ĐIỀU TRỊ HC THẬN HƯ – VIÊM CẦU THẬN CẤP

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MỤC TIÊU :

1. **Chẩn đoán HCTH ở trẻ em : chú ý thể hay gặp : nguyên phát , sang thương tối thiểu .**
2. **Điều trị được HCTH thể nguyên phát , sang thương tối thiểu : lần đầu , tái phát xa , tái phát thường xuyên , kháng corticoid .**
3. **Chẩn đoán được VCTC ở trẻ em**
4. **Điều trị được VCTC hậu nhiễm liên cầu**

HỘI CHỨNG THẬN HƯ :

1. ÑÒNH NGHÓA

- **Hội chứng thận hư** (HCTH) là một hội chứng lâm sàng bao gồm:
  - Phù
  - Tiểu đạm > 50mg/kg/ngày hay > 1g/m^2/ngày (hay > 40mg/m^2/giờ) hay protein/creatinine > 2 mg/mg
  - Albumine máu < 25g/l, đạm máu < 55g/l
  - Tăng lipid máu (cholesterol> 2,2g/l).

2. NHẮC LẠI CƠ CHẾ BỊNH SINH :

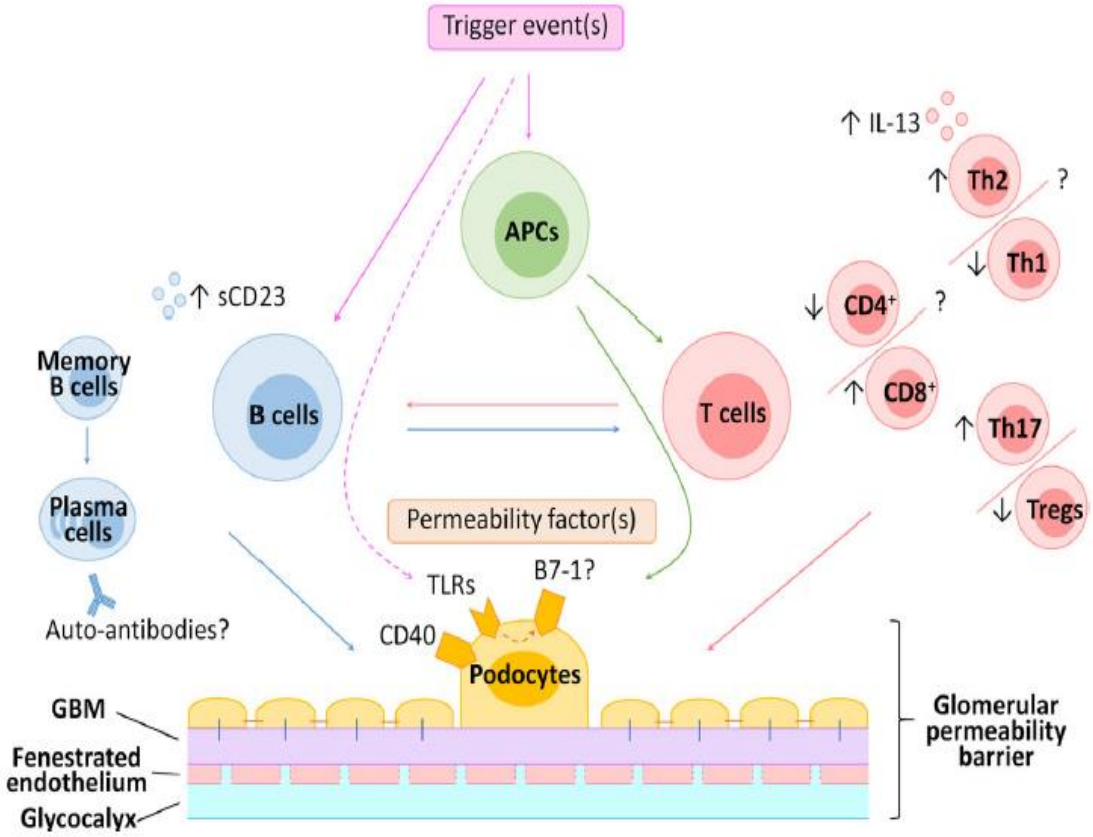


Fig. 1 Pathogenic mechanisms responsible for the disruption of the glomerular permeability barrier in idiopathic nephrotic syndrome (INS). Trigger events, such as infections, vaccination or allergens, can stimulate antigen-presenting cells (*APCs*) and B cells, which in turn can activate T cells by antigen presentation and cytokine production. Several T-cell alterations have been described in INS: a reduction of $CD4^+$ T helper (*Th*) cells associated with a prevalence of $CD8^+$ cytotoxic T cells, an imbalance between Th2 and Th1 cells with an increase in the production of the Th2-specific interleukin-13 (*IL-13*) and a reduced frequency and function of regulatory T cells (*Tregs*) opposed to an increased activity of Th17 cells. B-cell alterations have also been observed: an increased release of the soluble form of CD23 (*sCD23*—the immunoglobulin E receptor), a correlation between memory B-cell recovery and relapse after rituximab treatment and the presence of circulating anti-CD40 autoantibodies. In addition to the leukocyte-produced soluble factors, such as cytokines and autoantibodies, other circulating permeability proteins (i.e. hemopexin, the soluble form of the urokinase-type plasminogen activator receptor, the cardiotrophin-like cytokine factor 1, and a hyposialylated form of the angiopoietin-like-4 glycoprotein) can directly affect podocytes, leading to foot process effacement and disruption of the glomerular permeability barrier. Furthermore, podocytes can also sense microbial products by specific toll-like receptors (*TLRs*) and can express costimulatory molecules, such as CD40 and B7-1 which are able to induce activation of T cells. *APCs* Antigen-presenting cells, *TLRs* Toll-like receptors, *GBM* glomerular basement membrane

Table 1 Effects of the current immunosuppressive therapy of idiopathic nephrotic syndrome on different cells

Immunosuppressive treatment	Effects	References
Corticosteroids		
T cells	Apoptosis (in vitro and in vivo)	[82, 83]
	Inhibition of activation and cytokine production (in vitro and in vivo), also by inhibiting NF-kB activation (in vivo and in vitro)	[82, 84, 85]
	Inhibition of migration into inflamed tissues (in vitro and in vivo)	[82]
	Distinct steroid sensitivity in different Th cell subsets	[86]
	Indirect induction of regulatory T cells by generation of tolerogenic dendritic cells and myeloid-derived suppressor cells (in vitro and in vivo)	[87, 88]
B cells	Apoptosis (in vitro and in vivo)	[89, 90]
	Suppression of early activation and proliferation (in vitro)	[91]
	Partial effect of high-dose treatment on T-cell-dependent antibody production from plasma cells (in vivo)	[83, 90]
Podocytes	Induction of actin filament stability (in vitro)	[92, 93]
	Reduction of apoptosis (in vitro)	[92, 94]
	Inhibition of VEGF and IL-6 cytokine production (in vitro)	[64, 92]
Cyclophosphamide		
T cells	No effect on total T cells (in vivo)	[95]
	Impairment of regulatory T cell expansion and function (in vivo)	[96]
B cells	Reduction of total B cells (in vivo)	[95]
	No effect on circulating memory B cells or plasma cells (in vivo)	[95]
	Inhibition of splenic short-lived plasma cell differentiation (in vivo)	[97]
Podocytes	Preservation of podocyte structure (in vivo)	[98]
Calcineurin inhibitors		
T cells	Inhibition of activation and cytokine production by inhibiting NFAT and NF-kB activity (in vitro and in vivo)	[99–101]

Calcineurin inhibitors		
T cells	Inhibition of activation and cytokine production by inhibiting NFAT and NF-kB activity (in vitro and in vivo)	[99–101]
	Impairment of regulatory T cell expansion (in vitro and in vivo)	[102]
B cells	Inhibition of naïve but not total B cell proliferation and plasma cell differentiation (in vitro)	[103]
	Inhibition of T cell-dependent immunoglobulin production (in vitro and in vivo)	[90, 104, 105]
Podocytes	Induction of actin filament stability (in vitro and in vivo)	[92, 106, 107]
	Inhibition of calcium influx TRPC-6-mediated (in vitro)	[108]
	Protection against mitochondria-dependent apoptosis by inhibiting MAPK signaling pathway (in vitro)	[107]
Antiproliferative agents		
T cells	Inhibition of proliferation and migration into inflamed tissues (in vitro and in vivo)	[109]
	No effect on the frequency of total and regulatory T cells (in vitro and in vivo)	[95, 102]
B cells	Inhibition of naïve and memory B cell proliferation (in vitro)	[90, 109, 110]
	Inhibition of plasma cell differentiation (in vitro and in vivo)	[90, 95, 105, 109, 110]
	No effect on antibody production from plasma cells (in vitro)	[110]
Podocytes	Reduction of podocyte hypertrophy and apoptosis (in vitro and in vivo)	[111]
Rituximab		
T cells	Indirect modulation of T-cell homeostasis by impairment of B–T cell crosstalk (hypothesis and in vivo)	[112, 113]
	Potential direct depletion of $CD20^+$ T cells (in vivo)	[114]
	Inhibition of Th17 response (in vivo)	[115]
	Restoration of regulatory T cell number and function (in vivo)	[116]
B cells	Induction of apoptosis, antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity (in vitro and in vivo)	[117]
	Depletion of all differentiation stages of B cells, excluding lymphoid precursors and plasma cells (in vivo)	[118]
	Delay of recovery of memory B cells (in vivo)	[51]
	Controversial results about the effect on antibody production from plasma cells	[118]

Table 1 (continued)

Immunosuppressive treatment	Effects	References
Podocytes	Induction of actin filament stability and reduction of apoptosis by binding and preventing SMPDL-3b downregulation (in vitro)	[53]
	inhibition of proteinuria in an animal model of xenotransplantation by binding SMPDL-3b (in vivo)	[54]

NF-kB, Nuclear factor-kappaB; Th cells, T helper cells; VEGF, vascular endothelial growth factor; IL, interleukin; NFAT, nuclear factor of activated T-cells; TRPC-6, transient receptor potential cation channel, subfamily C, member 6; MAPK, mitogen-activated protein kinase; SMPDL-3b, sphingomyelin phosphodiesterase acid-like 3B

AETIOLOGY/PATHOGENESIS IN NS

- **Still to be fully elucidated**
- **The original theory about T cell secreted factors causing it is no longer supported**
- **Secretion of angiopoietin like 4 (Angptl4) from podocytes in human and experimental forms NS explain clinical/pathological picture**

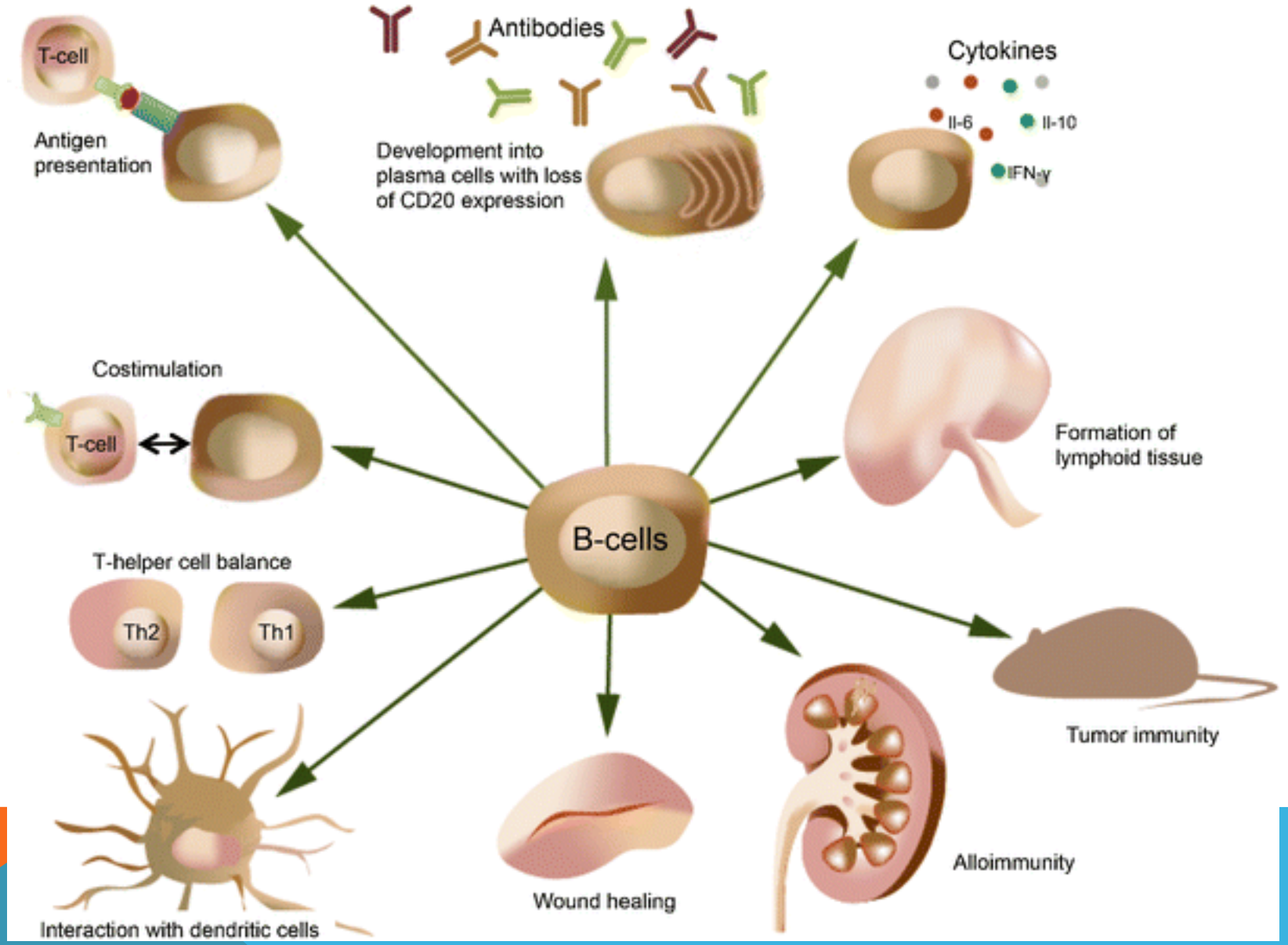
PROPOSED IMMUNOLOGIC PATHOGENESIS FOR IDIOPATHIC NEPHROTIC SYNDROME (INS)

In 1974 Shalhoub hypothesized that INS is a disorder of T-cell function because of the association with Hodgkin's disease & remission after measles infection.

Supported by immunologic findings of a certain lymphokine & the response to treatment with T-cell-specific immunosuppressants like calcineurin inhibitors.

Recent data showed that B-cell immunity is also altered in INS with persisting hypogammaglobulinemia in remission or an increase in the B-cell activation markers in steroid dependency.

Also, the therapeutic effect of immunosuppressants acting on B-cells (cyclophosphamide, MMF) supports the role of altered B immunity in INS.



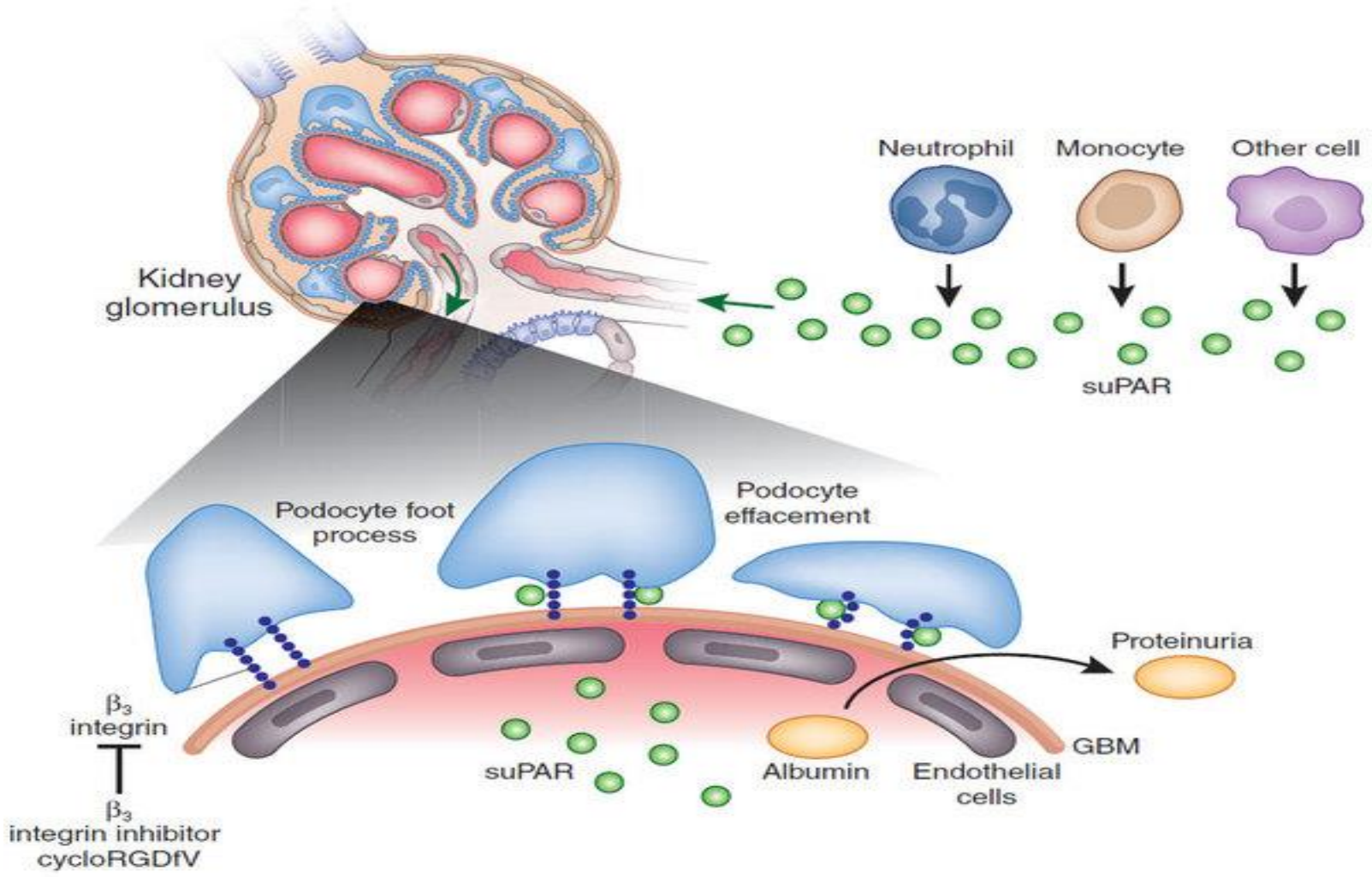
B-cells are multifunctional & regulate immune homeostasis in many ways. Is rituximab effective in childhood nephrotic syndrome? Yes & No, Kemper et al. Peds Neph '14

T-CELL DYSFUNCTION IN INS

T cells presumed to synthesize a circulating permeability factor(s), Pf, that alters normal glomerular protein permselectivity.

T-cell process may inhibit or down-regulate a permeability inhibitor factor that normally prevents proteinuria.

Podocyte target?



suPAR is produced by neutrophils, monocytes and perhaps other cells, such as T cells and enters the kidney glomerulus and binds and activates β3 integrin, one of the major proteins anchoring podocytes to the underlying glomerular basement membrane (GBM). Increased plasma levels of suPAR lead to increased β3 integrin activation, thus leading to podocyte dysfunction and effacement and proteinuria characteristic of FSGS.

PERMEABILITY FACTOR IN INS

Therapeutic use of plasma exchange with immunoabsorption to protein A may remove Pf indicating that it circulates with IgG.

Factor crosses placenta to induce transient neonatal proteinuria.

Factor found in plasma from patients with podocin mutations so not unique to idiopathic FSGS.

POSSIBLE IMMUNOLOGICAL BASIS FOR NEPHROTIC SYNDROME

Pf derived from lymphoid cells.

Association of NS with primary immunological disorders: lymphoma, leukemia, thymoma, Kimura's disease & Castleman's disease & use of interferon support hypothesis.

Cultured T cells from nephrotic patients synthesize a Pf that cause proteinuria when injected into rats.

Is MCNS a manifestation of a primary allergic disorder? No known triggering allergens.

Infectious causes: viral genome, HIV, hep C, P19.

POTENTIAL IMMUNOLOGIC MECHANISMS OF PODOCYTE INJURY

Reorganization of actin cytoskeleton:

- foot process effacement, molecular re-characterization of slit diaphragms, apoptosis, detachment from GBM.

De-differentiated podocytes can proliferate & cell outcome dependent upon interplay of genetic & epigenetic factors.

Podocytes express cytokine and chemokine receptors as well as Toll Like receptors (TLRs)

Respond to immune stimuli, Pf, cytokine imbalance, immune complex injury, with rare genomic variants affecting susceptibility or resistance to immune triggers

IMMUNE-MEDIATED INS

Evidence does support differences between lymphocyte phenotype, cytokine expression profile, & lymphocyte function between relapses and remissions.

Increased levels of IgE & IL-13 may mediate proteinuria via induction of CD80 (B7-1) expression.

CD80 is a transmembrane protein on B cell surfaces & other antigen presenting cells involved in T-cell co-stimulation once bound to CD28 receptor.

Expressed in podocytes causing actin reorganization & proteinuria.

Urinary CD80 levels are elevated in MCD but not FSGS & return to normal with remission. Ling et al Ped Neph ’15

LONG TERM RENAL OUTCOMES OF IDIOPATHIC NEPHROTIC SYNDROME

Adult course

- SSNS persists into adult life in 27-42% of children with frequently relapsing or steroid dependent course. Risk factors for relapses as adult:younger age at onset, frequent relapses, use of alkylating agents and cyclosporin

End stage kidney disease

- SSNS with minimal change < 1%
- SRNS with FSGS/IgM nephropathy 12-40%

3. NHẮC LẠI CHẨN ĐOÁN :

1. Chẩn đoán xác định:

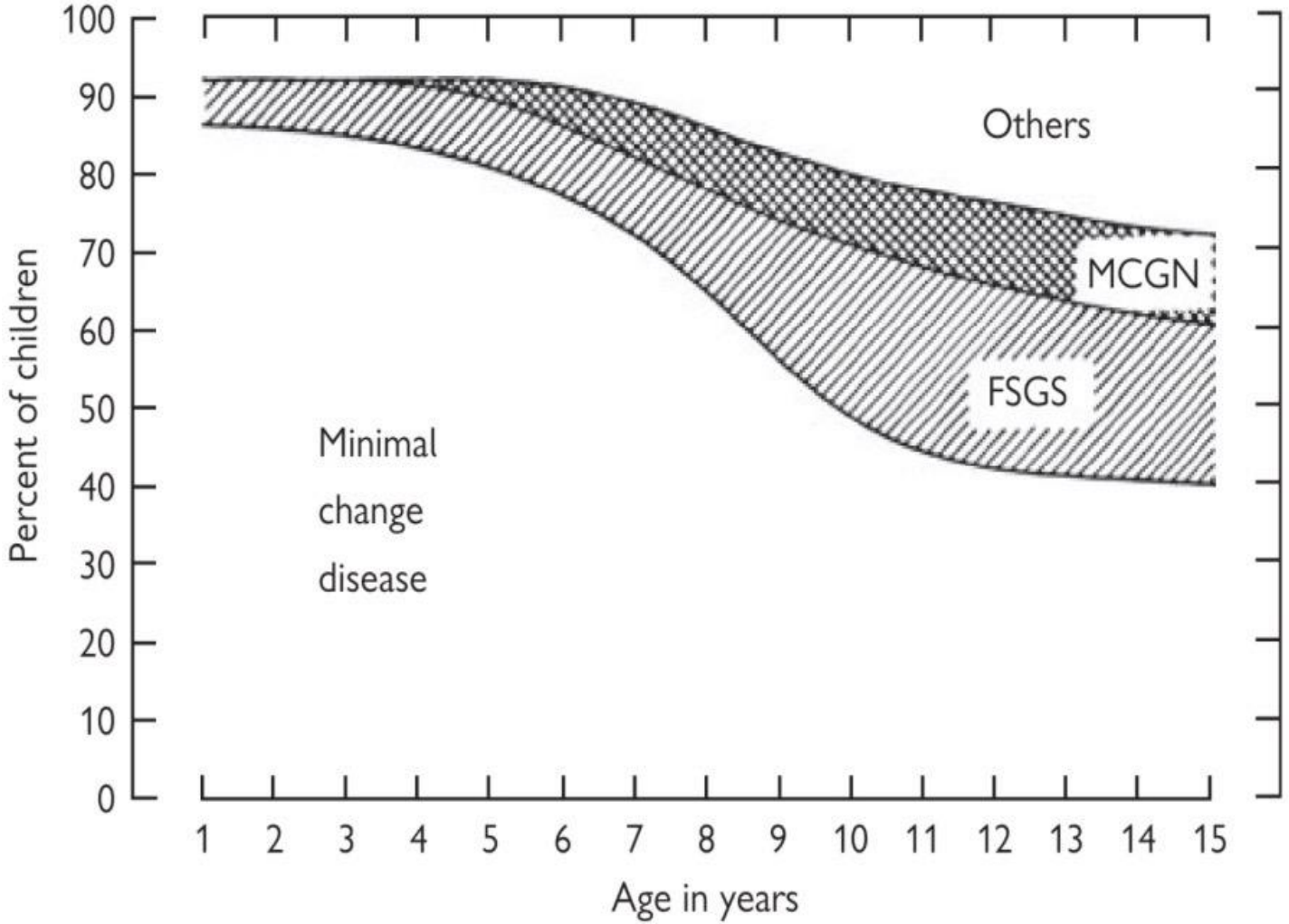
- **Phù**
- **Đạm máu ↓ < 55 g/l, Albumin máu ↓ < 25 g/l**
- **Cholesterol máu ↑ > 2,2 g/l**
- **Đạm niệu/ 24 giờ : > 50 mg/kg/ ngày,**

hay Protein niệu/ Creatinine niệu > 2 (mg/mg).

2. THỨ PHÁT?

3. THỂ TỐI THIỂU ?

	NGUYÊN PHÁT	THỨ PHÁT
TE	> 90%	
NL	75 %	


100
90
80
70
60
50
40
30
20
10
0
Percent of children
Others
MCGN
FSGS
Minimal
change
disease
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Age in years

NGHI TỐI THIỂU :

-TUỔI

-KHÔNG :

- TIỂU MÁU ĐẠI THỂ
- HA CAO
- SUY THẬN

-BỔ THỂ bt

-KHÔNG NGOÀI THẬN : MALAR RASH or PURPURA

4. ĐIỀU TRỊ :

4.1 ĐIỀU TRỊ LẦN ĐẦU :

REGIMENS FOR STEROID TREATMENT OF FIRST EPISODE OF SSNS

- **ISKDC regimen 1966**
  - Prednisolone at 60mg/m^2/day (max 80mg) for 4 weeks
  - Prednisolone at 40mg/m^2/day (max 60mg) for 3 of 7 days for 4 weeks
- **APN regimen 1979**
  - Prednisolone at 60mg/m^2/day (max 80mg) for 4 weeks
  - Prednisolone at 40mg/m^2/day (max 60mg) given on alternate mornings for 4 weeks
- **APN regimen 1993**
  - Prednisolone at 60mg/m^2/day (max 80mg) for 6 weeks
  - Prednisolone at 40mg/m^2/day (max 60mg)

  on alternate mornings for 6 weeks

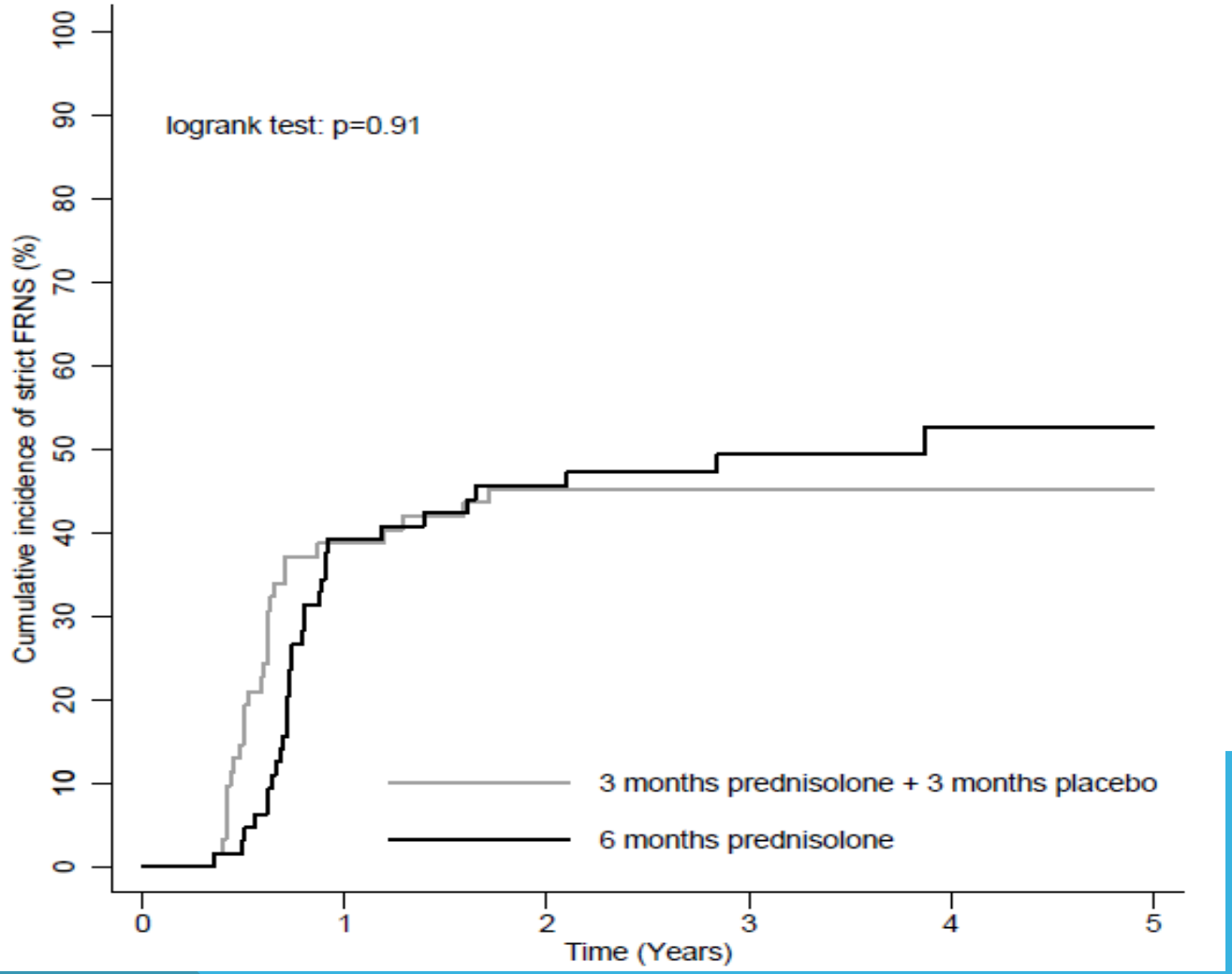
ĐIỀU TRỊ

Điều trị lần đầu: HCTH NGUYÊN PHÁT NGHI TỐI THIỂU:

Phác đồ 6-6

- **6 tuần tấn công: Prednisone 2mg/kg/ngày**
  1 lần sáng uống sau ăn.
- **6 tuần cách ngày: Prednisone 1,5mg/kg/ cách ngày**
  Uống 1 lần duy nhất vào buổi sáng sau ăn.

INCREASED DURATION OF PREDNISOLONE DOES NOT REDUCE RISK OF FREQUENTLY RELAPSING SSNS- DOSE NOT DURATION IS THE FACTOR



Teeninga et al. JASN 2013

4.2 ĐIỀU TRỊ TÁI PHÁT

4.2.1 Tái phát lần đầu:

Prednisone 2mg/kg/ngày cho đến khi đạm niệu (-) 3 ngày liên tiếp, tối thiểu 14 ngày .

Sau đó: Prednisone 1,5 mg/kg/cách ngày, trong 4 tuần.

ĐIỀU TRỊ TÁI PHÁT

4.2.2 Tái phát thường xuyên, hoặc lệ thuộc corticoid:

Prednisone 2mg/kg/ngày cho đến khi đạm niệu (-) 3 ngày liên tiếp
Sau đó : Prednisone 1,5 mg/kg/ cách ngày, trong 4 tuần
Tiếp theo giảm liều dần, rồi duy trì: 0,1- 0,5mg/kg/cách ngày trong 3-12th
TPTX : 3-6th
Phụ thuộc : 9-12th

EFFECTIVE STEROID SPARING AGENTS FOR SSNS

Cyclophosphamide	2 mg/kg/day	8-12 weeks
Chlorambucil	0.1-0.2 mg/kg/day	8-12 weeks
Levamisole	2.5 mg/kg on alt days	12 months or more
Cyclosporin*	4-5 mg/kg/day in 2 doses	12 months or more
Tacrolimus*	0.1 mg/kg/day in 2 doses	12 months or more
Mycophenolate mofetil	1200 mg/m^2/day in 2 doses	12 months or more
Rituximab	375 mg/m^2 per dose	?once /once yearly as required

* Starting dose; monitor levels

ĐIỀU TRỊ TÁI PHÁT THƯỜNG XUYEN , PHỤ THUỘC :

MMF
CYCLOSPORINE
TACROLIMUS

4.3 ĐIỀU TRỊ THỂ KHÁNG CORTICOID :

Thể kháng corticoid:

- **sinh thiết thận**

MCNS, MESP-GN, FSGS :

Cylosporine: **5mg/kg/ngày**

Hay Tacrolimus 0,15 mg /kg chia 2

Prednisone:

1mg/kg/cách ngày x 5 tháng

FSGS
BỊNH CẦU THẬN MANG
VIEM CẦU THẬN TĂNG SINH MANG

VIÊM CẦU THẬN CẤP :

NHẮC LẠI CHẨN ĐOÁN :

1. **HC VCTC ?**
2. **VCTC DO SAU NHIỄM TRÙNG ?**
3. **NẾU KHÔNG NGHI SAU NT, XEM XÉT C :**
   - C_3 GIẢM
   - HAY C_3 BÌNH THƯỜNG

ĐIỀU TRỊ : VCTC SAU LIÊN CẦU:

KS

HA CAO :

VỪA : FUROSEMIDE, ỨC Ca

CC : PIV NICARDIPINE, LABETALOL, HYDRALAZINE

SUY TIM , PHÙ PHỔI CẤP :

TỔN THƯƠNG THẬN CẤP :

VCT TIẾN TRIỂN NHANH : MP ± ĐỘC TẾ BAO