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Therapies for Glomerular Diseases in Children

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ABSTRACT

Nephrotic syndrome is an important chronic disease of childhood, with a steroid sensitive course in most patients. Research on pathogenesis has emphasized the importance of T-lymphocyte dysregulation and vascular permeability factors that alter podocyte function and glomerular permselectivity. Mutations in genes that encode important podocyte proteins and therapeutic targets within podocytes have been identified. A hypothesis unifying available evidence on pathogenesis is yet to be proposed. An important proportion of patients have difficult disease course, characterized by frequent relapses, steroid dependence or steroid resistance, requiring therapy with alternative immunosuppressive agents. Clinical studies support the use of levamisole, cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors (CNIs) and rituximab in patients with frequent relapses or steroid dependence. The management of steroid-resistant nephrotic syndrome is difficult and patients failing to achieve remission show progressive renal damage. Prospective studies in patients with steroid sensitive and steroid resistant nephrotic syndrome are the basis of current guidelines while ongoing studies will help identify and formulate effective and safe therapies.

Keywords: Calcineurin inhibitors, focal segmental glomerulosclerosis, minimal change disease, Rituximab.

Introduction

Glomerular diseases constitute a significant proportion of kidney diseases in children. They are responsible for a variety of clinical presentations that range from isolated hematuria and/or proteinuria, hypertension, acute nephritic or nephrotic syndrome, to acute kidney injury and chronic kidney disease of variable severity. Nephrotic syndrome is one of the most common chronic disorders of childhood with significant risk of acute and long-term morbidity. However, its pathogenesis remains unclear and therapies are largely empirical. This review focuses on the current understanding with respect to the pathogenesis and management of idiopathic nephrotic syndrome.

Nephrotic Syndrome

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia (albumin <2.5 g/dL), hyperlipidemia and edema. Data from single, multicenter or nationwide studies show that the incidence of nephrotic syndrome varies from 2-7 and prevalence 14-16 per 100000 children (1, 2). More than 90% are primary (idiopathic); a secondary cause is rare. Most (~80%) children with the idiopathic form of illness show remission following therapy with oral steroids. The prognosis in these cases is

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favorable, in contrast to patients who are steroid resistant.

Pathology

Histological studies by the International Society for Kidney Disease in Children (ISKDC) and our center show that almost three-quarter patients have insignificant glomerular changes on light microscopy (minimal change disease) (3). While immunofluorescence examination is usually normal, ultrastructure reveals effacement of podocytes. About 40-70% patients with steroid resistant and 5-10% cases with sensitive nephrotic syndrome have focal segmental glomerulosclerosis (FSGS). FSGS is classified, into five morphologic variants, based on location of sclerosis: tip lesions, cellular variant, perihilar lesions, collapsing FSGS and FSGS not otherwise specified (4). Collapsing glomerulopathy is associated with HIV, heroin intake and parvovirus infection. About 10-15% of patients with steroid resistance show features of C3 glomerulopathy, membranous nephropathy or IgA nephropathy.

Pathogenesis

The filtration barrier comprises of capillary endothelial fenestrations, glomerular basement membrane (GBM) and interdigitating podocyte processes. Studies show that podocytes are critical in maintaining selective filtering function. Application of high-throughput next-generation sequencing shows defects in genes encoding key proteins of podocytes in 80-100% cases with congenital nephrotic syndrome (onset <3 months age), and 50-60% of infantile-onset, 65-70% of familial and 25% of sporadic steroid resistant disease (2, 5, 6). Mutations in many genes are recognized: those encoding structural elements of slit diaphragm or podocyte cytoskeleton (*NPHS1, NPHS2, CD2AP, TRCP6, ACTN4, MYO1E*), proteins in the GBM (*LAMB2*), mitochondrial genes (*COQ2*), transcription factors (*WT1, LMX1B*), cubilin (*CUBN*), rhoGDIα (*ARHGDIA*) and inverted formin 2 (*INF2*). Although most patients with inherited forms of steroid resistance do not respond to immunosuppressive agents, partial response to calcineurin inhibitors (CNIs) is reported. Disease due to genetic defects is likely to progress to end-stage kidney disease and unlikely to recur in the allograft (2, 7, 8).

There is evidence of immune dysfunction in steroid sensitive disease. Altered cell mediated immunity and T-helper type 2 (Th2) polarization is proposed to, through undefined mechanisms, result in increased glomerular permeability. Recent studies suggest that the steroid sensitive illness is associated with an imbalance between Th 17 cells and regulatory T (Treg)-cells (9, 10). Deficiency or dysfunction of Treg cells may allow activation of effector T-cells to secrete factors that mediate glomerular permeability or increase oxidant production (11). Conversely, stimulation of Treg cells following measles or B-cell depletion with rituximab, induce sustained remission in minimal change disease (12, 13). Recent studies suggest that increased podocyte expression of CD80, soluble angiopoietin-like 4 (ANGPTL4) and microRNA might have a role in pathogenesis of proteinuria (14-17).

Finally, podocytes are recognized as a target for antiproteinuric interventions. Incubation of podocytes with corticosteroids, CNIs and rituximab has been shown to stabilize the actin cytoskeleton and restore distribution of key podocyte proteins, ameliorating proteinuria.

Circulating Factors

The soluble mediator hypothesis, supported by recurrence of nephrotic range proteinuria following transplant in 20-40% patients with idiopathic FSGS, induction of proteinuria and podocyte effacement in rats, or increase in vascular permeability in guinea pigs by supernatants from T-cells, is an accepted paradigm for disease pathogenesis. A number of

circulating factors have been proposed, including soluble urokinase plasminogen activating receptor (suPAR), interleukin (IL)-13, cardiotrophin like cytokine-1, tumor necrosis factor-α hemopexin and c-Maf inducing protein (18, 21).

Evaluation

Most patients with idiopathic nephrotic syndrome have steroid sensitive illness. The course varies with 35-40% having a single episode or 1-2 relapses and 55-60% showing multiple relapses that occur infrequently or frequently. Investigations at the onset include: (i) urinalysis; (ii) blood levels of urea, creatinine, albumin, cholesterol; and (iii) complete blood counts. Additional investigations, apart from a tuberculin test and chest X-ray, are rarely required. Most patients do not require a kidney biopsy. A biopsy is required at onset if a cause other than minimal change disease is suspected, such as: (i) age at onset <1 year or >16 year; (ii) gross or persistent microscopic hematuria, or low C3; (iii) renal failure not attributable to hypovolemia; (iv) suspected secondary cause; and (v) sustained severe hypertension. A renal biopsy is considered later for steroid resistance or if therapy with CNIs is planned (2, 22-24).

Steroid resistance is diagnosed if patients continue to show non-response (3-4+ proteinuria, edema or hypoalbuminemia) despite therapy with prednisolone in adequate doses for 4-8 weeks (23, 24). Recent recommendations suggest awaiting remission for 6-8 weeks while tapering corticosteroids; the use of pulse steroids to confirm resistance is not recommended. Patients with steroid resistant nephrotic syndrome require: (i) 24-hour quantitation of proteinuria; (ii) estimation of glomerular filtration rate; and (iii) renal biopsy. Testing for mutations are currently not recommended due to variable availability and high cost of testing and unclear association with response to therapy (2, 5, 24). Screening for genetic mutations is recommended for patients with family history of similar renal disease, those presenting in the first 3-6 months of life and those not responding to therapy with steroids and CNIs.

Steroid Sensitive Nephrotic Syndrome (SSNS)

Collaborative international efforts of ISKDC and Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) (25, 26) have helped refine the treatment of nephrotic syndrome. A number of expert groups have proposed guidelines for the diagnosis and management of patients with SSNS (Table 1) (22, 27, 28).

Initial Episode

Although the ISKDC proposed that the initial prednisolone therapy comprise of 4 weeks daily and 4 weeks intermittent treatment (25), there was evidence that prolongation of therapy to 12 weeks was better in terms of reducing the risk of frequent Relapses (26). Few experts suggested that extending therapy to 24 weeks was even better. Four recently published well designed RCTs that enrolled almost 800 patients emphasize that prolonged initial therapy for 4-6 months is not useful in modifying the course of the disease, or reducing subsequent need for steroids and other agents (29-31). Given this data and risk of corticosteroid adverse effects, we do not recommend prolongation of initial therapy beyond 12 weeks.

Frequent relapses

Risk factors for the occurrence of frequent relapses or steroid dependence include an early age of onset (<3 years), delayed time to initial remission, and brief initial corticosteroid therapy (2, 31). Patients with frequent relapses are at risk of corticosteroid toxicity as well as complications of nephrotic syndrome, including infections, thrombosis and dyslipidemia. Many patients require therapy with steroid sparing agents that maintain remission while limiting

exposure to corticosteroids; agents used are listed in Fig. 1 and Table 1. Medications that have been used for this purpose include long-term prednisolone, levamisole, cyclophosphamide, mycophenolate mofetil, cyclosporine, tacrolimus and rituximab (32-37). Since few RCTs have compared the relative efficacy of these medications, most guidelines do not specify the order or choice of therapy (22, 27, 28).

Table 1: Guidelines for managing steroid sensitive nephrotic syndrome

	Indian Society of Pediatric Nephrology (ISPN) 2008 (22)	**Kidney Disease: Improving Global Outcomes (KDIGO) 2012(27)**
Initial episode	Prednisolone 2 mg/kg (max. 60 mg) daily for 6 wk 1.5 mg/kg (max. 40 mg) alternate day (AD) for 6 weeks; discontinued without taper	Predniso(lo)ne 60 mg/m^2 daily for 4-6 weeks 40 mg/m^2 AD for 2-5 months, taper Total duration: ≥12 weeks
Relapse; infrequent relapses	Prednisolone 2 mg/kg daily until remission[#] 1.5 mg/kg AD for 4 weeks; discontinued	Prednisolone 60 mg/m^2 daily till remission[#] 40 mg/m^2 AD for ≥4 weeks
Frequent relapses, steroid dependence	Long term AD prednisolone: 0.5-0.7 mg/kg for 9-18 months	Long term prednisolone: lowest dose AD for ≥3 months Administer daily during respiratory & other infections Consider low dose daily without major adverse effects, if AD therapy ineffective
	Corticosteroid sparing agents: Steroid threshold >0.5-0.7 mg/kg; steroid toxicity	*Corticosteroid sparing agents*: Use if steroid toxicity
	Levamisole: 2-2.5 mg/kg AD for 1-2 years	Levamisole: 2.5 mg/kg AD for ≥1 year
	Cyclophosphamide[$1]: 2 mg/kg daily for 12 weeks Chlorambucil: Not recommended	Alkylating agents: For frequent relapses, dependence; avoid second course; initiate therapy in remission
	Calcineurin inhibitors[$2]: Cyclosporine 4-5 mg/kg, tacrolimus 0.1-0.2 mg/kg daily for 1-2 years; monitor levels if toxicity, non-compliance, unsatisfactory response is suspected	Calcineurin inhibitors: Cyclosporine or tacrolimus for ≥1 year; use latter if unacceptable cosmetic side effects with cyclosporine; monitor levels during therapy
	Mycophenolate mofetil: 800-1200 mg/m^2 daily for 1-2 years	Mycophenolate mofetil: 1200 mg/m^2 daily for ≥1 year
	Mizoribine, azathioprine: Not mentioned	Mizoribine, azathioprine: Suggest that not be used
	Rituximab: Not mentioned	Rituximab: If failing other agents, serious adverse effects

[#]Urine protein trace or nil or urine protein to creatinine ratio <200 mg/g for 3 consecutive days;
[$1]Prefer CNIs if: significant steroid toxicity, severe relapses (with hypovolemia or thrombosis), poor compliance or difficult follow up;
[$2]Prefer CNIs if: continued dependence or frequent relapses despite treatment with agents listed previously.

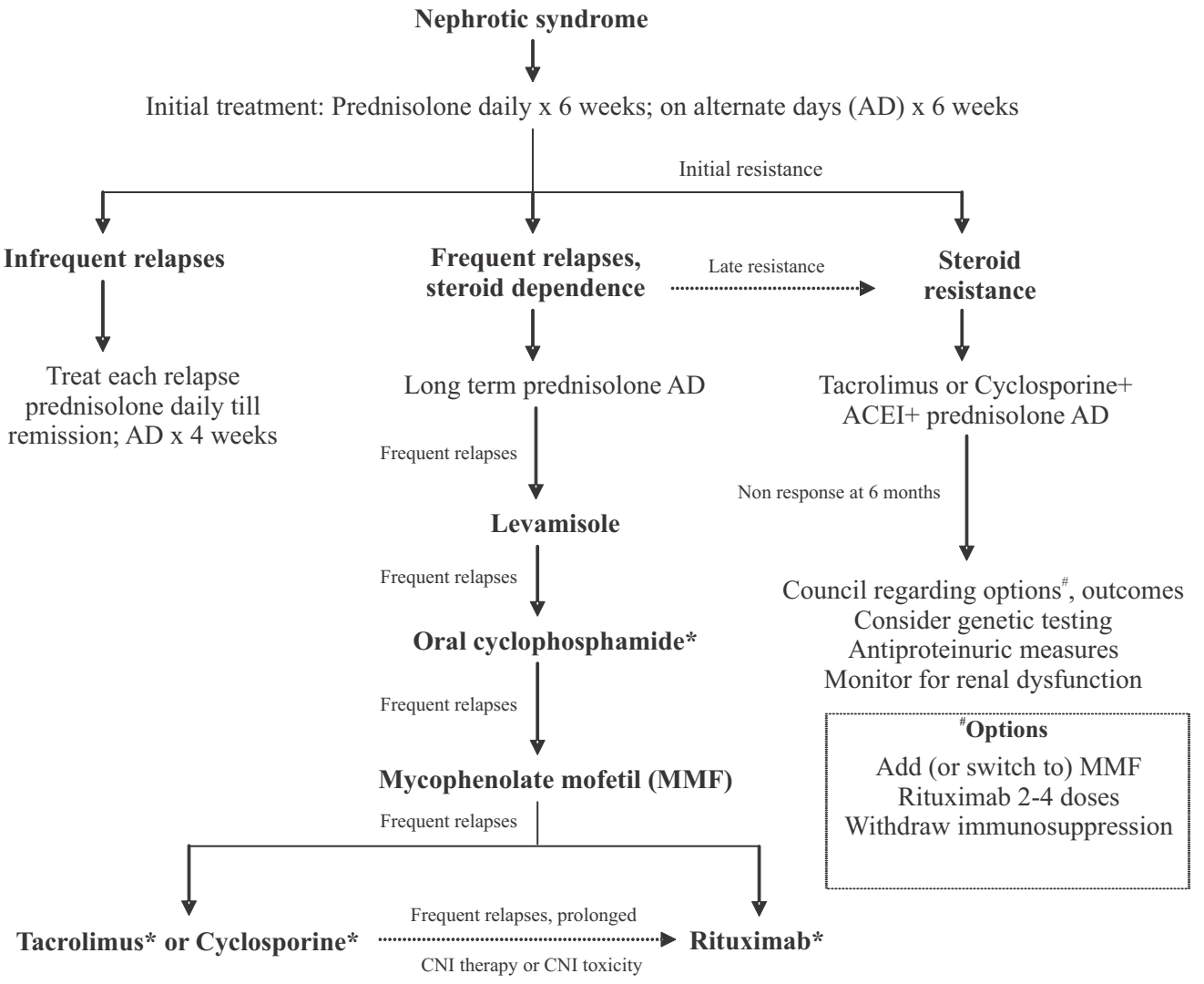

Fig. 1: Summary of therapy of steroid sensitive and steroid resistant nephrotic syndrome Medications are usually recommended in order from top to bottom. Agents marked with asterisk (*) are preferred in patients with significant steroid toxicity (cataract, severe stunting, obesity) or if relapses are associated with severe complications (thrombosis, severe infections). Patients with steroid resistance should receive treatment with a calcineurin inhibitor (CNI), an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker and tapering doses of prednisolone. Since response to other strategies is less satisfactory and non-response to CNI is associated with adverse outcomes, further immunosuppression should be considered following counseling regarding efficacy, safety and costs of various options.

Management of Steroid Resistant Nephrotic Syndrome

Therapy of patients with steroid resistant nephrotic syndrome is difficult, with variable response to immunosuppression, adverse effects of prolonged therapy and risk of progressive renal damage. Table 2 and Fig. 1 summarize guidelines on the evaluation, management and definitions of response (23, 24, 28). Most regimens combine daily therapy with a CNIs, angiotensin converting enzyme (ACE) inhibitors, and alternate day prednisolone (23, 24, 28, 38, 39). Cyclosporine A (CsA) and

Table 2: Guidelines for management of steroid resistant nephrotic syndrome

	Indian Society of Pediatric Nephrology, 2009 (23)	**Kidney Disease: Improving Global Outcomes (KDIGO), 2012 (24)**
Definition	Lack of remission[#] despite treatment with prednisolone at 2 mg/kg/day for 4 weeks; exclude systemic infections	Lack of remission[#] despite treatment with predniso(lo)ne for 8 weeks (2 mg/kg/day for 4 wk; 1.5 mg/kg on alternate days for 4 wk)
Evaluation	Kidney biopsy Serum creatinine, albumin Screen for mutations: Familial or congenital forms; patients with initial resistance	Kidney biopsy eGFR; 24-hr or spot protein, creatinine Screen for genetic mutations
Therapy	Choice based on preference and costs (i) Calcineurin inhibitor (CNI): cyclosporine or tacrolimus: efficacy 60-80% (ii) Cyclophosphamide: efficacy ~40% (I.V.), 25% (oral) (iii) I.V. methylprednisolone, oral cyclophosphamide: efficacy 30-50%	CNI with low dose prednisolone: Efficacy 69-86% Patients without remission to CNI at 6 months Mycophenolate mofetil efficacy ~33% High-dose corticosteroids efficacy ~47% Combination of agents: Do **not** use cyclophosphamide or rituximab
	Non immunosuppressive therapies ACE inhibitors or ARB Statins if dyslipidemia >6 months	Non immunosuppressive therapies ACE inhibitors, ARB: Use in all; proteinuria reduction 33-62%
Assess response at 6-months	Both complete and partial remission acceptable Complete remission: trace/negative protein; Up/Uc<0.2 mg/mg Partial remission: 1-2+ proteinuria; Up/Uc 0.2-2 Non-response: 3-4+ proteinuria; Up/Uc >2; blood albumin <2.5 g/dL	Both complete and partial remission acceptable Complete remission: proteinuria <0.3 g/24-hr; Up/Uc <300 mg/g Partial remission: proteinuria >0.3 g but <3.5 g/24-hr; decrease in proteinuria by ≥50%
Duration of therapy	Discontinue CNI if no remission at 6 months CNI for 2-3 year if complete/partial remission Longer if no nephrotoxicity on repeat biopsy	Discontinue CNI if no remission at 6 months Continue CNI for ≥ 12 months if complete/partial remission at 6 months
Monitoring	Trough cyclosporine 80-120 ng/ml; tacrolimus 5-8 ng/ml eGFR: Maintain±20% of baseline Rebiopsy: Therapy >2-3 yr; suspected toxicity	Relapse after achieving remission: Treat with oral corticosteroids Use previously successful medication Use alternative agent to minimize cumulative toxicity

[#]Urine protein trace or nil or urine protein to creatinine (Up/Uc) ratio <200 mg/g for 3 consecutive days.

ACE-angiotensin converting enzyme; ARB-angiotensin receptor blockers; CNI-calcineurin inhibitor; eGFR-estimated glomerular filtration rate; Up/Uc-spot urine protein to creatinine ratio.

tacrolimus appear to have similar efficacy and low rates of adverse effects (40). The aim of therapy is to induce and maintain remission of proteinuria, while avoiding medication related adverse effects. Patients are monitored closely until response to therapy is demonstrated, and then every 3-4 months (23). While complete remission is associated with high rates of renal

survival, even partial remission is associated with satisfactory outcomes, compared to those with non-response (41). Consensus is lacking on the optimal duration of treatment with CNIs. The agent is usually continued for 2-3 years, followed by one of the following: (i) tapering to the lowest effective dose, and continued for another 1-2 years; (ii) exclude nephrotoxicity on renal histology, and continue therapy; and (iii) switch treatment to a less toxic agent, e.g. mycophenolate or rituximab.

Given the overall limited efficacy in pediatric patients and risk of significant toxicity, KDIGO and Canadian guidelines suggest not using cyclophosphamide for patients with steroid resistance (24, 28). However, the relatively low cost of IV cyclophosphamide still allows it to be an option in resource limited settings (23). Despite initial interest (42), the efficacy of rituximab in inducing remission in patients with steroid and CNI-resistant nephrotic syndrome is limited (43). A RCT on 31 children with steroid and CNI-resistant nephrotic syndrome failed to show benefits of additional rituximab therapy in ameliorating proteinuria at 3 and 6 months (44). Our experience on 58 patients with steroid- and CNI-resistance confirms limited efficacy, with complete and partial remission in 12.1% and 17.2% patients, respectively (36). Similar to previous findings, response to rituximab was better in patients with prior response to a CNI and unsatisfactory in those with FSGS. Therapy with rituximab is likely to maintain remission, reduce relapses and enable withdrawal of steroids and CNIs.

Outcomes

Most patients with steroid sensitive nephrotic syndrome show satisfactory outcomes. Morbidity due to infections has declined with their prompt diagnosis and use of vaccines. Steroid toxicity remains a major concern in patients with frequent relapses or steroid dependence. Follow-up of the initial ISKDC cohort revealed that almost 80% patients were in sustained remission at 8 years from diagnosis (25); other series suggest that ~25% patients continue to relapse into adulthood (45). Ten-year follow-up of patients who received CsA for frequent relapses in a randomized study showed that 17.4% and 50% continued to suffer infrequent or frequent relapses, respectively, into adulthood (46).

Outcomes in patients with steroid resistance are less satisfactory. Patients with minimal change disease show better prognosis than those with FSGS. The chief factor predicting renal outcome is the response of proteinuria to therapy rather than histology. Renal survival varies from 72-94% at 5 years, with resistance to CNIs and presence of FSGS predicting adverse outcomes (47, 48).

Recurrence of FSGS after Transplantation

Almost 30% of patients with idiopathic FSGS undergoing transplantation develop allograft recurrence, with risk of delayed allograft function and loss (30-50% at 5-year) (49). Recurrence of proteinuria occurs within hours to days after the transplant, and is characterized by hypoalbuminemia and foot process effacement. Risk factors for recurrence include: (i) white ethnicity; (ii) early onset of disease (<15-year); (iii) late rather than initial resistance; (iv) non-genetic forms of disease; (v) progression to end-stage disease within 3-year from onset; and (vi) nephrectomy of native kidneys prior to transplant (49-51). Disease recurrence is attributed to circulating permeability factors, the precise nature of which is unknown.

Despite the risk of recurrence, live donors are preferred in view of better overall outcome. Pre-transplant plasmapheresis is used to decrease the risk of recurrence (52). Therapy for patients with recurrent FSGS include one or more of the following: (i) intensive and prolonged plasmapheresis (53); (ii) rituximab (375 mg/m^2/week for 2-4 weeks) (43); (iii)

immunosuppression, including high dose CsA, cyclophosphamide (2-2.5 mg/kg/day for 3 months) instead of Mycophenolate Mofetil; (iv) I.V. immunoglobulin (500 mg/kg/dose once a week); and (v) ACE inhibition. Results of treatment with I.V. abatacept are unsatisfactory. Patients with refractory illness might benefit by intensive lipid apheresis, using specially designed columns (54).

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