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INVITED REVIEW

Differences in glucocorticoid use in childhood vasculitis

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ABSTRACT

This review aimed to explore the differences in glucocorticoid use across various subtypes of childhood vasculitis, focusing on their effectiveness, potential side effects, and tapering strategies to minimize toxicity. A comprehensive review was conducted to evaluate the clinical applications of glucocorticoids in pediatric vasculitis subtypes. Recommendations from recent studies and guidelines were assessed, focusing on glucocorticoid protocols for conditions such as IgA vasculitis, Kawasaki disease, polyarteritisnodosa, ANCA-associated vasculitis, and Takayasu arteritis. Glucocorticoid tapering strategies and toxicity indices, such as the Pediatric Glucocorticoid Toxicity Index (pGTI), were also analyzed. Glucocorticoid use varied across vasculitis subtypes. For IgA vasculitis, mild cases were managed with oral prednisolone, while severe nephritis required intravenous methylprednisolone and immunosuppressants. In Kawasaki disease, corticosteroids were used for refractory cases alongside IVIG and aspirin. Severe polyarteritis nodosa cases showed better outcomes with cyclophosphamide and high-dose glucocorticoids, whereas non-severe cases benefitted from low-dose glucocorticoids and NSAIDs. ANCA-associated vasculitis studies reported no significant correlation between glucocorticoid dose and outcomes, although side effects were dose-dependent. In Takayasu arteritis, children generally received lower doses than adults, based on adult treatment guidelines. The pGTI was highlighted as a valuable tool to monitor and assess glucocorticoid toxicity in pediatric patients. Glucocorticoids remain a cornerstone of treatment in pediatric vasculitis, but their use must be carefully tailored to balance efficacy and toxicity. Early tapering and transitioning to alternative therapies, when feasible, are critical to minimizing adverse effects.

Keywords: Glucocorticoids, pediatric vasculitis, glucocorticoid tapering, pGTI (Pediatric Glucocorticoid Toxicity Index).

Introduction

Steroid treatment is widely used in pediatric vasculitis cases, although it varies according to the vasculitis subtype. Most treatment protocols include intensive induction followed by maintenance therapy. Glucocorticoids are the most potent anti-inflammatory agents used in the treatment of rheumatic diseases. These agents are synthetic analogues of endogenous molecules produced by the body. Glucocorticoids show anti-inflammatory and immunosuppressive effects in both early and late phases of inflammation. Their main effects on the immune system are mediated through T lymphocytes [1]. Since the side effects associated with long-term systemic use of these agents are an important issue, the risk/benefit ratio should be carefully evaluated in theuse of glucocorticoids in children, including pediatric vasculitis cases (Table 1) [2].

The aim of glucocorticoid treatment should be to prevent or minimise toxicity as much as possible. For this purpose, glucorticoids with short half-life should be preferred. Prednisone is the most commonly used oral agent among other synthetic steroid analogues due to it slow risk/benefit ratio in children. A single daily administration in the morning is recommended. Dose reduction should be planned in a personalised manner according to the patient. Vitamin D should be supplemented with calcium to prevent osteoporosis [3].

Table 1. Side effects and mechanisms related to glucocorticoid drugs in children

Growth suppression	The most undesirable long-term effect, especially in young children
	Inhibition of IGF-1 production
	Decrease in chondrocyte proliferation
Central nervous system	Psychosis (high dose, first 4 days)
	Acute onset euphoria, mania
	Depression in the late period
	Pseudotumour cerebri
Osteoporosis	Directly reduces bone formation
	Reduces calcium absorption
	Increases urinary calcium excretion
	Increases bone destruction
	Treatment everyother day is not preventive
Muscle disorders	After high dose
	Myopathy, atrophy of proximal muscles
	Pain, tenderness
	Muscle enzymes and EMG may be normal
Cataract	>9 mg/m^2 prednisone equivalent dose and
	significant risk in use for> 1 year
Infection and Immunity	Effects due to immunesuppression
Cardiovascular system	Hypertension
	Dyslipidaemia
Hematological changes	Lymphopenia
	Notrofilia

The perioperative management of children receiving glucocorticoids should be carefully planned. Patients receiving any dose of glucocorticoids for less than three weeks [4], patients receiving less than 5 mg/day prednisone (or equivalent) in the morning for any period [5] and patients receiving less than 10 mg prednisone (or equivalent) every other day [6] do not require additional glucocorticoids perioperatively. However, perioperative glucocorticoid use is required in patients with functional suppression of the hypothalamo-pituitary-adrenal (HPA) axis who use more than 20 mg/day prednisone (or equivalent) for more than three weeks or who develop Cushing's syndrome clinically. However, in patients receiving 5-20 mg/day prednisone (or equivalent) for more than three weeks, perioperative evaluation is also required in these patients in terms of possible HPA axis suppression [5].

The classification criteria for the most prevalent vasculitides in childhood, including immunoglobulin A vasculitis/Henoch-Schonlein purpura (IgAV/HSP), Kawasaki Disease (KD) , polyarteritis nodosa (PAN), granulomatous polyangiitis/Wegener granulomatosis (GPA/WG), and Takayasu arteritis (TA), were established and validated at the 2008 Ankara Consensus Conference with the support of the European League Against Rheumatism (EULAR), Pediatric Rheumatology European Society (PReS), and the Pediatric Rheumatology International Trials (PRINTO) (Table 2) [7].

IgAV/HSP

IgAV/HSP is the most common vasculitis in childhood and is frequently observed in the age range of 3-15 years [8]. Nontrombocytopenic purpura, arthritis/arthralgia, gastrointestinal system involvement and renal involvement constitute the clinical picture. According to Ankara 2008 classification criteria for IgAV/HSP in children, typical purpura (mandatory criterion) with lower limb predominance and at leastone of the following; abdominal pain, histopathology (typical leucocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposits), arthritis/arthralgia, and renal involvement (proteinuria or hemorrhagia) are needed [7].

Table 2. Classification of childhood vasculitis [6]

Predominantly large sized vessel vasculitis	**Takayasu arteritis**
Predominantly medium-sized vessel vasculitis	Childhood polyarteritis nodosa Cutaneous polyarteritis Kawasaki disease
Predominantly small-sized vessel vasculitis	Granulomatous √ Wegener granulomatosis * √ Churg-Strauss syndrome* Nongranulomatous √ Microscopicpolyangitis √ Henoch-Schönlein purpura √ Isolated cutaneous leukocytoclastic vasculitis √ Hypocomplementemic urticarial vasculitis
Other vasculitides	Behçet disease Vasculitis secondary to infection, malignancy and drugs Vasculitis associated with connective tissue diseases Isolated central nervous system vasculitis Cogan sydrome Unclassified

*This classification was established prior to the eradication of eponyms and histopathological subclassification by the 2012 Chapel Hill Consensus on Nomenclature of Systemic Vasculitis.

A pediatric initiative (Single Huband Access point for pediatric Rheumatology in Europe; SHARE) has developed recommendations by European experts based on systematic literature reviews [9-11]. According to the SHARE recommendations for IgAV the conditions indicating steroid treatment are orchitis, cerebralvasculitis, pulmonary hemorrhage, and other severe organ/life-threatening vasculitic involvement. In these cases, oral corticosteroid (CS) (prednisolone/prednisone) doses of 1-2 mg/kg/day and methylprednisolone (10-30 mg/kg, maximum 1 g/day for three consecutive days) in severe cases are recommended [11].

SHARE recommendations for the treatment of pediatric IgAV nephritis (IgAVN) are evaluated separately according to mild, moderate, and severe involvement of the disease. According to these oral prednisolone is recommended as first-line treatment for patients with mild IgAV nephritis. For patients with moderate IgAV nephritis, oral prednisol or pulsed intravenous (i.v.) methylprednisolone (IVMP) has been recommended as first-line treatment. In severe IgAV nephritis, treatment with high-dose CS and i.v. cyclophosphamide to induce remission and lower-dose CS in combination with azathioprine (AZA) or mycophenolate mofetil (MMF) as maintenance therapy is usually recommended [11].

In a study of a total of 359 children with IgAVN, 108 patients (30%) received oral steroids alone, 207 patients (51%) received three methylprednisolone pulses followed by oral steroids, and 44 patients (12.5%) were followed up without steroids in a study published in 2023, involving 14 centres in France, aimed at evaluating the role of steroids on IgAVN outcomes. When 32 children treated with oral steroids alone were compared with 32 matched control patients who did not receive steroids, one year after disease onset, the IgAVN remission rate was similar between these two groups (62% vs. 68%, respectively). When 93 children treated with oral steroids alone were compared with 93 matched control patients treated with oral CSs followed by three methylprednisolone pulses, the IgAVN remission rate was not different between these two groups (77% vs. 73%, respectively). The benefit of oral steroids and methylprednisolone pulses alone cannot be determined on the basis of this observational study and randomised controlled trials are needed [12].

Kawasaki disease

Kawasaki disease (KD) is a vasculitis that predominantly affects medium and small sized

arteries. There is nospecific test to diagnose KD, but according to the American Heart Association, patients are classified as having KD if they have a fever lasting at least 5 days (a mandatory criterion) and four of the following criteria: oropharyngeal changes, peripheral limb changes or changes in the perineal region, bilateral conjunctival injection, polymorphous rash, cervical lymphadenopathy [13].

According to SHARE recommendations for the treatment of KD, intravenous immunoglobuline (IVIG), 2 g/kg single dose, and aspirin (30-50 mg/kg/day, 4 divided doses) should be started in the first 10 days of the disease as initial treatment of KD. A second IVIG infusion, most commonly 2 g/kg i.v., is recommended as a treatment option in patients with refractory KD. Corticosteroids are recommended in high-risk patients, those who are resistant to IVIG (with or without a second IVIG dose), those with Kobayashi score≥5 , hemophagocytic lymphohistiocytosis, shock clinic, patients younger than 1 year of age, patients with coronary aneurysm. If CS sare indicated, the following regimens would be reasonable:

Regimen 1: Methylprednisolone 0.8 mg/kg i.v. for 5-7 days or until C-reactive protein (CRP)normalises; then oral prednisone/prednisolone 2 mg/kg/day and discontinued over the next 2-3 weeks.

Regimen 2: Methylprednisolone 10-30 mg/kg (maximum 1 g/day) once daily for 3 days, followed by oral prednisone/prednisolone 2 mg/kg per day until day 7 or until CRP normalizes. Then it can be planned to be discontinued within the next 2-3 weeks (10).

According to European consensus-basedrecommendations for the diagnosis and treatment of rare pediatric vasculitides; IVMP 10-30 mg/kg (max 1g/day) is used for 3 days in induction treatment and then oral prednisone is started. Oral prednisolone is given as 1-2 mg/kg/day (max 60 mg/day). After the first month of treatment, the dose is reduced to 0.8 mg/kg/day and it is recommended to reduce the dose to 0.2 mg/kg (or 10 mg, whichever is lower) in the 6th month by decreasing the dose every month at a dose of 0.1-0.2 mg/kg/day. There commended dose of prednisolone in the maintenance phase is 0.1-0.2 mg/kg/day. Incase of minor relapse during the maintenance phase, prednisolone treatment is increased to 0.5 mg/kg/day, followed by a return to the basal steroid dose in 4 weeks. In case of refractory disease or failure in primary induction, IVMP (10-30 mg/kg maximum 1 gr/day) is given for 3 days, the prednisolone dose is increased to 1 mg/kg/day and decreased to 0.25 mg/kg/day in 4 weeks, and subsequent dose reductions are recommended according to the clinical picture [9].

Childhood Polyarteritis Nodosa

According to EULAR/PRINTO/PRES, Ankara 2008 criteria, the diagnosis of PAN in childhood is defined as the presence of necrotising vasculitis or angiographic abnormality in medium or small sized arteries (mandatory criterion) togethe rwith skin involvement (livedo reticularis, skin nodules, superficial or infarcts), myalgia or muscle tenderness, hypertension, peripheral neuropathy and renal involvement [7]. PAN treatment recommendations in children are based on retrospective pediatric data and recommendations for adult PAN patients. In patients presenting with skin involvement, in the absence of severe systemic inflammation and other major organ involvement, nonsteroidalanti-inflammatory drugs (NSAIDs) and/or CS therapy alone may be appropriate with careful monitoring of clinical and laboratory parameters [9].

According to the American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa 2021, the treatment approach of active PAN differs according to whether the disease is severe or non-severe. For newly diagnosed patients with active, severe PAN, it is recommended to start treatment with cyclophosphamide and high-dose glucocorticoids instead of high-dose glucocorticoid salone. For newly diagnosed patients with active, non-severe PAN, treatment with non-glucocorticoid immunosuppressive agents and glucocorticoids is conditionally recommended instead of glucocorticoids alone. The optimal duration of glucocorticoid therapy for PAN (e.g. taper every 6 months or longer than 6 months) is not wellestablished and therefore the duration of therapy should be guided by the patient's clinical condition, values and preferences [14].

ANCA Associated Vasculitis

Chen et al., [15] analysed patients younger than 18 years with pAAV, biopsy-confirmed pauci-immune glomerulonephritis according to their initial steroid therapy doses of none, low-moderate (≤90mg/kg) and high (>90mg/kg) cumulative IVMP and low (<0, 5mg/kg/day prednisone equivalent), moderate (0.5-1.5mg/kg/day) and high (>1.5mg/kg/day) oral steroid doses of patients, comparing baseline characteristics and 12-month outcomes (eGFR, glucocorticoid-related side effects). Renal failure at diagnosis and plasmapheresis use were associated with high-dose IVMP. Rates of glucocorticoid-related adverse effects ranged from 15-31% across dose levels, and glucocorticoid dosing did not associate with 12-month outcomes. In this study, higher glucocorticoid doses were not associated with better outcomes [15].

Takayasu Arteritis

Takayasu Arteritis is defined as granulomatous arteritis that predominantly affects the aorta and/or its major branches [16]. Given the lack of evidence in children and the higher level of evidence in adult studies of Takayasu arteritis, the EULAR recommendations on adult-onset large vessel vasculitis (related to Takayasu arteritis, not GCA) are used in pediatric Takayasu arteritis patients [9]. In a study published by Bolek et al., [17] with 154 adult and 25 pediatric patients in which the different course of Takayasu disease in adult and pediatric patients was investigated, it was reported that acute phase reactants were higher, abdominal involvement was more frequent, left ventricular hypertrophy, aortic valve insufficiency and hypertension were more frequent in children. It was also reported that the total steroid dose administered in pediatric patients was lower compared to adult patients [17]. Another study by Jales-Netoand his colleagues found that steroids and other immunosuppressive therapies were used similarly in adults and children [18]. In a cohort of 29 children and 48 adult patients from Canada, steroid-only treatment was to be more frequently used in adult Takayasu patients [17].

Steroid reduction regimens for pediatric patients

According to current recommendations for steroid with drawal regimen in children, it is applied in the following stages [19].

1-) Glucocorticoid dose should be reduced according to the underlying condition until 30 mg/m^2/day hydrocortisone equivalent is reached.

2-) Then, it should be reduced by 10-20% every 3-7 days until the patient reaches the physiological glucocorticoid dose (8-10 mg/m^2/day hydrocortisone equivalent).

3-) After reaching 8-10 mg/m^2/day hydrocortisone, a decision should be made whether to stop or continue hydrocortisone according to the morning cortisol level evaluation (by evaluating the recovery of the HPA axis).

In our center, if the steroids are used for more than 14 days, the basal ACTH and cortisol levels are checked and if there is no adrenal suppression, the treatment has been stopped. In case of adrenal suppression, the dose is reduced to 30 mg/m^2/day hydrocortisone, then reduced by 25% at 3-day intervals to 10 mg/kg/day hydrocortisone. After 2-4 weeks of use at this dose, the basal ACTH cortisol control is checked and if the HPA axis is suppressed, an ACTH stimulation test is performed; if HPA suppression is not detected, the steroid treatment has been discontinued.

Glucocorticoid toxicity index

A pediatric glucocorticoid toxicity index (pGTI) was developed to measure glucocorticoid-related morbidity and toxicity across the age range of 2–18 years. Using group consensus methods and multicriteria decision analysis, the pGTI organized glucocorticoid-related toxicities into health domains rated as minor, moderate, or major and weighted according to severity. The overall toxicity profile derived from the pGTI data is composed of two quantitative scores: (1) Cumulative Worsening Score; and (2) Total Improvement Score. The pGTI also includes a qualitative, unweighted GC adverse event record known as the Harm Checklist,

which documents less common toxicities that are potentially severe but unlikely to change with changing glucocorticoid doses. One hundred and seven (107) toxicity items are included in the pGTI and thirty-two (32) items are included in the Harm Checklist. This Checklist is designed to identify irreversible persistent toxicities despite reduced exposure to steroids. In conclusion, the development and initial evaluation of the pGTI, a glucocorticoid toxicity assessment tool intended for use in pediatrics and pediatric practice as well as in prospective, randomized clinical trials, is described. This tool can be used across clinical disciplines to assess the clinical and economic value of glucocorticoid-sparing therapies, as well as to quantify the impact of steroid toxicity. Given the wide spread use of glucocorticoid and the pace of immunological drug discovery, this tool may represent a significant advance in our ability to assess the utility of new pharmacologic agents [20].

Conclusion

Glucocorticoids are agents widely used in our pediatric rheumatology practice however side efects should always be considered, especially in childhood. Early discontinuation of therapy, switching to alternative treatments should be pursued for patients.

Author contribution

Study conception and design: YB, DÜ; draft manuscript preparation: YB, DÜ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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