE	Other notable AEs	Median/mean follow-up
Eculizumab [4–7]	Pediatric counts not reported in attached sources	—	—	—
Ravulizumab [1,3]	Pediatric counts not reported in attached sources	—	—	11.5 months (week 50)
Iptacopan [8–10]	Pediatric AE breakdown not reported in attached sources	—	—	—

Note: CDC meningococcal vaccination and chemoprophylaxis guidance applies to all C5 inhibitors (eculizumab, ravulizumab) [17]. Em dashes (—) indicate data not reported in sources. Pediatric-specific adverse event rates are limited or mixed with adult data across agents.

Durability and stopping

Weaning/retreatment strategies, relapse risk after discontinuation, and ≥12-month pediatric renal trajectories are incompletely documented across the attachments [1,3–7]. Uniform pediatric stop rules are not reported in attached sources [1,3–7].

Clinical implications

C5 blockade (eculizumab, ravulizumab) remains the most consistently supported approach for pediatric aHUS in the attachments, with acceptable safety under appropriate meningococcal disease prevention [1,3–7,17].

Safety in children

Meningococcal disease risk under C5 blockade

CDC guidance outlines meningococcal vaccination recommendations and the importance of chemoprophylaxis or accelerated vaccination when starting C5 inhibitors [17]. Many pediatric reports reference vaccination/prophylaxis requirements [1,3–7].

Other infections and adverse events

Infusion reactions, common infections, and discontinuations appear across pediatric cohorts, though pediatric-specific counts are not reported in attached sources [1,3–7].

Upstream agents

For iptacopan, attached reports describe acceptable tolerability with attention to monitoring; pediatric-specific AE breakdowns remain limited or mixed with adult data [8–10]. Factor D-related safety in pediatric C3G/aHUS is not reported in attached sources beyond experimental or early human contexts [11–13].

Clinical implications

Meningococcal prevention (vaccination and/or prophylaxis) is mandatory before starting C5 inhibitors in children. Clinicians should systematically review infection prophylaxis at each encounter [17].

Transplant scenarios

aHUS after transplant

The attachments acknowledge transplant risks and the use of C5 blockade for prevention/treatment; pediatric-only transplant outcome tables are not reported in attached sources where not explicitly present [1,4–7].

C3G after transplant

Recurrence under different strategies and pediatric graft outcomes with upstream (e.g., factor B) or downstream inhibition are not reported in attached sources unless stated in an individual PDF [8–10].

Clinical implications
Transplant planning for children with C3G or aHUS should include multidisciplinary discussion of peri-transplant complement inhibition; when pediatric-specific outcome data are limited, clinicians should consider genetics, relapse history, access and logistical factors, and family preferences in shared decision-making [1,4–10,14–16].

Practical considerations in pediatrics
When to favor downstream (C5) vs upstream
• **aHUS:** C5 blockade (eculizumab or ravulizumab) is most consistently supported by the attached pediatric evidence; ravulizumab offers less frequent dosing with similar efficacy in children [1,3].
• **C3G:** Consider upstream approaches (e.g., factor B inhibition) where access exists and clinical phenotype suggests complement amplification; acknowledge that pediatric data remain limited [8–10].
Vaccination and prophylaxis
Follow CDC meningococcal vaccination/prophylaxis before and during C5 blockade [17].

Monitoring
Track renal function (eGFR), proteinuria, hemolysis/TMA markers (aHUS), and growth parameters, though many pediatric-specific monitoring schedules are not reported in attached sources [1,3–10].

Stopping/retreatment
Uniform pediatric stop rules are not reported in attached sources. Decisions rely on genetics, relapse history, and shared decision-making [1,3–7,14–16].

Clinical implications
These considerations underscore the need for individualized treatment plans informed by disease phenotype, available evidence, local access to therapies, and family values when pediatric data are incomplete [1,3–10,14–17].

Evidence gaps & research needs
• Pediatric-specific C3G trials with upstream inhibitors (clear pediatric numerators/denominators, eGFR slope, remission, histology).
• Comparative effectiveness of upstream vs downstream strategies in defined pediatric phenotypes.
• Durability data (≥12–24 months), relapse after weaning, and growth outcomes.
• Transplant-focused pediatric cohorts for both C3G and aHUS.

Conclusion
In the attachments, pediatric aHUS responds consistently to downstream C5 blockade with manageable safety under meningococcal prevention measures. For pediatric C3G, upstream inhibition—especially factor B—offers a biologically coherent approach with early signals, but pediatric-only outcomes remain limited in attached reports.
Until larger pediatric datasets arrive, clinicians should individualize therapy: C5 blockade anchors pediatric aHUS care; upstream strategies in pediatric C3G may be considered where evidence and access allow, with close monitoring and transparent discussion of uncertainties.

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