English

CONTACT

厚生労働科学研究費補助金 難治性疾患政策研究事業 小児腎領域の希少・難治性疾患群の診療・研究体制の確立
研究代表者　石倉健司

キーワードから疾患を検索する

疾患名をご入力ください

検索

難治性疾患政策研究事業とは

難病の患者に対する医療等に関する法律（難病法）に規定されている難病を対象としています．具体的には，「発病の機構が明らかでない」，「治療方法が確立していない」，「希少な疾病」，「長期の療養を必要とする」の４要素を満たす難病及び小児慢性特定疾病等に対して，全ての患者が受ける医療水準の向上，また，QOL 向上に貢献することを目的としています．難病・小児慢性疾病対策を推進するため，本事業は，関連学会やナショナルセンター等と連携し，担当疾病に係る研究開発推進に貢献する…

詳細はこちら

小児腎臓病領域の難病とは

「難病」は，医学的に明確に定義された病気の名称ではありません．いわゆる「不治の病」に対して社会通念として用いられてきた言葉です．そのため，難病であるか否かは，その時代の医療水準や社会事情によって変化します．例えば，かつて日本人の生活が貧しかった時代には，赤痢，コレラ，結核などの伝染病は「不治の病」でした．その当時は有効な治療法もなく，多くの人命が奪われたという点で，これらの疾病はまぎれもなく難病でした．しかし，その後日本人の生活が豊かになり，…

詳細はこちら

腎臓の保存管理とは

慢性腎臓病（CKD）とは，2000年代に入り確立した新しい病気の概念で，原因にかかわらず，検尿の異常（とくに蛋白尿）や腎臓の機能の低下，あるいは超音波などの検査でわかる腎臓の形の異常がある状態のことを指します．将来透析，腎移植が必要な末期腎不全に進行する危険性が非常に高く，また心臓や血管，骨など全身の臓器に悪影響を及ぼすことも分かっています．世界的に膨大な数の患者さんが罹患していて，大きな問題になっています． 小児の慢性腎臓病は成人と少し状況が…

詳細はこちら

疾患一覧

アルポート症候群

アルポート症候群（Alport症候群）は慢性腎炎、難聴、眼合併症の症状を示す遺伝性の病気です。最も多いのはCOL4A5遺伝子の異常によるX染色体連鎖型アル…

詳細を見る

ギャロウェイモワト症候群

ギャロウェイ・モワト（Galloway-Mowat）症候群とは、頭部（脳神経）と腎臓の2つの臓器がうまく形成できず、小頭症、高度蛋白尿、耳介などの顔貌の…

詳細を見る

エプスタイン症候群

エプスタイン症候群とは、1) 巨大血小板性血小板減少症、2) 進行性腎障害、3) 感音性難聴の３つの症状を示す遺伝性の病気です。1) の巨大血小板性血小板…

詳細を見る

ネイルパテラ症候群

ネイルパテラ症候群（爪膝蓋骨症候群）は爪（形の異常）、肘関節（変

先天性腎尿路異常

先天性腎尿路異常（Congenital Anomalies of the Kidney and Urinary

先天性ネフローゼ症候群

普通は血液の中から漏れない蛋白が尿の中にたくさん出てしまい、血液中の

形)、膝蓋骨（小さいあるいは無い）、腸骨（突起がみられる）を４つの特徴とする遺伝性…

詳細を見る

Tract: CAKUT;「カクート」と呼びます）は、「腎臓」と「腎盂・尿管・膀胱…

詳細を見る

蛋白が減る（低蛋白血症）ことが特徴の疾患です。それに伴い、むくみ（浮腫）…

詳細を見る

ネフロン癆（ろう）

ネフロン癆（ろう）は、腎臓に嚢胞（球状の袋）ができる進行性の嚢胞性腎疾患です。ネフロン癆は腎臓の尿細管細胞に存在する一次繊毛の構造的、機能的…

詳細を見る

バーター/ギッテルマン症候群

これらの疾患は、先天性尿細管機能障害に伴い、低カリウム血症と代謝性アルカローシスを認め、それに伴う臨床症状を呈する症候群です。バーター…

詳細を見る

小児特発性ネフローゼ症候群

ネフローゼ症候群とは大量の蛋白尿のために、血液中の蛋白質（特にアルブミン）が減ってしまうこと（低蛋白血症/低アルブミン血症）が特徴の疾患…

詳細を見る

ロウ症候群

ロウ症候群とは、1)眼症状、2)中枢神経症状、3)腎症状の3つの症状を示す遺伝性の病気です。基本的には男の子に発症しますが、ごく稀に女の子にも発症すると…

詳細を見る

鰓耳腎症候群

鰓耳腎症候群(さいじじんしょうこうぐん)とはBOR(Branchio-oto-renal)症候群とも呼ばれ、頸瘻(けいろう)・耳瘻孔(じろうこう)・耳介の奇形など(鰓原性奇形…

詳細を見る

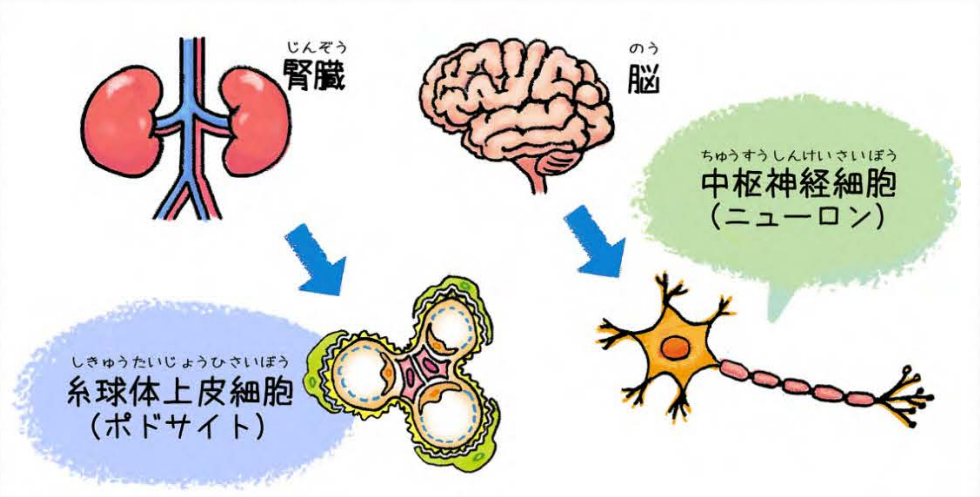
トップへ戻る

ギャロウェイ・モワト症候群

はじめに

ギャロウェイ・モワト（Galloway-Mowat）症候群とは、頭部（脳神経）と腎臓の2つの臓器がうまく形成できず、小頭症、高度蛋白尿、耳介などの顔貌の形態異常の3症状を認める症候群です。疾患名は1968年に最初に症例を報告した、英国小児科医2名の名前（GallowayとMowat）に由来しています。

原因としては、腎臓のろ過装置である「糸球体」を構成する「糸球体上皮細胞（ポドサイト）」と脳を構成する神経細胞である「ニューロン」とに共通する細胞の機能障害があり、腎臓と脳の形成過程に異常を来すと推測されていますが、いまだ原因となる確定的な染色体異常や遺伝子変異は見つかっていません。



ギャロウェイ・モワト症候群の診断

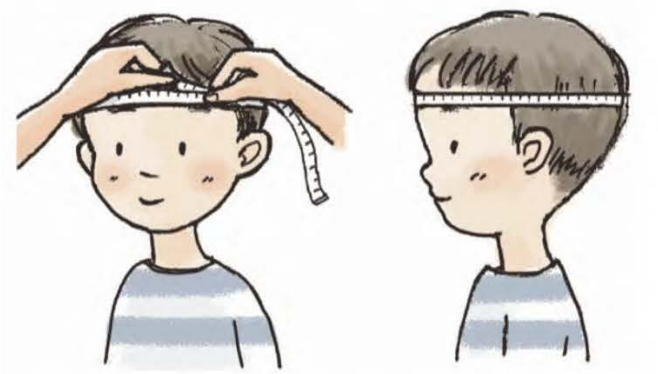
必須症状(3項目)

1. 小頭症 頭囲が年齢や性別を合わせた標準値の3%より小さい。
2. 治療抵抗性か治療抵抗性と考えられる高度蛋白尿
   （尿蛋白/クレアチニン比≧1.0g/gCr、または一日尿蛋白量≧1g）
3. 耳介など顔貌の形態異常

   大きくて柔らかい耳、後方に回転している耳、耳介の位置が低いなどの耳の異常、その他顔面の形成異常（額が狭い、顎が小さい、口蓋が高い、目と目の間が離れている）など。

頭囲の測定方法

頭囲は眉間 (鼻根部より上部で前頭骨上)から後頭部の後頭骨上、最も後ろに突出している部分を巻き尺で測定する。1mm単位まで計測する。
※前方は左右の眉の直上、後方は後頭部の一番突出しているところを通る周径を測定します。前方はひたいの最突出部を通らないことに注意しましょう。



乳幼児頭囲発育パーセンタイル曲線（平成22年調査）

(cm)

年・月・日齢	男子 パーセンタイル値						
	3	10	25	50 中央値	75	90	97
出生時	30.5	31.5	32.5	33.5	34.5	35.0	36.0
30日	33.8	34.7	35.7	36.7	37.6	38.3	39.1
0年1～2月未満	35.1	36.1	37.0	38.0	38.9	39.6	40.4
2～3	37.1	38.1	39.0	39.9	40.9	41.6	42.4
3～4	38.6	39.5	40.4	41.4	42.2	43.0	43.7
4～5	39.7	40.6	41.4	42.3	43.2	44.0	44.7
5～6	40.4	41.3	42.1	43.0	43.9	44.7	45.4
6～7	41.0	41.9	42.7	43.6	44.5	45.2	45.9
7～8	41.6	42.4	43.3	44.2	45.0	45.8	46.5
8～9	42.1	42.9	43.8	44.6	45.5	46.3	47.0
9～10	42.5	43.4	44.2	45.1	46.0	46.7	47.5
10～11	42.9	43.7	44.6	45.5	46.4	47.2	47.9
11～12	43.2	44.1	44.9	45.9	46.8	47.5	48.3
1年0～1月未満	43.5	44.4	45.3	46.2	47.1	47.9	48.7
1～2	43.8	44.7	45.6	46.5	47.4	48.2	49.0
2～3	44.1	45.0	45.8	46.8	47.7	48.5	49.3
3～4	44.3	45.2	46.1	47.0	48.0	48.8	49.6
4～5	44.5	45.4	46.3	47.2	48.2	49.0	49.9
5～6	44.7	45.6	46.5	47.4	48.4	49.2	50.1
6～7	44.9	45.8	46.6	47.6	48.6	49.4	50.3
7～8	45.0	45.9	46.8	47.8	48.7	49.6	50.5
8～9	45.2	46.1	46.9	47.9	48.9	49.8	50.6
9～10	45.3	46.2	47.1	48.1	49.0	49.9	50.8
10～11	45.4	46.3	47.2	48.2	49.2	50.0	50.9
11～12	45.5	46.4	47.3	48.3	49.3	50.2	51.1
2年0～6月未満	45.9	46.8	47.7	48.7	49.7	50.6	51.5
6～12	46.5	47.4	48.3	49.2	50.2	51.1	52.0
3年0～6月未満	47.0	47.9	48.7	49.7	50.7	51.6	52.5
6～12	47.4	48.3	49.1	50.1	51.1	52.0	52.9
4年0～6月未満	47.8	48.6	49.5	50.5	51.4	52.3	53.2
6～12	48.1	49.0	49.8	50.8	51.7	52.6	53.5
5年0～6月未満	48.4	49.2	50.1	51.0	52.0	52.9	53.8
6～12	48.6	49.5	50.3	51.3	52.3	53.3	54.2
6年0～6月未満	48.8	49.7	50.6	51.6	52.7	53.7	54.7

年・月・日齢	女子 パーセンタイル値						
	3	10	25	50 中央値	75	90	97
出生時	30.5	31.2	32.0	33.0	34.0	34.5	35.5
30日	33.1	34.1	34.9	35.9	36.7	37.5	38.2
0年1～2月未満	34.3	35.2	36.1	37.0	37.9	38.7	39.4
2～3	36.2	37.1	38.0	38.9	39.7	40.5	41.2
3～4	37.5	38.4	39.3	40.2	41.1	41.8	42.5
4～5	38.5	39.4	40.3	41.2	42.0	42.7	43.4
5～6	39.3	40.1	41.0	41.9	42.7	43.4	44.1
6～7	39.9	40.7	41.6	42.4	43.3	44.0	44.7
7～8	40.4	41.3	42.1	43.0	43.8	44.5	45.2
8～9	40.9	41.8	42.6	43.5	44.3	45.0	45.7
9～10	41.4	42.2	43.1	43.9	44.8	45.5	46.2
10～11	41.7	42.6	43.5	44.3	45.2	45.9	46.6
11～12	42.1	43.0	43.8	44.7	45.6	46.3	47.0
1年0～1月未満	42.4	43.3	44.2	45.1	45.9	46.7	47.4
1～2	42.7	43.6	44.5	45.4	46.2	47.0	47.7
2～3	43.0	43.9	44.7	45.6	46.5	47.3	48.0
3～4	43.2	44.1	45.0	45.9	46.8	47.6	48.3
4～5	43.4	44.3	45.2	46.1	47.0	47.8	48.6
5～6	43.6	44.5	45.4	46.3	47.2	48.0	48.8
6～7	43.8	44.7	45.5	46.5	47.4	48.2	49.0
7～8	44.0	44.8	45.7	46.6	47.6	48.4	49.1
8～9	44.1	45.0	45.8	46.8	47.7	48.5	49.3
9～10	44.3	45.1	46.0	46.9	47.8	48.7	49.5
10～11	44.4	45.2	46.1	47.0	48.0	48.8	49.6
11～12	44.5	45.4	46.2	47.2	48.1	48.9	49.7
2年0～6月未満	44.9	45.7	46.6	47.5	48.5	49.3	50.2
6～12	45.5	46.3	47.2	48.2	49.1	50.0	50.8
3年0～6月未満	46.0	46.9	47.7	48.7	49.7	50.5	51.4
6～12	46.5	47.4	48.2	49.2	50.2	51.0	51.9
4年0～6月未満	47.0	47.8	48.7	49.6	50.6	51.5	52.3
6～12	47.4	48.2	49.1	50.0	51.0	51.9	52.7
5年0～6月未満	47.7	48.6	49.4	50.4	51.4	52.2	53.1
6～12	48.1	48.9	49.7	50.7	51.6	52.5	53.4
6年0～6月未満	48.3	49.1	50.0	50.9	51.9	52.8	53.7

ギャロウェイ・モワト症候群の症状

①脳に伴う症状

多くの場合、小頭症とともに精神運動発達遅滞や難治性てんかんを合併します。CT・MRIで、脳皮質形成異常（脳回異常、白質髄鞘形成不全）や小脳低形成などの脳の構造異常を認めることがあります。

②腎臓に伴う症状

ステロイドが効かないもしくは効かないと予測される高度蛋白尿（尿蛋白/クレアチニン比≧1.0g/gCr、または一日尿蛋白量≧1g）を認め、典型的な重症例では、出生3か月までに大量の蛋白尿（ネフローゼ症候群）を来たします。腎障害は進行性で腎不全に至ることが多いとされていますが、末期腎不全に至る年齢は３～10歳あるいはそれ以降と幅があります。

腎障害（蛋白尿）や小頭症（てんかん・発達遅滞）の程度が軽く、比較的良好な経過で成人に達する軽症例も見られます。また、てんかん症状が先に見られて、後にネフローゼ症候群が見られる場合もあります。腎生検では巣状分節性糸球体硬化症という組織を示すことが多いとされています。

③顔面の形成異常

耳介の異常（耳の位置が低い、耳が柔らかいなど）を伴います。その他の顔面の形態異常（額が狭い、顎が小さい、口蓋が高い、目と目の間が離れているなど）を伴うこともあります。

④その他の合併症

筋肉の緊張の低下があり、呼吸障害や嚥下障害を来すことがあります。斜視や食道裂孔ヘルニア（胃の入口の一部が横隔膜の上に滑り出した状態）の合併が見られることもあります。

ギャロウェイ・モワト症候群の治療

病気を根本的に治す方法はなく、病気に伴う症状を軽減する治療（対症療法）が主体となります。腎障害は進行性であるため、保存期（透析や腎移植が必要ではない程度の腎障害の時期）、透析期、腎移植期それぞれに必要な治療を行います。てんかんについては、長期の薬物療法が必要となります。

予後

一般に症状は進行性です。３か月までに発症する早期発症の重症型では、てんかんによる精神遅滞や腎機能障害が進行して１～２歳までに死亡することが多いとされています。しかしながら、患者さんごとに腎臓や神経の障害程度はさまざまで、成人期まで日常生活の大きな支障をきたさず、緩除に進行する例もあります。

Q&A

1. 腎臓病については有効な治療がありますか？

ギャロウェイ・モワト症候群による腎臓病であれば、病気に伴う症状を軽減する治療（対症療法）しかありません。ただし、治療可能な疾患が合併している可能性があるので腎臓専門医と相談してください。

2.「巣状分節性糸球体硬化症」は腎移植後に再発すると書かれていたりしますが、ギャロウェイ・モワト症候群で腎移植を行った場合にも腎臓病の再発の可能性があるのでしょうか？

「巣状分節性糸球体硬化症」という病名は、腎臓を組織学的にみた時につけられる病名で、原因には言及していません。大雑把に言うと、免疫が絡んでいるものと、遺伝的に腎臓の中の血液をろ過する構造の作り損いが起こっているものとあります。前者は腎移植後に高率に再発しますが、後者は再発しません。この疾患の腎病変は後者であり再発の心配は基本的にありません。

3. 次の子（患者の同胞となる）が欲しいなと考えています。その子も同じ病気になるのでしょうか？

遺伝子がわかっていないので難しいですが、多くは常染色体劣性遺伝と考えられており、そう考えると同胞ごとに約1／4の確率で同じ病気になります。ただし、明確にお答えすることはできないので、主治医とご相談ください。

本疾患の関連資料・リンク

厚生労働科学研究成果データベース
https://mhlw-grants.niph.go.jp/

Online Mendelian Inheritance in Man® (OMIM®)
http://www.ncbi.nlm.nih.gov/omim
遺伝疾患とその原因遺伝子および変異情報をまとめたデータベース

Genetic and rare diseases information center （GARD）
https://rarediseases.info.nih.gov/diseases/65/galloway-mowat-syndrome
National Institutes of Health (NIH)がベースに、希少疾患、遺伝病の情報提供を行っている。

Galloway WH, Mowat AP.
Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. J Med Genet ;5(4):319-321, 1968. PMID: 5713646
世界で最初のギャロウェイ・モワト症候群の症例報告（兄妹例）である。

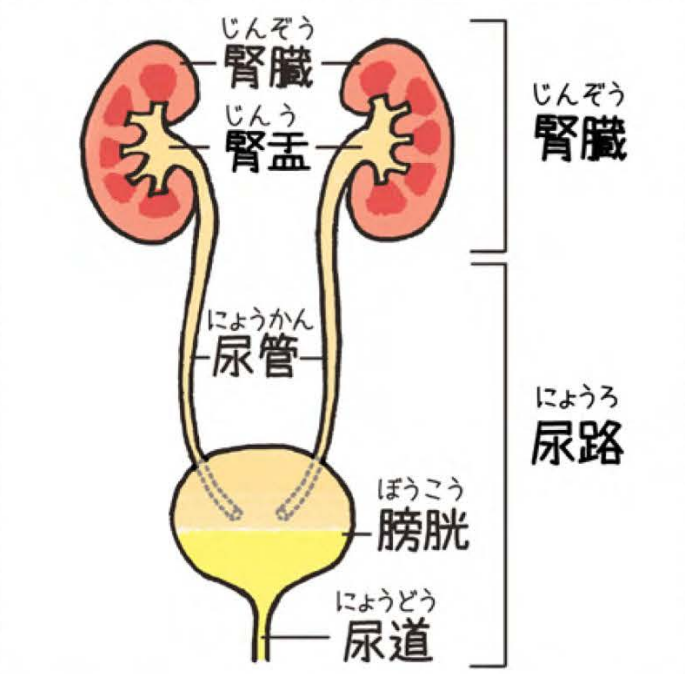
Keith J, Fabian VA, Walsh P, Sinniah R, Robitaille Y.
Neuropathological homology in true Galloway-Mowat syndrome. J Child Neurol ;26(4):510-517, 2011.PMID: 21233460
これまでに報告されているギャロウェイ・モワト症候群40症例の神経症状についての考察

塚口裕康　別冊 日本臨床 腎臓症候群(上編):
Galloway-Mowat 症候群(脳・腎糸球体異形成) page 411-419, 2012 日本臨床社

Galloway-Mowat 症候群(脳－肝糸球体異形成) page 411-413, 2012 日本臨床社
主として腎障害についての考察

乳幼児身体発育調査
http://www.mhlw.go.jp/toukei/list/73-22.html
平成22 年の乳幼児身体発育調査の結果をもとに、乳児の頭囲に関する発育曲線（パーセンタイル曲線）が作成され、調査結果は厚生労働省のホームページに掲載されている。

先天性腎尿路異常 (CAKUT)

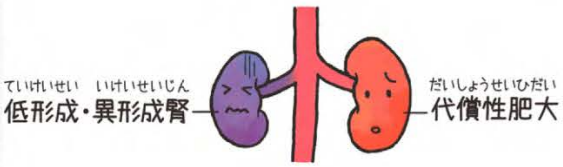


はじめに

先天性腎尿路異常（Congenital Anomalies of the Kidney and Urinary Tract: CAKUT;「カクート」と呼びます）は、「腎臓」と「腎盂・尿管・膀胱・尿道」といった“おしっこの通り道”である「尿路」に起こる病気です。多くの場合、お母さんのおなかの中でヒトの各臓器が作られていく過程で、「腎臓」や「尿路」の形や働きが適切に作られなかったことが原因です。

あなた（お子さん）はこの中のどの病気でしょうか

CAKUTはさまざまな病気が含まれます。ここではその一例を紹介します。



低形成腎

腎臓の大きさが普通よりも小さく、働きが悪い。

異形成腎

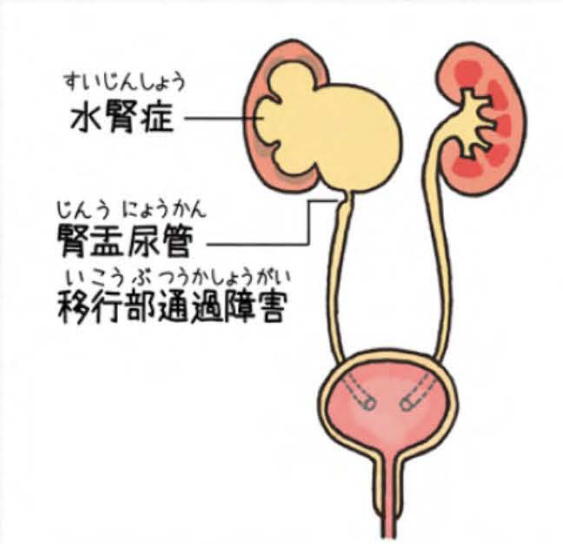
腎臓の構造が悪くうまく働かない。
片側のみ「低形成・異形成腎」の場合は、反対側の腎臓が大きくなっていることが多い（代償性肥大）。

多のう胞性異形成腎

腎臓の一部または全部が水風船のような水のたまり（のう胞）ができていて、働きがない。

腎瘢痕

腎臓が細菌感染などで障害をうけて傷あとを残して治った部分。

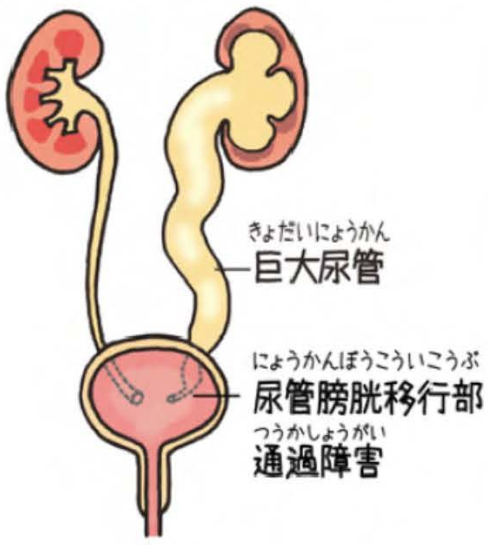


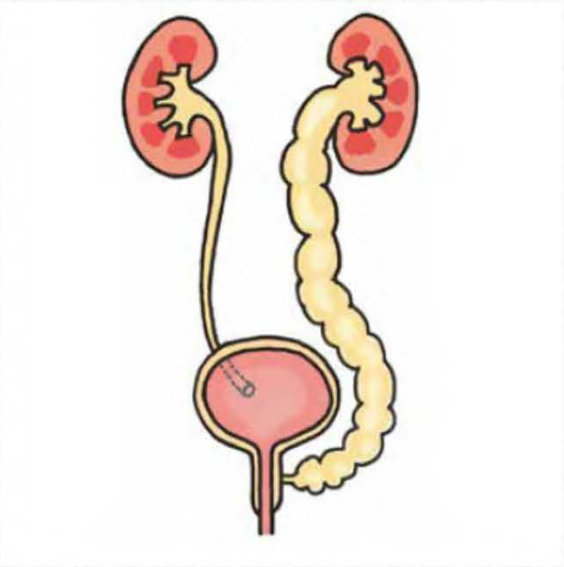
先天性水腎症

腎盂が尿管につながる部分がせまくなっていて、おしっこの流れが悪くなり、腎盂がふくらんでいる。

巨大尿管

尿管が膀胱につながる部分がせまくなっていて、おしっこの流れが悪くなり、尿管が太くなっている。



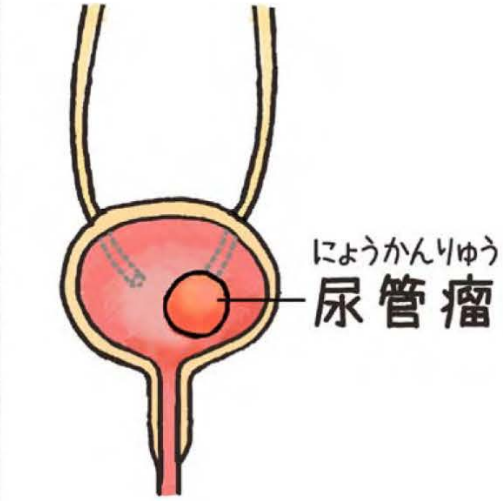


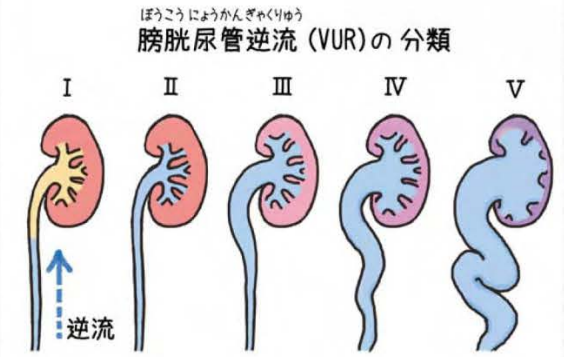
尿管異所開口

腎臓からつながる尿管が膀胱の適切な場所につながっていない。

尿管瘤

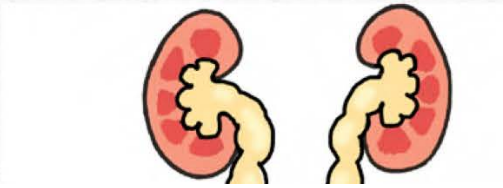
尿管が膀胱につながる部分で、膀胱の中に瘤のようにふくらみ、
おしっこの流れが悪い。





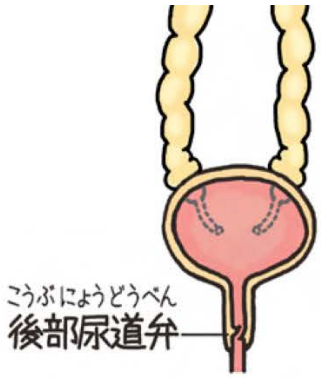
膀胱尿管逆流

膀胱内のおしっこが尿管や腎臓に逆戻りする（普通はこのような
逆流はありません）。
逆流の程度は5段階に分類される。



後部尿道弁

尿道がせまくなっていて、おしっこが出しにくい



腎臓の働き

＊低形成・異形成腎のお子さんは、もともと他のお子さんよりも尿量が多いことも特徴の一つです。

治療法

1. 薬物療法

高血圧や尿蛋白は長く続くと、腎臓の働きを悪くする可能性があります。 これらを抑えることにより、末期腎不全への進行を少しでも遅くすることを目的としています。　高血圧を伴うCAKUTの小児では、レニンアンジオテンシン系阻害薬を中心とした血圧を下

げる治療を行います。 これらの薬は血圧を下げる働き以外に、蛋白尿を減らす働きや腎臓を守ってくれる働きもあると考えています。

a) 血圧管理

適切な血圧にすることで、低形成・異形成腎においても腎臓の働きが悪くなるのを抑える可能性があります。 血圧が高い場合には年齢・体格に合わせた血圧になるように、お薬で血圧を下げる治療を行います。 血圧を下げるお薬にはレニンアンジオテンシン系阻害薬、カルシウム受容体拮抗薬などがあります。

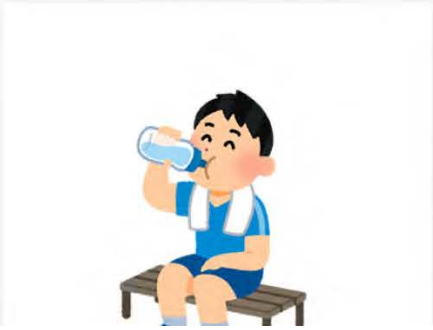
b) 尿蛋白を減らす効果
腎臓を守る効果

尿蛋白を認める場合は、尿蛋白を減らすことにより腎臓の働きを悪くするのを抑える可能性があります。 日本の腎臓の働きが悪い小児（CAKUTの小児が62%を占める）を対象とした研究では、 尿蛋白が腎臓の働きを悪くする危険因子でした。

レニンアンジオテンシン系阻害薬、カルシウム受容体拮抗薬のいずれも、 脱水時に急激に腎臓の働きを悪化させる可能性があります。特に乳幼児など、 経口摂取が安定せず脱水となる危険性の高い小児の場合は、脱水になりやすい時 （水が飲めない・嘔吐・下痢など）にはお薬を飲むことをやめる、などの対応が必要となることがあります。 主治医に相談してください。

2.水分摂取・塩分(ナトリウム)摂取

尿量の多いCAKUT（特に低形成・異形成腎）の小児では、 水分・塩分の補充をすることで腎臓の働きが悪くなるのをゆるやかにし、成長を促す可能性があります。 尿量の多いCAKUTの小児では、尿からたくさんの水分・塩分が出ていってしまいます。 特に低形成・異形成腎では腎臓の働きが悪くなっても、尿量が多い状態が続き脱水となることがあります。 適切な水分や塩分を保つことは筋肉の成長に必要なので、不足すると成長



障害も引き起こします。

血液検査でナトリウム低下を認めなくても、塩分不足の可能性があります。 そのため体重減少や血液検査で水分不足の結果などがあれば、塩分および水分を補充することが必要です。 母乳や普通ミルクには塩分がほとんど含まれていません。 したがって、乳児が塩分不足を認める場合には、塩分補給を目的とした塩分の多いミルクとして、 明治低カリウム・中リンフォーミュラ（標準濃度15％でNa27mEq/L　商品名：明治8806H）を使用することがあります。 このミルクは塩分の含有量が多いほか、カリウムが普通ミルクよりも抑えられていることが特徴です。 また、乳児期から慢性腎臓病の状態にある小児では食欲が低下していることがあるため、 チューブ栄養などを用いた水分や塩分の補充が必要となることがあります。

3. 栄養療法

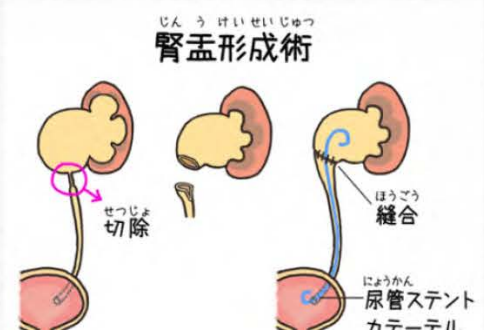
CAKUTの小児もほかの小児と同じように、十分な栄養を摂取することが重要です。 体格などにより異なりますが、「日本人の食事摂取基準(2015年版)」 を指標にするのがよいと考えられます。

推定エネルギー必要量（kcal/日）

	男児	女児
0-5か月	550	500
6-8か月	650	600
9-11か月	700	650
1-2歳	950	900
3-5歳	1300	1250
6-7歳	1550	1450
8-9歳	1850	1700
10-11歳	2250	2100
12-14歳	2600	2400
15-17歳	2850	2300
18-29歳	2650	1950

4. 手術療法

CAKUTには、尿路のどこかに流れが悪い部位がある、尿路が適切な場所につながっていない、 普通では存在しない尿の逆流がある、といった病態が多いです。 これらを直すのが手術療法です。

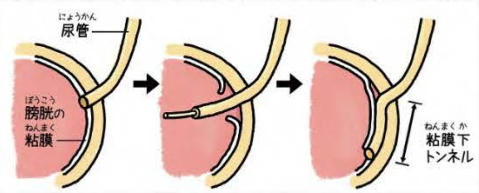


a) 腎盂形成術

先天性水腎症の治療です。 腎盂が尿管につながるせまい部分を切り除き、腎盂と尿管を新しく縫い直します。
縫合部の腫れやむくみが取れるまで尿管ステントカテーテルを留置します。

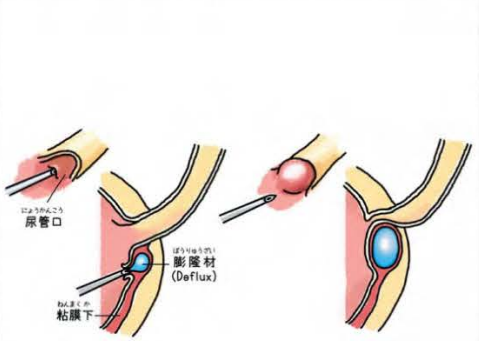
b) 逆流防止術

膀胱尿管逆流の治療です。



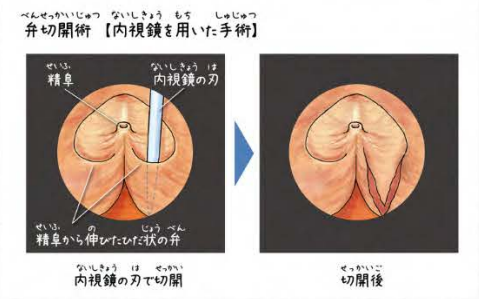
b-1) 膀胱尿管新吻合術

膀胱と尿管を粘膜下トンネルを作って新たに縫い直し、膀胱から尿管への尿の逆流がおこらないようにします。 巨大尿管、尿管異所開口、尿管瘤でも同様の縫い直す手術を行います。 巨大尿管では尿管が膀胱につながるせまい部分を、尿管瘤では瘤の部分を切り除いてから縫合します。



b-2) 内視鏡的注入療法

内視鏡で膀胱内を観察しながら尿管口の近くにDeflux（デフラックス）という膨隆材を注入して、 膀胱から尿管への尿の逆流がおこらないようにします。



c) 経尿道的弁（瘤）切開術

後部尿道弁や尿管瘤の治療です。尿道から細い内視鏡を入れて、 内視鏡の先に付けたメスで弁や瘤を切開して、尿の流れをよくします。

Q&A

Q.

CAKUTの小児では予防接種を
打っても大丈夫ですか？

A.

感染症にかかりやすく重症化する可能性もあるため、 積極的に予防接種を行うことを推奨しています。不活化ワクチン、 生ワクチンともに健康な小児と全く変わらないスケジュールで接種することが 望ましいと考えています。

Q.

お薬はどのくらいの期間飲まなければいけないのですか？

A.

内服を開始した場合、基本的にはずっと継続が必要です。 しかし、腎臓の働きの悪さの程度や食事の状況、腎代替療法 （透析や移植）開始により、必要な内服薬や期間は大きく異なります。

Q.

運動しても大丈夫ですか？

A.

運動制限をしても腎臓の働きが悪くなることを抑えられるかは明らかではないため、 運動制限は推奨されていません。 ただし激しい運動部活動による長期的な腎への影響は明らかではなく、合併する高血圧や心不全では病状に応じた運動制限が必要となります。 一方で運動制限は精神的なストレスも含めて生活の質を低下させ、 過度の運動制限では骨折などの重大な副作用をもたらす可能性があります。 現状ではこれらのことを総合的に考慮する必要があります。

Q.

食べてはいけない食べ物は
ありますか？

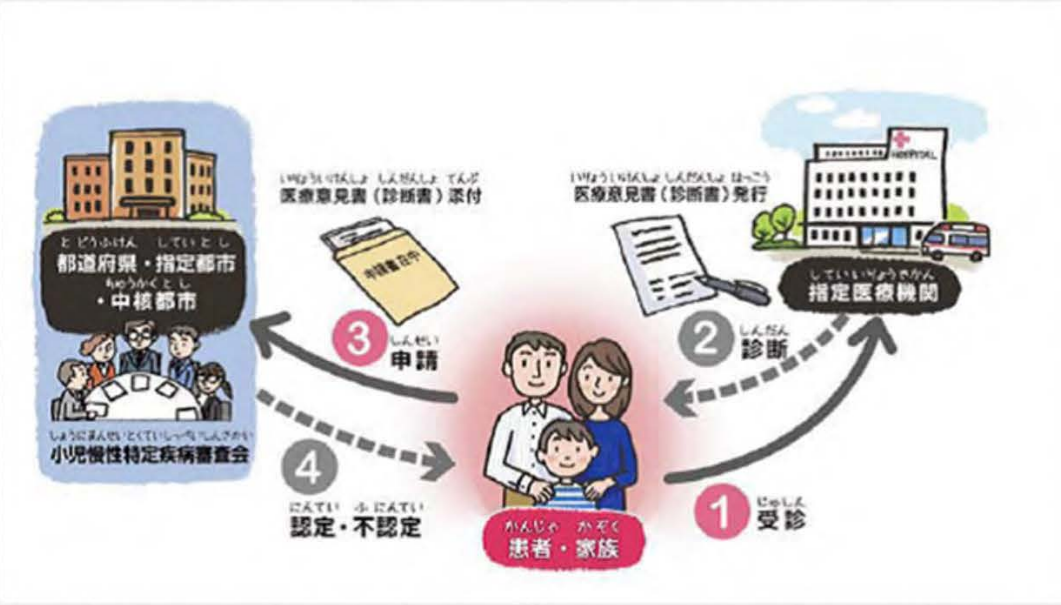
A.

小児の場合は、たんぱく質を制限することで腎臓の働きが悪くなるのを抑えられるかは 明らかではなく、成長のことを考えるとたんぱく制限は推奨されていません。 高血圧を伴う場合は、塩分を制限すると血圧が下がり、 腎臓の働きが悪くなるのを抑える可能性があります。 しかし、尿量が多く、塩分を失いやすい小児では塩分制限はすべきではありません。 更に、腎臓の働きの悪さの程度によって、食事の制限が必要となることがあります。 末期腎不全に至ると、血液検査の結果により、電解質（カリウムやリンなど）の摂取制限が 必要となることがあります。

医療費の助成制度について

医療費の助成制度について

「小児慢性特定疾病」による医療費助成制度が受けられます　CAKUTの一部は「小児慢性特定疾病」の対象疾患になっています。 このため、CAKUTと診断された場合は、あなたの病気が「小児慢性特定疾病」 の対象になっているかどうかを主治医に確認してください。多くの場合、 腎臓の働きが悪くなっている場合に対象となります。「小児慢性特定疾病」 の対象になっている場合は、所定の申請手続きを行い認定されるとご自身のご病気に 伴う医療費の助成が受けられます。



「小児慢性特定疾病」の申請手続きについて

小児慢性特定疾病の医療費助成の申請については以下のとおりです。

1. 指定医療機関にて受診を受ける。
2. 指定医療機関にて診断後、医師より小児慢性疾病の医療意見書を手交してもらう。
3. 2で手交された医療意見書を添付の上、医療費助成の申請を都道府県、指定都市、中核市に提出する。 申請のための書類(医療受給者証申請書)に関しては、各都道府県、指定都市、中核都市にお尋ねください。
4. 小児慢性特定疾病審査会にて審査を行う。
5. 都道府県、指定都市、中核市より「認定」・「不認定」をご通知する。

※医療受給者証の有効期限は原則1年です。継続して受給したい場合には、毎年申請手続きを行ってください。

用語解説

慢性腎臓病
（Chronic Kidney Disease：CKD）とは

慢性腎臓病（CKD）とは尿検査、血液検査、画像検査（超音波、CT、MRI、造影検査、核医学検査など）で腎臓の働きが悪い状態です。 腎臓の働きの悪さの程度によって、表のようなステージに分けられます。 血液検査でのクレアチニンの値から、腎臓で濾過できる量（推定GFR値）を計算することができ、その値で分類します。

末期腎不全

腎臓の働きが悪くなり、透析や腎移植が必要な状態です。CKDステージ5の状態です。

腎代替療法

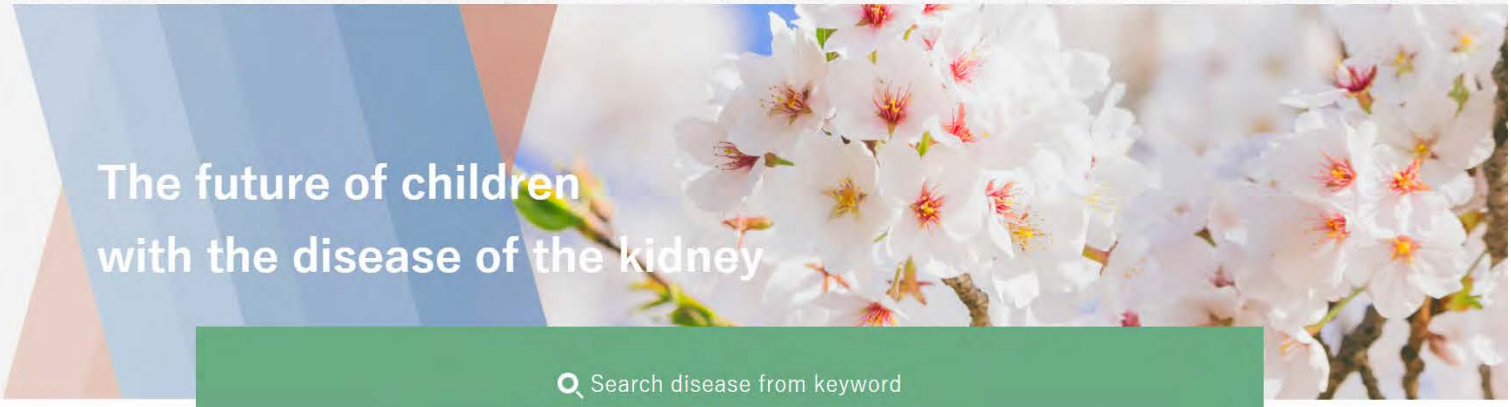
透析（血液透析、腹膜透析）や腎移植のことです。CKDステージ5になると必要となります。

CKD ステージ	重症度の説明	推算 GFR 値 (mL/分/1.73m²)	腎臓の働き	治療法
1	腎障害あり GFR は正常または亢進	90 以上	75-100%	CKD の診断と治療の開始 合併症の治療 CKD 進展を遅らせる治療
2	腎障害あり GFR 軽度低下	60-89	50-75%	上記に加えて 腎障害進行度の評価
3	GFR 中等度低下	30-59	25-50%	上記に加えて腎不全合併症を把握し治療する
4	GFR 高度低下	15-29	12.5-25%	上記に加えて 透析・移植を準備する
5	末期腎不全	15 未満	12.5%未満	（症状によっては） 透析または移植の導入

この病気に関する資料・関連リンク

小児慢性特定疾病情報センター
(低形成腎)https://www.shouman.jp/disease/details/02_16_037/
(多嚢胞性異形成腎)https://www.shouman.jp/disease/details/02_16_040/

低形成・異形成腎を中心とした先天性腎尿路異常(CAKUT)の腎機能障害進行抑制のためのガイドライン
https://minds.jcqhc.or.jp/docs/minds/Suppression-of-renal-dysfunction-of-congenital-renal-urinary-tract-abnormalities(CAKUT)-centered-on-hypoplasia_dysplasia-kidney/full-text.pdf



The future of children with the disease of the kidney

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search

Research project on intractable diseases

In order to promote measures against intractable diseases and childhood chronic diseases, the research team of this project has established a research system covering all intractable diseases and others. The intractable disease medical support network centered on the intractable disease medical treatment cooperation base hospital has been put into operation as a medical care provision system for intractable diseases. This project is expected to contribute as a commander for…

More

Intractable diseases in the kidney area of children

This research group is in cooperation with the Japanese Society of Pediatric Kidney Diseases and the Pediatrics Society, Understanding the medical condition based on national epidemiological survey mainly on intractable diseases of kidney area that develops in childhood and children's chronic specific diseases, establishment and revision of medical treatment guidelines based on evidence, diagnosis criteria, severity classification, medical treatment guidelines Organize and disseminate.…

More

Conservative management of CKD

Chronic kidney disease (CKD) is a new disease concept established in the 2000s. Irrespective of the cause of the disease, it refers to a condition in which there is an abnormality in the urinalysis, a decrease in the function of the kidney, or an abnormality in the shape of the kidney which is known by the examination such as ultrasound. It is known that the risk of progression to end-stage renal failure requiring dialysis and kidney transplantation in the future is extremely…

More

List of diseases

Alport syndrome

Alport syndrome is a hereditary chronic nephritis and often progresses to end-stage renal failure. Patients with chronic nephritis do not experience any symptoms…

More detail

Galloway Mowat syndrome

Galloway-Mowat syndrome is a disorder presenting with three symptoms, microcephaly, heavy proteinuria, and facial morphological abnormalities such as malformed ears, due to developmental dysplasia of two organs, the head…

More detail

Epstein syndrome

Epstein syndrome is a hereditary disease characterized by 3 symptoms: 1) macrothrombocytopenia, 2) progressive renal dysfunction, and 3) sensorineural hearing loss. As for 1) macrothrombocytopenia, giant platelets…

More detail

Nail-patella syndrome

Congenital anomalies of the

Congenital nephrotic

Nail-patella syndrome

Nail–patella syndrome is a hereditary disease characterized by dysplastic nails (nails with abnormal shape), absent or hypoplastic patellae (small or missing knee caps), elbow dysplasia (elbow deformities), and iliac horns …

More detail

kidney and urinary tract

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are a cause of disease in the “kidney” and “urinary tract,” which is the path urine travels through (e.g., renal pelvis, ureter, bladder…

More detail

syndrome

It is a disease characterized by protein, which does not normally leak from the blood, going out into the urine in large quantities, leading to a decrease in serum protein level (hypoproteinemia). Due to this, various…

More detail

Nephronophthisis

Nephronophthisis is a progressive cystic kidney disease characterized by cysts (round sacs) developing in the kidneys. Nephronophthisis is considered to be caused by structural and functional…

More detail

Barter syndrome・Gittermann syndrome

These diseases are syndromes where congenital renal tubular dysfunction causes hypokalemia and metabolic alkalosis, as well as their associated clinical symptoms. Bartter syndrome usually occurs from…

More detail

Pediatric idiopathic nephrotic syndrome

Nephrotic syndrome is a disease characterized by low levels of protein (especially albumin) in the blood (hypoproteinemia/hypoalbuminemia) due to large amount…

More detail

Lowe syndrome

Lowe syndrome is a hereditary disease characterized by three groups of symptoms: 1) eye manifestations, 2) central nervous manifestations, andd 3) kidney manifestations. The d…

More detail

Branchio-oto-renal syndrome

Branchio-oto-renal syndrome (BOR) is a disease characterized by cervical fistula, aural fistula, and auricular anomaly, etc. (known as “branchiogenic anomalies”) associated with hearing loss and kidney deformity…

More detail

Back to top

Galloway Mowat syndrome

1.What is "Galloway-Mowat Syndrome?"

Galloway-Mowat syndrome is a disorder presenting with three symptoms, microcephaly, heavy proteinuria, and facial morphological abnormalities such as malformed ears, due to developmental dysplasia of two organs, the head (cranial nerves) and the kidneys. The name of the disease comes from two English pediatricians named Galloway and Mowat who first described the disease in 1968.

The cause of the disease is believed to be cellular dysfunction, common to renal glomerular epithelial cells and CNS neuron, disrupting the organogenesis process of the renal glomerulus and brain, but a definitive chromosomal abnormality or genetic mutation that leads to the disease has not yet been found.

2.Diagnostic Criteria

The Japan Intractable Diseases Information Center defines Galloway-Mowat syndrome as "a syndrome associated with external malformations (facial/limb malformation) and muscular symptoms (limb hypotonia, esotropia), presenting with two cardinal features, central nervous system manifestations (intractable epilepsy, psychomotor retardation) and kidney damage (glomerulosclerosis)." However, since these are tentative diagnostic criteria designed to include a wide range of patients, other diseases associated with kidney damage and central nervous system manifestations are also included. Over 70 cases have been reported up to 2017, revealing that microcephaly, heavy proteinuria, and facial morphological abnormalities such as malformed ears occur at high frequencies. Therefore any condition meeting all three of the following diagnostic criteria shall be regarded as Galloway-Mowat syndrome.

1. Microcephaly
2. Heavy proteinuria resistant or likely to be resistant to treatment (urine protein/creatinine ratio ≥ 1.0 g/gCr or urine protein ≥ 1.0 g/day)
3. Facial morphological abnormalities such as malformed ears

Obligatory symptoms (3 items)

1) Microcephaly

Head circumference measured around the forehead and the back of the head is 3% smaller than the standard value corresponding to the age and gender.

2) Heavy proteinuria resistant or likely to be resistant to treatment

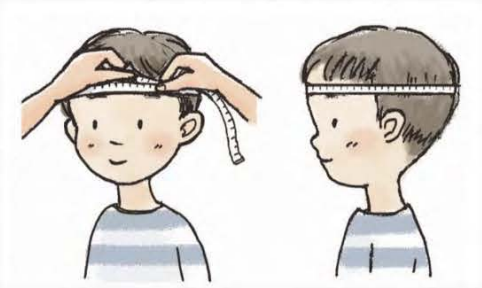
Urine protein/creatinine ratio ≥ 1.0 g/gCr or urine protein ≥ 1.0 g/day

3) Facial morphological abnormalities such as malformed ears

Malformed ears such as large and soft ears, posteriorly rotated ears, and low-set ears; other facial dysplasia (narrowed forehead, microgenia, high-arched palate, hypertelorism), etc.

Differential diagnosis

Congenital disorders of glycosylation, mitochondrial respiratory chain disorders (mitochondrial cytopathy), peroxisome, disorders of lipid metabolism, disorders of amino acid metabolism, disorders of glucose metabolism (glycogen storage diseases, galactosemia), infections (TORCH)



Method of measuring head circumference

Head circumference is measured using a tape measure from between the eyebrows (on the frontal bone higher than the root of nose) around to the most prominent part of the occipital bone on the back of the head. Measurement should be made to the millimeter.

Head circumference is measured from right above the eyebrows around to the most prominent point of the back of the head. Note that the most prominent point of the forehead should not be passed.

3.Symptoms

Microcephaly, heavy proteinuria, and facial morphological abnormalities such as malformed ears occur at high frequencies. Many patients have concurrent

psychomotor retardation or intractable epilepsy in addition to microcephaly. Dysplasia of the cerebral cortex (convolutional abnormalities, white matter dysmyelination) and cerebellar hypoplasia may be found on CT/MRI. Heavy proteinuria resistant or likely to be resistant to treatment (urine protein/creatinine ratio ≥ 1.0 g/gCr or urine protein ≥ 1.0 g/day) occurs, causing a large amount of proteinuria (nephrotic syndrome) by 3 months after birth and in typical and severe cases. Although kidney damage is progressive and often leads to renal failure, the age at which end-stage is reached ranges widely, from 3 to 10 years old or even older. On the other hand, there are patients with mild kidney damage (proteinuria) and microcephaly (epilepsy, growth retardation) who reach adulthood after a relatively favorable course of disease. In mild cases, in which nephrosis becomes apparent from approximately 1 to 3 years old, epileptic symptoms may precede. There are also cases where kidney function is preserved until adulthood and proteinuria remains moderate (dip stick method ˃ 2+, urine protein 0.5 g/day). Renal biopsy often shows focal segmental glomerulosclerosis (FSGS). Galloway-Mowat syndrome is sometimes associated with facial morphological abnormalities (narrowed forehead, microgenia, high-arched palate, hypertelorism), especially with ear abnormalities such as low-set ears, large and soft posteriorly rotated ears, etc. Muscular hypotonia is common, which may cause respiration disorder/dysphagia, and concurrent eye squint and esophageal hiatus hernia are observed.

4.Treatment

Treatment is mainly symptomatic. Kidney damage is progressive. Treatment is conducted as necessary for each period of maintenance, dialysis, and kidney transplantation. Long-term drug therapy is necessary for epilepsy.

5. Living with the disease

—Symptoms are generally progressive. An early-onset severe type, occurring within 3 months, often leads to death by 1-2 years of age after progression of psychomotor retardation (caused by status epilepticus) and kidney dysfunction. However, the degree of damage of the kidney and nerves varies and there are cases in which progression is slow without significantly affecting daily life until adulthood. Close attention should be given to hypoproteinemia caused by heavy proteinuria and complications associated with renal dysfunction. Drug therapy is prescribed at the onset of epilepsy and educational intervention is continued for those with psychomotor retardation.

6.Relevant materials

Head circumference growth level (by age, and gender) Percentile curves of head circumference in infants (boys) (survey in 2010)(cm)

Age in days/months/years	Boys Percentile 3	10	25	50 Median	75	90	97
At birth	30.5	31.5	32.5	33.5	34.5	35.0	36.0
30 days	33.8	34.7	35.7	36.7	37.6	38.3	39.1
0 year							
1-＜2 months	35.1	36.1	37.0	38.0	38.9	39.6	40.4
2-3	37.1	38.1	39.0	39.9	40.9	41.6	42.4
3-4	38.6	39.5	40.4	41.4	42.2	43.0	43.7
4-5	39.7	40.6	41.4	42.3	43.2	44.0	44.7
5-6	40.4	41.3	42.1	43.0	43.9	44.7	45.4
6-7	41.0	41.9	42.7	43.6	44.5	45.2	45.9
7-8	41.6	42.4	43.3	44.2	45.0	45.8	46.5
8-9	42.1	42.9	43.8	44.6	45.5	46.3	47.0
9-10	42.5	43.4	44.2	45.1	46.0	46.7	47.5
10-11	42.9	43.7	44.6	45.5	46.4	47.2	47.9
11-12	43.2	44.1	44.9	45.9	46.8	47.5	48.3
1 year							
0-＜1 month	43.5	44.4	45.3	46.2	47.1	47.9	48.7
1-2	43.8	44.7	45.6	46.5	47.4	48.2	49.0
2-3	44.1	45.0	45.8	46.8	47.7	48.5	49.3
3-4	44.3	45.2	46.1	47.0	48.0	48.8	49.6
4-5	44.5	45.4	46.3	47.2	48.2	49.0	49.9
5-6	44.7	45.6	46.5	47.4	48.4	49.2	50.1
6-7	44.9	45.8	46.6	47.6	48.6	49.4	50.3
7-8	45.0	45.9	46.8	47.8	48.7	49.6	50.5
8-9	45.2	46.1	46.9	47.9	48.9	49.8	50.6
9-10	45.3	46.2	47.1	48.1	49.0	49.9	50.8
10-11	45.4	46.3	47.2	48.2	49.2	50.0	50.9
11-12	45.5	46.4	47.3	48.3	49.3	50.2	51.1
2 years							
0-＜6 months	45.9	46.8	47.7	48.7	49.7	50.6	51.5
6-12	46.5	47.4	48.3	49.2	50.2	51.1	52.0
3 years							
0-＜6 months	47.0	47.9	48.7	49.7	50.7	51.6	52.5
6-12	47.4	48.3	49.1	50.1	51.1	52.0	52.9
4 years							
0-＜6 months	47.8	48.6	49.5	50.5	51.4	52.3	53.2
6-12	48.1	49.0	49.8	50.8	51.7	52.6	53.5
5 years							
0-＜6 months	48.4	49.2	50.1	51.0	52.0	52.9	53.8
6-12	48.6	49.5	50.3	51.3	52.3	53.3	54.2
6 years							
0-＜6 months	48.8	49.7	50.6	51.6	52.7	53.7	54.7

Head circumference growth level (by age, and gender) Percentile curves of head circumference in infants (girls) (survey in 2010)(cm)

Age in days/months/years	Girls Percentile 3	10	25	50 Median	75	90	97
At birth	30.5	31.2	32.0	33.0	34.0	34.5	35.5
30 days	33.1	34.1	34.9	35.9	36.7	37.5	38.2
0 year							
1-＜2 months	34.3	35.2	36.1	37.0	37.9	38.7	39.4
2-3	36.2	37.1	38.0	38.9	39.7	40.5	41.2
3-4	37.5	38.4	39.3	40.2	41.1	41.8	42.5
4-5	38.5	39.4	40.3	41.2	42.0	42.7	43.4
5-6	39.3	40.1	41.0	41.9	42.7	43.4	44.1
6-7	39.9	40.7	41.6	42.4	43.3	44.0	44.7
7-8	40.4	41.3	42.1	43.0	43.8	44.5	45.2
8-9	40.9	41.8	42.6	43.5	44.3	45.0	45.7
9-10	41.4	42.2	43.1	43.9	44.8	45.5	46.2
10-11	41.7	42.6	43.5	44.3	45.2	45.9	46.6
11-12	42.1	43.0	43.8	44.7	45.6	46.3	47.0
1 year							
0-＜1 month	42.4	43.3	44.2	45.1	45.9	46.7	47.4
1-2	42.7	43.6	44.5	45.4	46.2	47.0	47.7
2-3	43.0	43.9	44.7	45.6	46.5	47.3	48.0
3-4	43.2	44.1	45.0	45.9	46.8	47.6	48.3
4-5	43.4	44.3	45.2	46.1	47.0	47.8	48.6
5-6	43.6	44.5	45.4	46.3	47.2	48.0	48.8
6-7	43.8	44.7	45.5	46.5	47.4	48.2	49.0
7-8	44.0	44.8	45.7	46.6	47.6	48.4	49.1
8-9	44.1	45.0	45.8	46.8	47.7	48.5	49.3
9-10	44.3	45.1	46.0	46.9	47.8	48.7	49.5
10-11	44.4	45.2	46.1	47.0	48.0	48.8	49.6
11-12	44.5	45.4	46.2	47.2	48.1	48.9	49.7
2 years							
0-＜6 months	44.9	45.7	46.6	47.5	48.5	49.3	50.2
6-12	45.5	46.3	47.2	48.2	49.1	50.0	50.8
3 years							
0-＜6 months	46.0	46.9	47.7	48.7	49.7	50.5	51.4
6-12	46.5	47.4	48.2	49.2	50.2	51.0	51.9
4 years							
0-＜6 months	47.0	47.8	48.7	49.6	50.6	51.5	52.3
6-12	47.4	48.2	49.1	50.0	51.0	51.9	52.7
5 years							
0-＜6 months	47.7	48.6	49.4	50.4	51.4	52.2	53.1
6-12	48.1	48.9	49.7	50.7	51.6	52.5	53.4
6 years							
0-＜6 months	48.3	49.1	50.0	50.9	51.9	52.8	53.7

7.Reference materials for this disease

Database on Health and Labour Scientific Research
https://mhlw-grants.niph.go.jp/

Online Mendelian Inheritance in Man® (OMIM®)
http://www.ncbi.nlm.nih.gov/omim
Database summarizing information on genetic diseases and their causal genes, as well as mutations

Genetic and rare diseases information center (GARD)
https://rarediseases.info.nih.gov/diseases/65/galloway-mowat-syndrome
National Institutes of Health (NIH)-based provision of information on rare diseases and genetic diseases

Galloway WH, Mowat AP.
Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. J Med Genet; 5(4):319-321, 1968. PMID: 5713646 The world's first case report of Galloway-Mowat syndrome (brother-sister case)

Keith J, Fabian VA, Walsh P, Sinniah R, Robitaille Y. Neuropathological homology in true Galloway-Mowat syndrome.
J Child Neurol ;26(4):510-517, 2011.PMID: 21233460 Consideration of nervous symptoms in 40 reported cases of Galloway-Mowat syndrome

Hiroyasu Tsukaguchi Special issue, Japanese Journal of Clinical Medicine, Renal Syndrome (volume

1):

Galloway-Mowat syndrome (brain and glomerular dysplasia) pages 411-419, 2012 Nippon Rinsho Consideration mainly of kidney damage

Physical growth survey of infants and young children

http://www.mhlw.go.jp/toukei/list/73-22.html

Growth curves (percentile curves) of head circumference in infants were prepared based on the results of the 2010 physical growth survey of infants and young children, and the survey results are posted on the Ministry of Health, Labour and Welfare's website.

This leaflet was prepared by funding from the research group on Establishment of a clinical and research system for rare / intractable pediatric renal diseases (H29-nanchitou(nan)-ippan-039) supported by a Health Labour Sciences Research Grant (Research on Intractable Diseases Policy). Please note that the information in this leaflet may be changed or updated. Please also note that we are not responsible for any information in this document or any problems arising from the content included in this leaflet.

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Establishment of a clinical and research system for rare / intractable pediatric renal

diseases

Galloway-Mowat Syndrome Study Group

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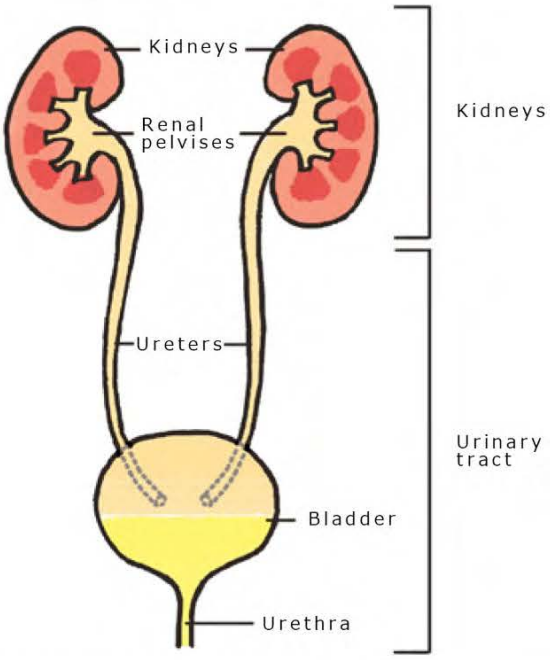
(Sites listed in the order of the Japanese syllabary)

Health Labour Sciences Research Grant Research project on intractable diseases Establishment of management and research system for rare and intractable diseases in the kidney area of children Principal investigator Kenji Ishikura

Congenital anomalies of the kidney and urinary tract

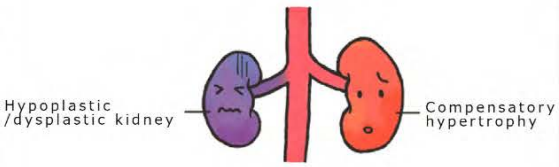


Introduction

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are a cause of disease in the “kidney” and “urinary tract,” which is the path urine travels through (e.g., renal pelvis, ureter, bladder, and urethra). In many cases the cause of disease is that the shape and function of the kidney or the urinary tract were not properly formed during the development process of each human organ in the mother’s womb.

What type of disease does your child have?

CAKUT includes various diseases. Here are some examples



Hypoplastic kidney

One kidney is smaller than usual and has poor function.

Dysplastic kidney

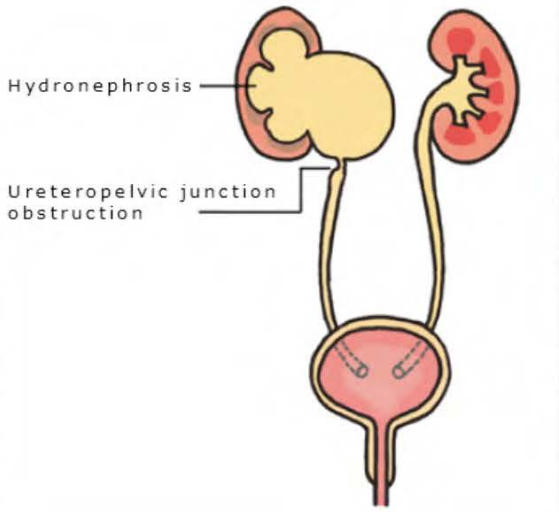
Structures of the kidney do not function well.
If only one kidney is hypoplastic/dysplastic, the kidney on the other side tends to enlarge (compensatory hypertrophy).

Multicystic dysplastic kidney

Water balloon-like pool of fluid (cysts) is formed in part of or the entire kidney and the kidney has no function.

Renal scarring

Part of the kidney that had been damaged by bacterial infections, etc. has recovered with scarring.

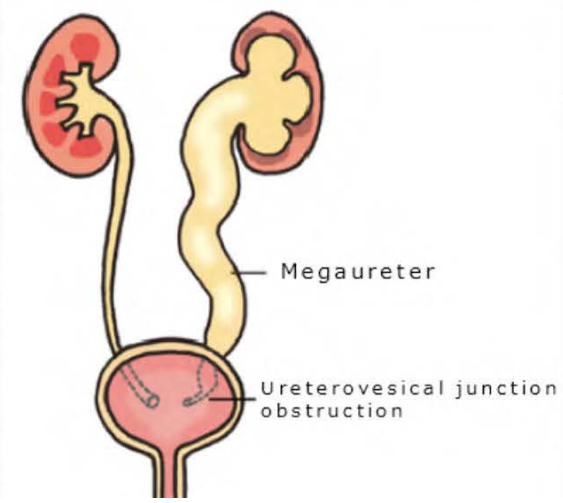


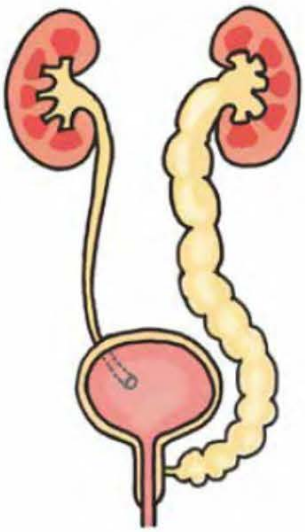
Congenital hydronephrosis

The part where the renal pelvis is connected to the ureter is narrowed, resulting in poor urine flow and a swollen renal pelvis.

Megaureter

The part where the ureter is connected to the bladder is narrowed, resulting in poor urine flow and an enlarged ureter.



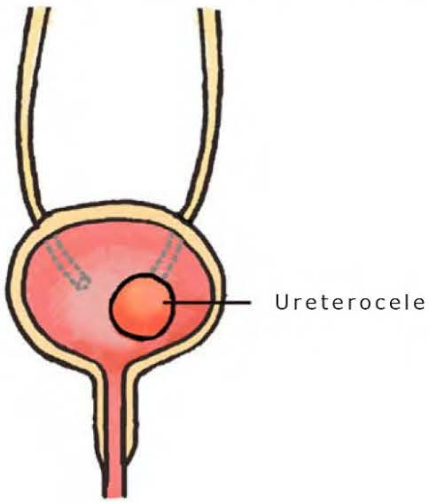


Ectopic ureter opening

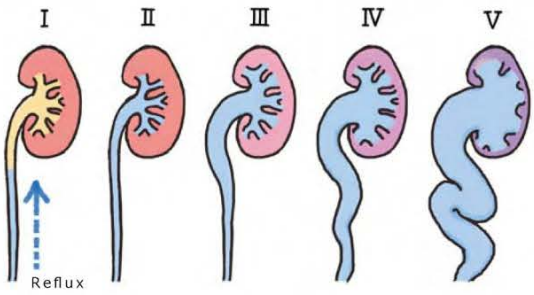
A ureter, a tube from the kidney, does not connect properly to the bladder.

Ureterocele

The portion of the ureter connected to the bladder swells up like a lump inside the bladder, resulting in poor urine flow.

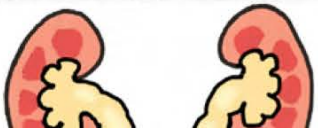


Classification of vesicoureteral reflux (VUR)



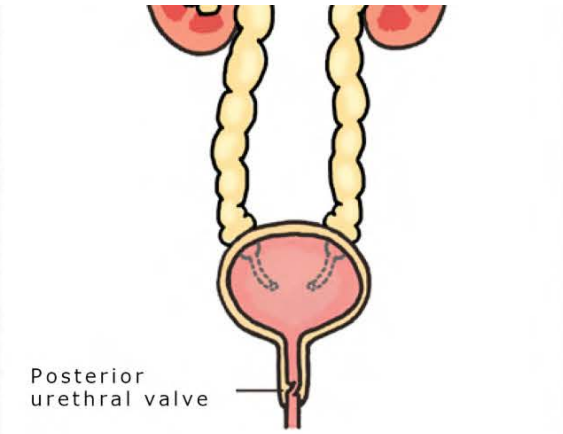
Vesicoureteral reflux

Urine in the bladder flows backward into the ureters/kidneys.
(Usually such reflux does not occur.)
Reflux is classified into five grades depending on the severity.

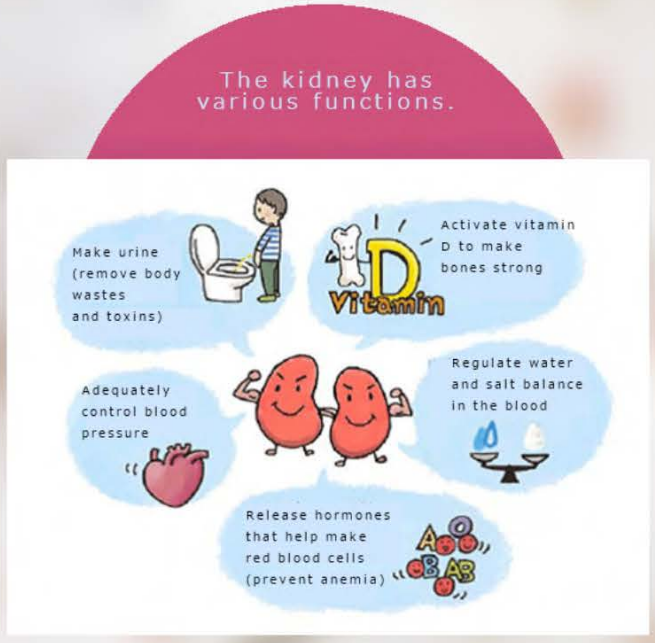


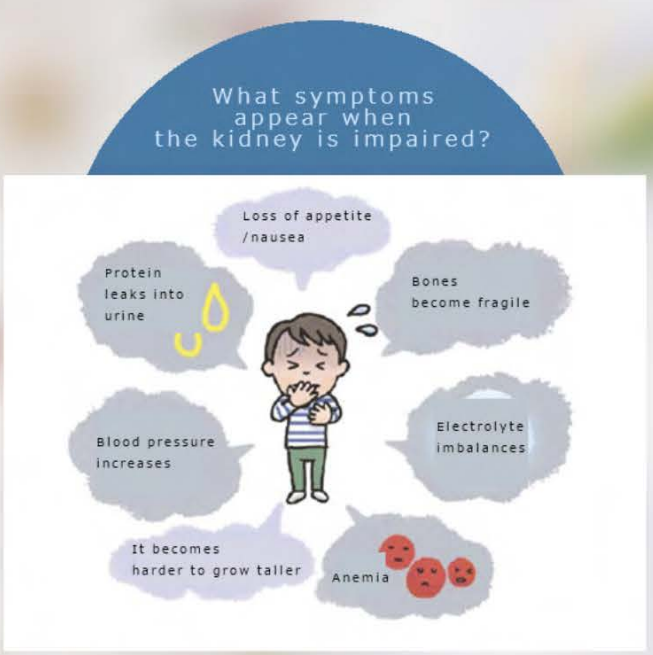
Posterior urethral valves

Narrowing of the urethra, which makes it difficult to pass urine.



Functions of the kidney





*One of the characteristics of children with hypoplastic/dysplastic kidneys is that they have an inherently high urine output compared to other children.

Treatment

1 . Drug therapy

If hypertension or urine protein persists for a long time, kidney function may be impaired. The purpose of drug therapy is to delay the progression to end-stage kidney disease for as long as possible by managing hypertension/urine protein. For children with CAKUT associated with hypertension, treatment to lower the blood pressure is performed using mainly inhibitors of the renin-angiotensin system. These drugs are considered to be able to reduce protein urine and protect the kidneys, in addition to lowering blood pressure.

a) Blood pressure management

Keeping blood pressure at an appropriate level may also prevent kidney function from being impaired in children with hypoplastic/dysplastic kidneys. If blood pressure is high, drug therapy will be used to lower the blood pressure to the level of the age/body size of the child. Blood pressure-lowering drugs include inhibitors of the renin-angiotensin system and calcium receptor antagonists

b) Effect to reduce urine protein
Effect to protect the kidney

If urine protein is detected, reducing urine protein may prevent kidney function from being impaired. In a study conducted in Japanese children with impaired kidneys (children with CAKUT accounted for 62%), urine protein was a risk factor for impairment of kidney function.

Both inhibitors of the renin-angiotensin system and calcium receptor antagonists can rapidly deteriorate kidney function during dehydration. In the case of children, especially infants, at risk of dehydration due to unsteady oral intake, it may become necessary to take measures, such as ceasing the medicine, when dehydration is likely to occur (e.g. unable to drink water/vomiting/diarrhea). Please consult your child's doctor.

2.Fluid intake/salt (sodium) intake

Supplementing fluid/salt may slow deterioration of kidney function and promote growth in children with CAKUT who have a high urine output (especially those with hypoplastic/dysplastic kidneys). A large amount of fluid/salt is lost through urine in children with CAKUT with a high urine output. Especially in children with hypoplastic/dysplastic kidneys, a high urine output may persist after kidney function is impaired, leading to dehydration. Since keeping an adequate amount of fluid and salt is necessary for muscle growth, lack of fluid/salt can cause growth disorder.

A lack of salt is possible even if decreased sodium (hyponatremia) was not detected in a blood test. Supplementing salt and fluid is therefore needed if there has been weight loss or a blood test result showing a lack of fluid. Breast milk and regular milk contain very little salt. Therefore if a lack of salt is found in infants, Meiji low-potassium/medium-phosphorus formula (standard concentration 15%, Na 27 mEq/L; brand name, Meiji 8806H) may be used as a formula with a high salt content for the purpose of supplementing salt. This milk is characterized by a high salt content and a low level of potassium compared to regular milk. As children who have had chronic renal disease since infancy may have a poor appetite, fluid/salt replacement using tube feeding, etc. may become necessary.

3. Nutrition therapy

It is important that children with CAKUT have adequate nutrition similar to other children. Although it depends on the physical body size, etc., the “Dietary Reference Intakes for Japanese 2015” is recommended as an index.

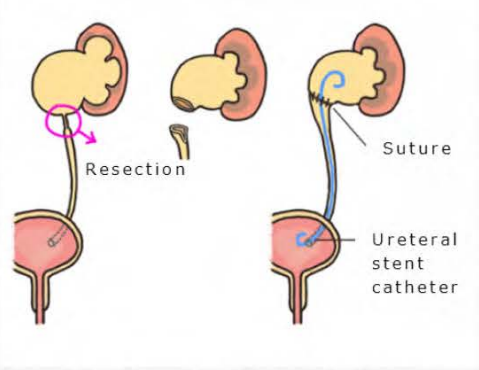
Estimated Energy Requirement (kcal/day)

	Boys	Girls
0-5 months	550	500
6-8 months	650	600
9-11 months	700	650
1-2 years	950	900
3-5 years	1300	1250
6-7 years	1550	1450
8-9 years	1850	1700
10-11 years	2250	2100
12-14 years	2600	2400
15-17 years	2850	2300
18-29 years	2650	1950

4. Surgical treatment

Common clinical conditions among patients with CAKUT are: an area in the urinary tract where urine flow is poor; the urinary tract is not connected appropriately; and urine reflux, which usually does not occur. Surgical treatment is performed to fix these problems.

Pyeloplasty

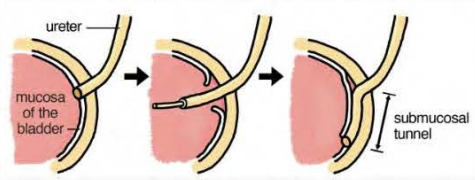


a) Pyeloplasty

This is the treatment for congenital hydronephrosis. The narrow area where the renal pelvis joins the ureter is removed and the renal pelvis and ureter are stitched together. The ureteral stent catheter is left in place until swelling or edema at suture site resolves.

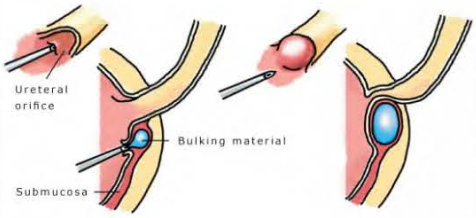
b) Antireflux surgery

This is the treatment for vesicoureteral reflux.



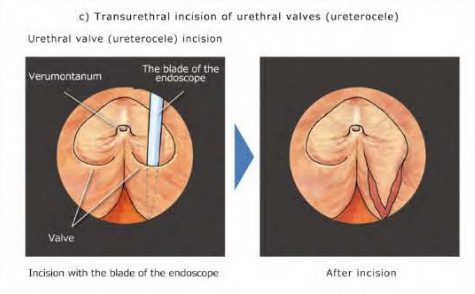
b-1) Ureteroneocystostomy

The ureter and bladder are stitched together anew by creating a submucosal tunnel so that urine reflux from the bladder to the ureters does not occur. A similar surgical procedure of stitching is performed also for megaureter, ectopic ureter opening, and ureterocele. For megaureter, stitching is done after the narrowed part where the ureter is connected to the bladder is removed and for ureterocele, after the lump is removed.



b-2) Endoscopic injection therapy

While examining inside the bladder with an endoscope, a bulking material called Deflux is injected into the region near the ureteral orifice so that urine reflux from the bladder to the ureters does not occur.



c) Transurethral incision of urethral valves (ureterocele)

This is the treatment for posterior urethral valve and ureterocele. A thin endoscope is inserted through the urethra and the valve or ureterocele is cut open with a surgical knife attached to the tip of the endoscope to make urine flow easier.

Q.

Can children with CAKUT receive vaccinations?

A.

Children with CAKUT are prone to infections, which may become serious, and vaccinations are therefore highly recommended. It is considered desirable to receive vaccinations, with inactivated or live vaccine, following exactly the same schedule as healthy children.

Q.

How long should medication be taken?

A.

When oral medication is started, it needs to be continued in principle. However, the required oral medication and duration will be greatly different depending on how severely the kidney function is impaired, dietary status, and whether renal replacement therapy (dialysis, transplantation) has been started.

Q.

1. Is it ok to be physically active?

A.

Since it is not clear whether physical restrictions can protect patients from further impairing their kidney function, restriction of physical activities is not recommended.

Q.

Are there any foods that should not be eaten?

A.

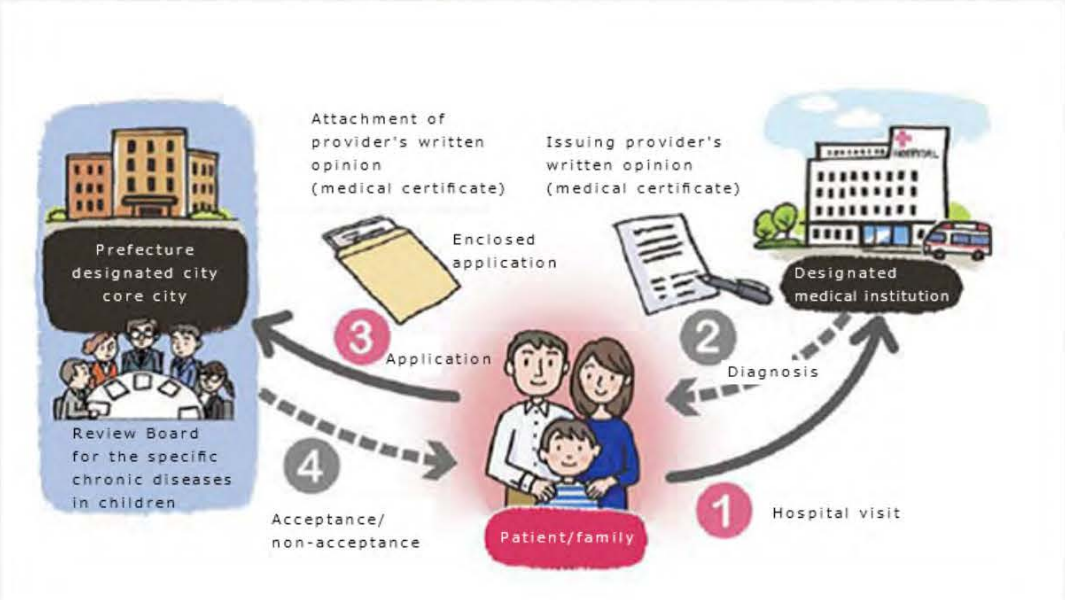
Since it is not clear whether protein restrictions can protect

However, the long-term influence of intense sports club activities on the kidney is not clear and for patients with hypertension or cardiac failure as a complication, restriction of physical activities based on their disease conditions is necessary. On the other hand, restriction of physical activities may cause mental stress and lower quality of life, and excessive restriction of physical activities may lead to serious side effects such as broken bones. These matters need to be considered comprehensively under present circumstances.

patients from further impairing their kidney function, restriction of protein is not recommended considering their physical growth. If accompanied by hypertension, restriction of salt may lower the blood pressure and protect kidney function from further impairment. However, salt should not be restricted in children who have a high urine output and who are more likely to lose salt. Moreover, dietary restriction may become necessary depending on how severely the kidney function is impaired. When end-stage renal failure is reached, restriction of electrolytes (potassium, phosphorus, etc.) may become necessary depending on the results of blood tests.

Medical expenses subsidy program

The medical expenses subsidy program is available for “Specific Chronic Diseases in Children.” Some of the CAKUT diseases fall under “Specific Chronic Diseases in Children.” Therefore, if you are diagnosed with CAKUT, check with your doctor whether your disease falls under “Specific Chronic Diseases in Children.” Cases where kidney function is impaired are often included in “Specific Chronic Diseases in Children.” If your disease falls under “Specific Chronic Diseases in Children,” and you go through a prescribed procedure, you will be eligible for a medical expenses subsidy.



Application procedures for a medical expenses subsidy for “Specific Chronic Diseases in Children”

The application for a medical expenses subsidy for specific chronic diseases in children is shown below

1. Visit a designated medical institution.
2. After being seen at the designated medical institution, ask the doctor to personally deliver the medical provider’s written opinion regarding specific chronic diseases in children.

3. After attaching the personally delivered medical provider's written opinion described in item 2, submit the medical expenses subsidy application to your prefecture/designated city/core city. For information regarding documents (medical care recipient certificate application form) for application, please contact your prefecture/designated city/core city.
4. Your application will be reviewed by the Review Board for the specific chronic diseases in children.
5. You will receive notification of acceptance or non-acceptance from your prefecture/designated city/core city.

※In principle, a medical care recipient certificate is valid for 1 year. Please apply for a certificate every year if you want to continue receiving benefits.

Glossary

Chronic Kidney Disease (CKD)

CKD can be classified into stages as shown in the Table below depending on how severely the kidney function is impaired. The ability of the kidneys to filter out waste (estimated GFR rate) can be calculated from the creatinine level on a blood test and the stages are classified using the calculated values.

End-stage kidney disease

End-stage kidney disease is a condition where kidney function has been impaired and dialysis or kidney transplantation is necessary. The CKD stage is 5.

Renal replacement therapy means dialysis (hemodialysis, peritoneal dialysis) and kidney transplantation. Renal replacement therapy becomes necessary when CKD reaches stage 5.

CKD Stage	Severity description	Estimated GFR (mL/min/1.73 m²)	Kidney function	Treatment
1	Kidney damage Normal or increased GFR	≥ 90	75-100%	Diagnosis of CKD and start of treatment Treatment of complications Treatment to delay CKD progression
2	Kidney damage Slight reduction in GFR	60-89	50-75%	Assessment of progression of kidney damage in addition to the above
3	Modest reduction in GFR	30-59	25-50%	Detect and treat renal failure complications in addition to the above
4	Severe reduction in GFR	15-29	12.5-25%	Preparation of dialysis/transplantation in addition to the above
5	End-stage kidney disease	< 15	< 12.5%	Introduction of dialysis or transplantation (depending on symptoms)

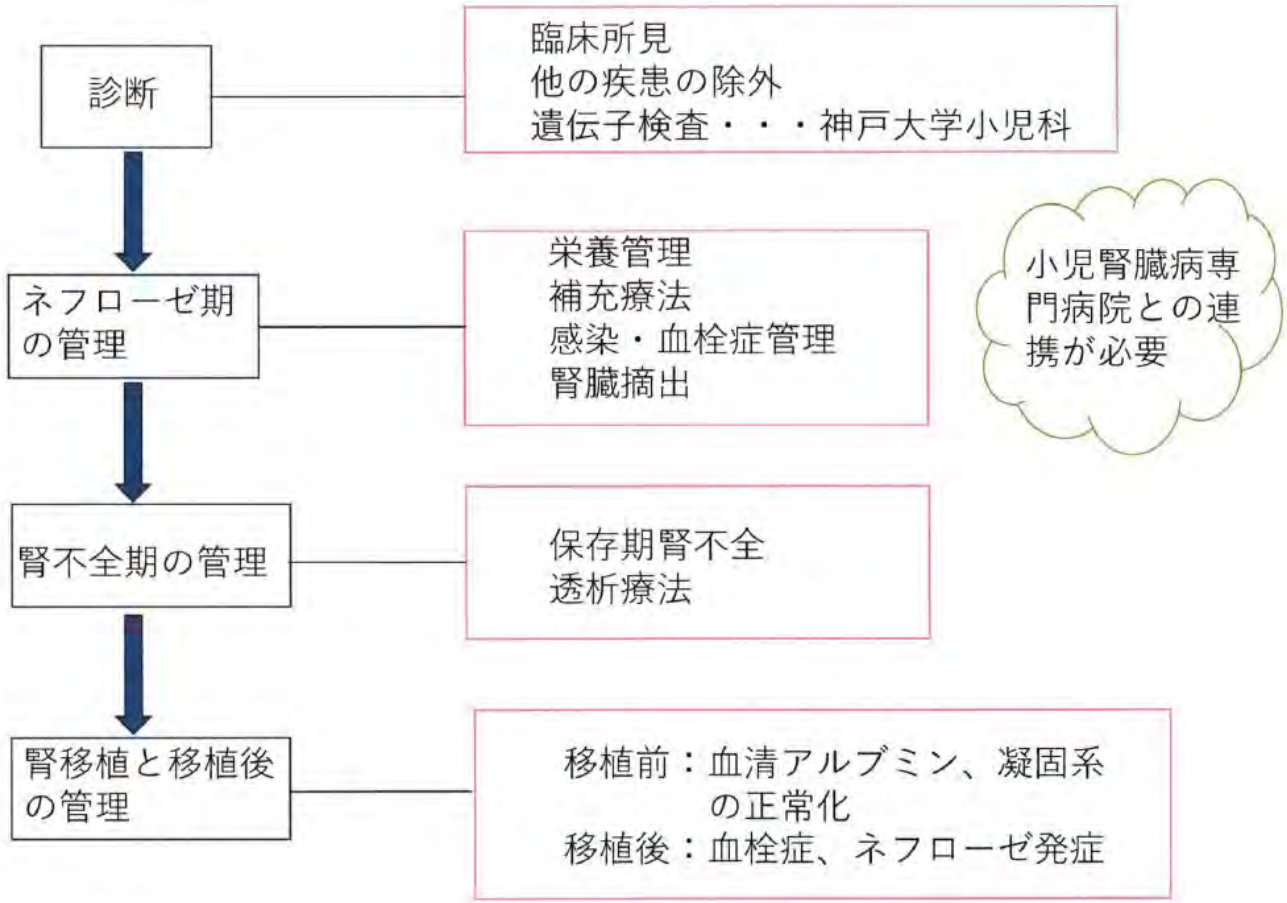
「フィンランド型先天性ネフローゼ症候群の診断・管理の手引き」

はじめに

生後 3 か月以内に発症するネフローゼ症候群を先天性ネフローゼ症候群と言い、フィンランド型先天性ネフローゼ症候群（CNF）はその代表的疾患である。フィンランドでは新生児およそ 8000 人に 1 人の頻度で発症するが、本邦の発症頻度は明確ではなかった。出生後間もなくから高度のネフローゼ症候群がみられ、敗血症や血栓症など生命を脅かす重篤な合併症があるため、かつては管理困難で予後不良な疾患であった。 1990 年以降に診断と管理指針がフィンランドから提示され、それをもとに各国の状況に見合った管理がなされるようになり治療成績が大きく改善して来た。最終的な治療法は腎移植になるが、出生後の診断から始まり、ネフローゼ期、腎不全期(保存期・透析期)、腎移植期それぞれに必要不可欠な管理がある。

今回、今までの厚労省研究結果によって得られた本邦における診断、管理状況を踏まえた上で、「フィンランド型先天性ネフローゼ症候群の診断・管理の手引き」を作成することになった。希少で重篤な疾患であることから、ランダム化比較試験などはなされていないため、ケースシリーズや症例報告などを参考にして手引きの作成を行った。今後も改訂を行っていく予定であるが、管理にあたっている医師の助けになれれば幸いだと考えている。

診断・治療のフローチャート



第1章　診断

CNF を含む生後１年以内に発症するネフローゼ症候群（生後３カ月以内を先天性ネフローゼ症候群、以後を乳児ネフローゼ症候群と呼ぶ）には，種々の疾患が含まれる（表１参照）。CNF に関しては、臨床症状と検査所見で暫定的に診断し、対症療法を行ないながら、可能な範囲で腎組織や遺伝子情報を加えて総合的に診断するという流れになる。

CNF にみられる以下のような臨床・検査所見が診断のための補助となる。

・母体の血清・羊水中の α フェトプロテイン濃度の高値

・ 胎盤重量が出生体重の 25%以上

・ 血清アルブミン濃度：1.0g/dL 未満

・ タンパク尿：2.0g/dL 以上（血清アルブミン濃度 1.5g/dL 以上に補正した場合）

・先天性ネフローゼ症候群を呈する他疾患を除外（表１参照）

・生後６か月まで，腎機能正常（Cr 0.2-0.3mg/dl）

・家族歴あり

（近親婚の有無　同胞の情報は有用）

参考所見

・*NPHS1* 遺伝子の異常

・ 腎組織上の NPHS1 蛋白の免疫染色異常

表1　先天性・乳児ネフローゼ症候群の分類

疾患	原因遺伝子:(遺伝子座)
原発性	
フィンランド型先天性ネフローゼ（CNF）	*NPHS1*（19q13.1）
びまん性メサンギウム硬化（DMS）	*WT1*（11p13）
	PLCE1（10q23）
巣状糸球体硬化症	*NPHS2*（1q25-31）
	PLCE1
Denys-Drash 症候群	*WT1*
Pierson 症候群	*LamB2*（1q31）
nail-patella 症候群	*LMX1B*（9q34）
Herlitz 致死型表皮水泡症	*LamB3*（1q32）
Galloway-Mowat 症候群	
微小変化型ネフローゼ症候群	
ミトコンドリア異常	コエンザイム Q10 合成系（COQ2 COQ6 ADCK4）
その他	
二次性	
感染症	
先天性梅毒　トキソプラズマ	
マラリア　サイトメガロウイルス	
風疹　B 型肝炎　HIV	
全身性エリテマトーデス（SLE）	

抗 NEP 抗体の母体からの移行

第 2 章　管理

ステートメント

1. 浮腫の管理

① 生命を脅かす二次的な合併症の原因となる高度蛋白尿に対して、経静脈的なアルブミン製剤の補充を行う（投与例は以下の通り）。またアルブミン製剤の投与時には適宜フロセミド 0.5-1.0 mg/kg を併用する。

例　20%アルブミン製剤　1-2 g/kg/2 時間　1 日 1-3 回

20%アルブミン製剤　2-4 g/kg/6-8 時間　1 日 1 回

20%アルブミン製剤　2-4 g/kg/24 時間持続投与

② アンジオテンシン変換酵素阻害薬（カプトプリル 1-5 mg/kg/day）やインドメタシン（1-5 mg/kg/day）で尿蛋白を減少させることが可能である。これらの薬物療法で管理に難渋する場合は腎臓を摘出する。

③ 本邦では片腎摘出で浮腫の管理が可能なことが多い。その後、上記②の薬物療法を追加しても管理に難渋する場合は、対側腎を摘出し腹膜透析を導入する。

④ 免疫抑制療法は根拠に乏しく、避けるべきである。

2. 栄養療法

高カロリー（100-130kcal/kg/day）、高蛋白（3-4g/kg/day）を目標に投与する。

3. 補充療法

ビタミン D（アルファカルシドール 0.1-0.3 μg/day など）や総合ビタミン製剤、そしてマグネシウム（50 mg/day）やカルシウム（500-1000 mg/day）やカリウムなどのミネラルも補充する。甲状腺ホルモンは TSH 5μIU/mL 以下を目標

に投与する。

4.合併症の管理

① 血栓症予防のため生後 4 週頃から抗血小板薬(アスピリンやジピリダモール)と抗凝固薬（ワルファリンカリウム）を投与する。

② 予防的な抗菌薬やガンマグロブリンの投与は推奨しない。敗血症を疑った場合は、早期に血液培養検体を採取し広域抗菌薬を投与するとともに、必要に応じてガンマグロブリンを投与する。

③ ワクチンは積極的に行うが、腎移植に備えた抗体獲得のための反復投与は高度な蛋白尿や浮腫が軽減してからが望ましい。

5.透析療法

フィンランド型先天性ネフローゼ症候群（CNF）は体格の小さい乳幼児期に透析導入になることが多く、血液透析では連日に近い頻度の透析が必要となってしまう。在宅治療を目指すためには、腹膜透析を選択することが多い。

解説

CNF は、小児特発性ネフローゼ症候群とは異なり根本的な疾患治癒のための治療法が存在しない疾患である。治療の最終目標は、自己腎機能を廃絶させ、腎移植を行うことである。そのため、その治療は、ネフローゼ期、腎不全期、腎移植後の 3 段階に分けて考える。ネフローゼ期では、高度蛋白尿に伴う浮腫ならびに喪失物質の補充が管理の中心となり、感染症や血栓症などの合併症の予防を

行いながら、適切な栄養管理を行い、患児の成長発達を促す。腎不全期には多くの患児は腹膜透析をうけ、最終的な目標である腎移植が可能となる体格を目指していく（1-4)。

1.浮腫の管理

アルブミン製剤の補充と利尿薬

CNF における 1000-10000mg/dL といった高度蛋白尿の場合は、生命を脅かす浮腫や栄養失調、成長障害など二次的な合併症が必発である。このような場合は、経静脈的なアルブミン製剤の補充が必須となる。補充のために中心静脈カテーテル留置を行う場合には、内頚静脈を第一選択とする。腎移植のために尺径静脈を温存し、将来の内シャント作製のために鎖骨下静脈への留置も避けることが望ましい。中心静脈カテーテル留置に伴い血栓症（肺塞栓症など）や菌血症を来した報告もあり (5)、メリット・デメリットのバランスを患児毎に考慮し留置の適応を判断する必要がある。

高度蛋白尿の場合、アルブミン補充を行っても血清アルブミン値の上昇は一時的であるため、目標の血清アルブミン値は定めない。アルブミン製剤の漫然とした補充は避けるべきであり、その適応は、著明な胸水や腹水、重度の消化器症状、浮腫による重度の活動性低下、感染症合併時、外科的治療施行時などである。

CNF の児に対するアルブミン製剤は、欧米の成書では (6)、20%アルブミン 3-4g/kg/day を 1-3 回に分けて投与し徐々に夜間 1 回の長時間（6-8 時間）に移行する方法が記載されている。夜間の安定したアルブミン投与には中心静脈カテーテル留置が不可欠であり、その留置の有無や患児の状態に応じて複数の方法が選択肢となり、以下に例を示す。

① 20%アルブミン製剤 1-2g/kg/2 時間 1 日 1-3 回

② 20%アルブミン製剤 2-4g/kg/6-8 時間 1 日 1 回

③ 20%アルブミン製剤 2-4g/kg/24 時間持続投与。

周術期には③の 24 時間持続投与を考慮する。またアルブミン製剤の投与時には適宜フロセミド 0.5-1.0 mg/kg を併用する。

薬物療法

CNF の児において、アンギオテンシン変換酵素阻害薬（ACEI）やインドメタシンで尿蛋白を減少させることができたと報告されている（3, 7-10)。ACEI はレニンアンギオテンシン系を抑制することで輸出細動脈を選択的に拡張し糸球体濾過圧を下げることで尿蛋白を減少させ、ポドサイトの保護作用も有する（11)。CNF の児数人では、アンギオテンシンⅡ受容体拮抗薬を併用することでさらに尿蛋白を減少することができたと報告されている（12)。蛋白尿を減らすための第一選択薬としてカプトプリル 1-5 mg/kg/day を使用する。腎機能を頻回に確認することが重要であるとともに、低血圧によりなかなか極量まで使用できないことが多い。難治例の場合には、インドメタシン 1-5 mg/kg/day の追加を考慮する。インドメタシンは輸入細動脈を選択的に収縮し糸球体濾過圧を下げることで蛋白尿を減少させることができるが、追加の際には腎機能の評価に加え、腸管への血流障害による腸管虚血などに注意が必要である。Fin-major や Fin-minor など重度な変異（truncating mutation）がある CNF の児では ACEI やインドメタシンには反応しないが、変異によっては蛋白尿を減少させることが可能である（13, 14)。

腎臓摘出

薬物療法による浮腫および合併症の管理には限界があり、多くの症例で腎臓

摘出が必要となる。

片腎摘出により蛋白尿を減らし、アルブミン製剤の補充回数を減らすことが可能である(15, 16)。本邦では Fin-major、Fin-minor の変異例の報告は無く、フィンランドのような重症例が少ないため、片腎摘出で浮腫の管理が可能なことが多い。その実情を反映し、本邦の全国アンケート調査では CNF の児 33 例中 25 例に中央値 13 か月齢（3-96 か月齢）の時期に片腎摘出が行われており、一期的に両腎摘出を行った例はなかった。なお、片腎摘出後すぐに透析導入になることは比較的少ない。片腎摘出後も浮腫の管理に難渋する場合は、腎摘出前は副作用などで使い切れなかった ACEI やインドメタシンによる薬物療法の追加が有効な場合がある(3)。それでも管理に難渋する場合は、対側腎を摘出し腹膜透析 (PD) を導入する。

ここで移植を想定した自己腎摘出および移植までの経過は、主に①片腎摘➔対側腎摘➔府 PD➔腎移植、②片腎摘➔PD➔腎移植（移植時に対側腎摘）③腎移植と同時に片腎摘（移植床側の腎摘）の 3 つに分かれる（17)(一部変更)。内科的治療に奏効しない場合は、低年齢でも腎摘を考慮することになり、片腎摘出は平均 2.6 ヵ月、両腎摘出及び PD 施行まで平均 36.5 ヵ月、移植まで平均 54 ヵ月との報告がある（3)。基本的に、移植時、静脈（下大静脈もしくは総腸骨静脈）への吻合が容易な右側を移植床にすることが推奨されるため、移植に先行する片腎摘は左側が望ましい。以後、PD によって移植まで管理を行い、腎移植を行う。本邦において、移植腎は成人から提供されることが多いため、レシピエントが 15 kg以下の場合は、移植床拡大のために移植床と同側腎臓の摘出が考慮される。

一方、フィンランドで見られる Fin-major や Fin-minor に変異のある高度蛋白尿（10000 mg/dL 程度）の児では、片腎摘出で劇的に蛋白尿を減少させること

は難しいため、フィンランドでは、このような児に対して早い時期(7kg が目安)から一期的に両腎摘出を行い、PD を導入し、その後 10kg を目安に腎移植を行っている (2)。なお、生後 6 か月未満の両腎摘出では、レニンが不足し、著明な低血圧を呈することがあるので注意が必要となる (18)。

免疫抑制療法

CNF は希少な疾患であり、ステロイドやシクロスポリンなどの免疫抑制薬を使用した大規模な研究はない。CNF も含めた遺伝性のネフローゼ症候群 (NS) の報告においても、ステロイドやシクロスポリンによって寛解に至った症例はほとんどない(19-22)。ステロイド治療で寛解に至ったのはヨーロッパとトルコの先天性ネフローゼ症候群 (CNS)　45 人中 1 人のみであったが、その遺伝的背景は不明 (フィンランド型かどうかは明らかでない) である (23)。*NPHS1, NPHS2, WT1, PLCE1* の軽度な変異の場合に免疫抑制療法で改善をみたとの報告もあるが、そのメカニズムは不明である (24-27)。ステロイドやシクロスポリンがポドサイトに直接作用し、基底膜の安定化に寄与している可能性がある。しかしながら、CNF を含めた CNS の児は一般的にはポドサイトおよびその関連遺伝子に重度な変異を有することが多く免疫抑制療法には反応しない。本邦の全国アンケート調査では、CNF の 31 例中 3 例にステロイドを使用し全例が無効、また、30 例中 3 例に免疫抑制薬を使用し 1 例が部分寛解していたのみであった。以上より免疫抑制療法は根拠に乏しく避けるべきであると考える。

2. 栄養療法

CNF の児は、消化管の浮腫や腹水で食欲が低下し、吸収も不良である。2 歳までの乳幼児期には、栄養状態が精神運動発達を含めた成長を決定する主要因子

であるため（28)、必要なエネルギー摂取が経口で不十分な場合は必ず経鼻胃管や胃瘻などを用いた経管栄養を行う。経管栄養が困難な場合は中心静脈栄養（TPN）を考慮する。基本は、高カロリー（100-130 kcal/kg/day)、高蛋白（3-4 g/kg/day）ある（2, 11)。母乳や人工乳がまず使用されるが、エネルギーを稼ぐためにブドウ糖（粉飴）やMCTオイル（10-15 mL/day）などの脂肪乳剤の併用も有効である。

3.補充療法

ビタミンD（アルファカルシドール 0.1-0.3 μg/dayなど）や総合ビタミン製剤、マグネシウム（50 mg/day)、カルシウム（500-1000 mg/day)、カリウムなどのミネラルの補充も忘れてはならない。なお、投与量はそれぞれの正常値を目安に調整する。

トランスフェリン、トランスコバラミン、エリスロポエチンが尿中に喪失するため貧血になりやすい（29)。貧血に対するエリスロポエチンの投与は、尿中喪失があるため通常の慢性腎不全患者への投与量よりも大量に必要になることが多い。また、銅やセルロプラスミンの尿中への喪失による好中球減少と貧血も報告されており(30, 31)、その際は評価した上で補充を考慮する必要がある。

一般的にCNFも含めたネフローゼ症候群（NS）の児では、しばしば血清の甲状腺ホルモンが低値である（32-34)。CNSの5人中4人でTSHが上昇しており、甲状腺ホルモンの補充でTSHが低下すると報告されている（35)。血清の甲状腺ホルモン値の低値に対して、TSHが最初は正常であることもあるが、数か月で上昇してくる。よって生下時から甲状腺ホルモンを補充し、TSH 5μIU/mL以下を目標にその投与量を決定する。

大変まれではあるが CNF で副腎不全を呈することがあり、その場合はステロ

イドの補充が必要となる。副腎不全の機序として、CNF の患者で副腎の石灰化を認めることがあるため、副腎血栓の可能性があると報告されている (36)。

4.合併症の管理

死因となる血栓症の予防や感染症の対策が必須である。これらは永続的な神経合併症の原因にもなる (37)。

プラスミノーゲンやアンチトロンビンⅢ (ATⅢ) の尿中への喪失がタンパク合成で代償され、マクログロブリン、フィブリノゲン、トロンボプラスチン、凝固因子Ⅱ, Ⅴ, Ⅶ, Ⅹ, Ⅻが上昇する(38)。そのため血栓や重篤な凝固合併症が CNF を含めた NS の児で報告されている (39, 40)。本邦の全国アンケート調査では、CNF 35 例中 5 例で血栓症を呈していた。血栓症に対して生後 4 週頃から抗血小板薬 (アスピリン 3-5 mg/kg やジピリダモール) と抗凝固薬 (ワルファリンカリウム (PT-INR で 2 程度が目標)) を投与する。外科的な処置や血管の処置の際は抗血小板薬や抗凝固薬を 5-7 日前から中止し、ATⅢを正常化するため、一時的に ATⅢ 50 単位/kg を補充する。

ガンマグロブリンや補体 B 因子と D 因子の尿中への喪失により(41)、NS の児は特に肺炎球菌などの莢膜を有する細菌の感染症に罹患しやすい。本邦の全国アンケート調査では、CNF 32 例中 19 例で観察期間中に感染症の既往があった。CNF 21 例のネフローゼ期 (中央値 1.1 年) の感染症の種類や頻度を後方視的に分析した報告がある (42)。敗血症が 2.5 回/年、敗血症疑いが 2.5 回/年あったが、中心静脈カテーテルの有無は発症率に影響を与えなかった。また、予防的な抗菌薬やガンマグロブリンの投与は発症率を減らさなかった。以上より、予防的な抗菌薬やガンマグロブリンの投与は耐性菌の出現や輸血製剤の投与というデメリットを考慮し、推奨しない。しかし、敗血症を疑った場合は、早期に血液培

養検体を採取し広域抗菌薬を投与するとともに、必要に応じてガンマグロブリンを投与する。皮下注用ガンマグロブリン製剤については、他疾患における報告が数件あり(43-45)、今後の症例の蓄積が望まれる。なお、尿中への喪失により、CRP は低めとなるため注意する。また、腎摘により敗血症の発症率を減らすことが可能である。

腎移植後は生ワクチンの接種が困難となるため、通常の予防接種はすべて行い、任意ワクチンやニューモバックス®の接種も積極的に検討する。腎移植に備えた抗体獲得のための反復投与は、IgG が尿中に喪失するため高度な蛋白尿や浮腫がなくなってからが望ましい。

5.透析療法

本邦の全国アンケート調査では、CNF 33 例中 26 例に PD が行われており、中央値は 21 か月（4-90）であった。CNF は体格の小さい乳幼児期に透析導入になることが多く、血液透析では連日に近い頻度となってしまう。在宅治療を目指すためには、本邦においては PD を選択することが多い。透析用カテーテルを用いて血液透析を施行する際は、内頚静脈を第一選択とする。腎移植のために尨径静脈を温存し、将来の内シャント作製のために鎖骨下静脈への留置を避けることが望ましい。PD 管理の間に、全身状態の改善、筋肉量の増加、成長のキャッチアップが報告されている（46-48)。

CNF の児はしばしば尨径ヘルニアを合併するため、PD カテーテルを挿入する際には先行的に評価および治療を行うことを検討する。また移植時、移植床は右側になることが多いため PD カテーテルは左側に挿入するのが望ましい。

腎移植

移植する体格の目安として、身長 75-80cm、体重約 8-10kg になった時点で腎移植を考慮する（49)。本邦の全国アンケート調査では、CNF 35 例中 19 例で腎移植が行われており、中央値は 56 か月（34-96）であった。CNF 児への腎移植では、感染症による死亡と血栓症による移植腎喪失が問題となるため、PD 開始後に高度蛋白尿に伴う低蛋白・低ガンマグロブリン血症状態や過凝固状態から脱した状態で腎移植を行うことが望ましい（50, 51)。本邦における単施の検討では、血清アルブミン＞2.5g/dl となってから移植を行ったことにより、移植後血栓症の発生はなかったと報告されている（52)。低蛋白症の是正を計画的に行うことになるため、移植時期が調整できない献腎移植の選択は難しい。

腎移植後は生ワクチン接種が基本的に不可となるため、通常の予防接種はすべて行い、任意ワクチンやニューモバックス®の接種も積極的に検討する。腎移植に備えた抗体獲得のための反復投与は、IgG が尿中に喪失するため、高度な蛋白尿や浮腫が軽減してからが望ましい。

移植後のネフローゼ発症は、CNF における移植腎廃絶の原因の一つである。Fin-major/Fin-major の遺伝子を有する患児では、発症のリスクが高く、5 年生着率は 72%であったと報告されている（53)。ネフローゼに対する治療は、ステロイド、cyclophosphamide、rituximab、血漿交換の有用性が報告されている(53-59)。これら治療報告については主にフィンランドからであり、抗ネフリン抗体の関与が示されている。一方、本邦の症例における抗ネフリン抗体の関与は不明であるため rituximab、血漿交換の有用性が得られない可能性があり注意を要する。

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小児特発性ネフローゼ症候群診療ガイドライン 2020

2020 年 3 月 30 日

刊行にあたって

本ガイドラインは，厚生労働科学研究費補助金（難治性疾患政策研究事業）「小児腎領域の希少・難治性疾患群の診療・研究体制の確立」（研究代表者：石倉健司先生）の事業として，日本小児腎臓病学会の編集により作成されました．

本ガイドラインは，2013 年に日本小児腎臓病学会の事業として公表・出版された「小児特発性ネフローゼ症候群診療ガイドライン 2013」の改訂版となりますが，改訂に際しては，いくつかの改良点や特徴があります．

まず，本ガイドラインは，「Minds 診療ガイドライン作成の手引き 2014」に可能な限り準拠して作成されました．本ガイドラインで取り上げられたクリニカルクエスチョン（CQ）はいずれも厳選されたものであり，システマティックレビューでエビデンスが評価され，推奨グレード（推奨の強さとエビデンス総体の強さ）が示されています．

次に，本ガイドラインでは，作成初期の段階から，成人診療科（腎臓内科）の丸山彰一先生にご参画いただきました．近年の報告により，小児期発症ネフローゼ症候群患者の約 20 ～ 50% は小児期に治癒せず成人期に達することが明らかにされています．そのため，本ガイドラインでは，小児期発症ネフローゼ症候群患者の移行医療に十分に配慮しているのが特徴の一つです．

本ガイドラインは，2013 年のガイドラインで記載された薬物療法や一般療法の改訂に加えて，総論として，疾患概念・病因，定義，腎生検の適応，疫学，予後，そして遺伝学的検査の意義と適応が，さらに付記として，柑橘類摂取がカルシニューリン阻害薬血中濃度に与える影響，コエンザイム Q10 欠乏症に対する治療，ネフローゼ症候群の合併症（脂質異常症，血栓症，高血圧），医療助成制度がまとめられています．いずれの事項も最新の知見が，簡潔・明瞭に記述されており，小児の腎臓専門医のみならず成人の腎臓専門医，さらに一般小児科や成人診療科の先生方の日常診療に大いに役立ち，さまざまな場面で活用されるものと確信しております．

最後に，本ガイドラインの作成にご尽力いただいた作成委員のメンバーや関係者の皆様に心より敬意を表し，また深く感謝申し上げます．

2020 年 4 月

一般社団法人　日本小児腎臓病学会　理事長
服部元史

序文

このたび，「小児特発性ネフローゼ症候群診療ガイドライン 2020」の刊行にあたり一言ご挨拶申し上げます．小児特発性ネフローゼ症候群に対する日本小児腎臓病学会の最初のガイドラインは，2005 年に作成された「小児特発性ネフローゼ症候群薬物治療ガイドライン 1.0 版」です．その 8 年後，「小児特発性ネフローゼ症候群診療ガイドライン 2013」として改訂を行い，書籍刊行をいたしました．今回さらに最新知見とトピックを加え，厚生労働科学研究費補助金（難治性疾患政策研究事業）「小児腎領域の希少・難治性疾患群の診療・研究体制の確立」と日本小児腎臓病学会が協力のうえ，「小児特発性ネフローゼ症候群診療ガイドライン 2020」として刊行いたします．

小児特発性ネフローゼ症候群は，小児腎臓病領域で最も重要な疾患の一つです．本疾患は，わが国を含むアジアで頻度が高いことが近年の疫学研究で明らかになってきました．免疫抑制療法の発達によりかなり寛解率や再発のコントロールが改善してきましたが，いまだに難治例が存在します．そして患者の方々は，高度な浮腫や急性腎障害，高血圧，血栓症，感染症など様々な病態のため，その生活は大きく脅かされます．また寛解状態や再発抑制の多くは薬剤依存性であり，非常に長期間の療養を要します．

本ガイドラインは臨床医に対し，上に述べた小児特発性ネフローゼ症候群の診療上の問題点に関しての最新のエビデンスとそれに基づく推奨を示すことを目的に作成されました．そしてそれぞれの内容に応じて，クリニカルクエスチョン（CQ）形式と記述形式にて記載しました．薬物療法に関しては様々なエビデンスもあり，CQ 形式で問題点に対してダイレクトに答えるようにしています．一方必ずしも CQ 形式になじまないような疫学的な事項や，あるいはまだエビデンスが乏しい一般療法に関しては記述的に説明する形式をとりました．

さらに今回は，遺伝学的検査，移行医療などを積極的に取り上げました．これは単に小児特発性ネフローゼ症候群の診療にとどまらず，近年の小児医療の進歩，変化を反映したものです．予防接種に関する記述も，前回のガイドラインよりさらに詳細な記載としました．また付記でも様々なトピックを取り上げ，免疫抑制療法にとどまらない小児特発性ネフローゼ症候群診療の様々な側面をカバーし，複雑な診療を支援することを心がけました．

最後になりますが，本ガイドラインには多くのわが国発のエビデンスが取り上げられています．これはひとえに，長年，日本小児腎臓病学会が取り組んできたものの輝かしい成果だといえます．このように本学会のこれまでの努力が大きく反映された本ガイドラインが，少しでも小児特発性ネフローゼ症候群診療に貢献できることを祈念しています．

2020 年 4 月

厚生労働科学研究費補助金（難治性疾患政策研究事業）
「小児腎領域の希少・難治性疾患群の診療・研究体制の確立」研究代表者
石倉健司

目次

本書では以下のように表記した．
・副腎皮質ステロイド薬 … ステロイド
・Kidney Disease：Improving Global Outcomes … KDIGO
・International Study of Kidney Disease in Children … ISKDC

小児特発性ネフローゼ症候群診療ガイドライン 2020 委員一覧

編集

一般社団法人 日本小児腎臓病学会

作成

厚生労働科学研究費補助金(難治性疾患政策研究事業)
「小児腎領域の希少・難治性疾患群の診療・研究体制の確立(H29- 難治等(難)- 一般 -039)」
研究代表者 石倉健司
研究分担者 丸山彰一，濱田 陸

[ガイドライン統括委員会(50 音順)]

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患者会(東京「腎炎・ネフローゼ児」を守る会)

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査読委員

【日本小児腎臓病学会学術委員】(50 音順)

神田祥一郎	東京大学医学部小児科
清水正樹	金沢大学小児科

外部評価

【日本腎臓学会】

謝辞
第 1 章 総論「6 遺伝学的検査」の執筆に関して，森貞直哉先生(兵庫県立こども病院臨床遺伝科)に貴重なご助言を賜りましたことに，謹んで感謝申し上げます．

本ガイドライン 2020 の作成について

本ガイドライン 2020 は，日本小児腎臓病学会が厚生労働科学研究費補助金(難治性疾患政策研究事業)「小児腎領域の希少・難治性疾患群の診療・研究体制の確立(H29- 難治等(難)- 一般 -039)」の一事業として，主として日本小児腎臓病学会会員が企画・立案し，日本小児腎臓病学会の編集により作成された．

1 目的

小児特発性ネフローゼ症候群は，小児腎臓病領域で非常に重要な疾患である．わが国では 2013 年に行われた疫学調査により，1 年間に小児 10 万人に 6.5 人が発症し，欧米と比較して約 3 倍の頻度で発症することが明らかとなっている[1]．また 2000 年以降の調査では，実に 20 ～ 50% と高率に疾患活動性を保ったまま成人に移行することも報告されている[2-5]．そのため，小児特発性ネフローゼ症候群患者に対しては，副作用なども考慮しながら適切な長期の薬物療法ならびに一般療法を提供し，その管理の向上にあたることが重要であると考えられる．

それらを目的として，2005 年に「小児特発性ネフローゼ症候群薬物治療ガイドライン．1.0 版」，2013 年に「小児特発性ネフローゼ症候群診療ガイドライン 2013」が作成されている．国際的には KDIGO から「糸球体腎炎のための KDIGO 診療ガイドライン」が 2012 年に発表されており，そのなかで小児特発性ネフローゼ症候群の治療が触れられている．また成人領域では「エビデンスに基づくネフローゼ症候群診療ガイドライン 2014」続いてそのマイナー改訂版である「エビデンスに基づくネフローゼ症候群診療ガイドライン 2017」が作成されている．本ガイドラインは，2013 年以降の新たなエビデンスを含み，移行医療に関して日本腎臓学会とも協同した内容となるべく，「エビデンスに基づくネフローゼ症候群診療ガイドライン 2017」，「腎疾患の移行期医療支援ガイド－ IgA 腎症・微小変化型ネフローゼ症候群－」の作成委員とも連携をとりながら作成した．

本ガイドラインの対象疾患は，小児特発性ネフローゼ症候群のうち特に微小変化型，巣状分節性糸球体硬化症，びまん性メサンギウム増殖の小児期[骨端線閉鎖まで(目安として男児 17 歳頃，女児 15 歳頃)]の治療とした(膜性腎症，膜性増殖性糸球体腎炎や他の腎炎によるネフローゼ症候群は含まない)．ステロイドによる成長障害を考慮しなくてもよい時期に達した患者の治療に関しては適宜，成人領域のネフローゼ症候群診療ガイドラインも参考にしていただきたい．また，使用対象者は，小児腎臓病を専門とする医師に限定せず，広くわが国の小児科医，腎臓内科専門医とする．

2 作成手順

本ガイドラインは，「Minds 診療ガイドライン作成の手引き 2014」[6]に可能な限り準拠して作成した．ガイドライン作成委員として，ガイドライン統括委員会，ガイドライン作成チーム，システマティックレビューチームを編成した．ガイドライン作成チームは，小児腎臓病を専門とする医師を中心に腎臓内科専門医，ヘルスサイエンス情報専門員上級資格者を加えて編成した．さらに，患者とその家族の方々（患者会）にもご参加いただき，ご意見をいただいた．

システマティックレビューにおいては，スコープに従い，日本医学図書館協会の協力のもと検索式を用いて網羅的・系統的に文献検索を行い，エビデンスを評価した．主に用いたデータベースは，PubMed，医中誌 Web，The Cochrane Library で，検索対象期間は原則 2017 年 12 月までである．さらに，必要に応じて索外の追加を行い，適宜必要と考えられる文献を選択した．原則査読のある論文を選択し，言語は英語と日本語とした．

小児特発性ネフローゼ症候群は小児腎疾患のなかでは比較的頻度の高い疾患ではあるが，成人のネフローゼ症候群と比較すると患者数は少ない．また小児を対象とした介入試験も限られている．そのためエビデンスが存在する管理方法は限られたものとなる．よってクリニカルクエスチョン（clinical question：CQ）の作成は，薬物療法のなかでもエビデンスレベルを決定できる項目のみとし，その他の治療法は記述形式とした．CQ 形式で記載した項目では，冒頭にステートメントと推奨グレード［推奨の強さ（**表 1**）とエビデンス総体の強さ（**表 2**）］[6]を示し，解説のなかでその根拠をエビデンスに基づき記載した．推奨の強さとエビデンス総体の強さは，ガイドライン作成委員内で投票を行い 70% 以上の一致を採用条件とした．70% に達しなかった CQ に関しては，再度全員で意見交換を行い 70% の一致を得るまで再投票を行う方針とした．

2019 年 9 月に最終案について，査読委員 2 名（日本小児腎臓病学会学術委員）と外部評価（日本腎臓学会）の評価を受けた．さらに 2019 年 11 月に日本小児腎臓病学会のウェブサイトに公開し，パブリックコメントを募集した．これらについて，必要に応じて追記・修正を行い確定した．

表 1 推奨の強さ

[1]	強く推奨する
[2]	弱く推奨する（提案する）

表 2 エビデンス総体の強さ

A（強）	効果の推定値に強く確信がある
B（中）	効果の推定値に中程度の確信がある
C（弱）	効果の推定値に対する確信は限定的である
D（とても弱い）	効果の推定値がほとんど確信できない

3 主な改訂点について

＊「Minds 診療ガイドライン作成の手引き 2014」に準拠
＊ CQ を薬物療法の一部に限定し，CQ 形式と記述形式の混在する形式とした
＊ 初発時のプレドニゾロン投与方法に関する新たなエビデンスを記載
＊ 難治性ネフローゼ症候群に対するリツキシマブ治療の新たなエビデンスを記載
＊ 小児ネフローゼ症候群における遺伝学的検査の位置づけについて記載
＊ 移行医療に関して章を設けて記載

4 利益相反（COI）について

本ガイドラインの作成資金はすべて，厚生労働科学研究費補助金（難治性疾患政策研究事業）「小児腎領域の希少・難治性疾患群の診療・研究体制の確立（H29- 難治等（難）- 一般 -039）」により支出された．

作成にかかわったメンバーは，日本小児腎臓病学会の定める利益相反（conflict of interest：COI）に関する申告書を作成し，事務局で管理し，適正にマネジメントしている．

日本小児腎臓病学会の定める利益相反に関する開示事項に則り以下に開示する．

石倉健司：①無し，②無し，③無し，④無し，⑤無し，⑥旭化成ファーマ株式会社，ノバルティス ファーマ株式会社，⑦無し，⑧無し，⑨無し
郭　義胤：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
濱田　陸：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
丸山彰一：①無し，②無し，③無し，④協和キリン株式会社，中外製薬株式会社，大日本住友製薬株式会社，株式会社三和化学研究所，⑤無し，⑥ブリストル・マイヤーズ スクイブ株式会社，⑦アステラス製薬株式会社，アレクシオンファーマ合同会社，大塚製薬株式会社，協和キリン株式会社，第一三共株式会社，大日本住友製薬株式会社，武田薬品工業株式会社，鳥居薬品株式会社，ファイザー株式会社，持田製薬株式会社，旭化成ファーマ株式会社，中外製薬株式会社，帝人ファーマ株式会社，MSD 株式会社，田辺三菱製薬株式会社，バクスター株式会社，⑧無し，⑨無し
稲葉　彩：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
貝藤裕史：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
木全貴久：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
近藤秀治：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
佐古まゆみ：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
佐藤　舞：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
杉本圭相：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
田中征治：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
長岡由修：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
野津寛大：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
橋本淳也：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
三浦健一郎：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し

山本雅紀：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し
河合富士美：①無し，②無し，③無し，④無し，⑤無し，⑥無し，⑦無し，⑧無し，⑨無し

① 企業や営利を目的とした団体の役員，顧問職の有無と報酬（年間 100 万円以上）．
② 株式の保有と株式による利益（年間 100 万円以上），あるいは当該全株式の 5% 以上の所有の有無．
③ 企業や営利を目的とした団体からの知的財産権の対価として支払われた報酬（1 件あたり年間 100 万円以上）．
④ 企業や営利を目的とした団体から，会議の出席（発表，助言など）に対し，拘束した時間・労力に対して支払われた日当（講演料等）（一つの企業・団体からの年間 50 万円以上）．
⑤ 企業や営利を目的とした団体から，パンフレット，座談会記事等の執筆に対して支払われた原稿料等（一つの企業・団体から年間 50 万円以上）．
⑥ 企業や営利を目的とした団体から提供された研究費（一つの企業・団体から申告者個人または申告者が所属する部局（講座・分野）あるいは申告者が長となっている部局に割り当てられた総額が年間 100 万円以上）．
⑦ 企業や営利を目的とした団体から提供された奨学（奨励）寄附金（一つの企業・団体から年間 100 万円以上）．
⑧ 企業や営利を目的とした団体が提供する寄附講座に申告者が所属している場合．
⑨ 研究と直接無関係な旅行・贈答品等の提供（一つの企業・団体から年間 5 万円以上）．

またアカデミック COI にも配慮し，全国の小児腎臓病を専門とする医師から委員を選抜するとともに日本腎臓学会の学会員からもメンバーに加わっていただき委員構成を行った．

5 今後の予定

本ガイドラインは，書籍が発行されてから 1 年後を目途に，日本小児腎臓病学会のウェブサイトに公開する予定である．また，厚生労働科学研究費補助金（難治性疾患政策研究事業）「小児腎領域の希少・難治性疾患群の診療・研究体制の確立（H29- 難治等（難）- 一般 -039）」の事業として発刊後の本ガイドラインの臨床現場への浸透状況を評価し，次回改訂に反映させる予定である．

6 改訂予定

本ガイドラインは，わが国における小児特発性ネフローゼ症候群治療に対するガイドラインの 2 回目の改訂である．前回のガイドライン 2013 から今回の改訂までにも重要なエビデンスの追加や移行医療への着目など多くの変化が存在した．本ガイドライン作成中の 2018 年 12 月 31 日現在も進行中の臨床試験が存在することから，今後のエビデンスの追加状況や本ガイドラインの臨床現場への浸透状況などを考慮した 3 ～ 5 年後を目途に，次回の改訂を行う予定である．

7 使い方

エビデンスに基づく医療（evidence-based medicine：EBM）は現代医療に不可欠であるが，「エビデンスに基づいた医療＝ガイドライン」とは限らないことに注意が必要である．そもそも EBM は best research evidence（エビデンス），clinical expertise（臨床的技能），patients' values（患者の価値観）の統合であり，エビデンスのみが重要ということではない[7]．特に近年，informed consent をさらに進めた shared decision making（SDM），すなわち医療提供者と患者やその家族の方々が最善のエビデンスに基づき，患者にとって最善の治療法を選択することの重要性がクローズアップされており[8]，そのツールの一つとしてガイドラインが有用である．

また，ガイドラインの記載内容がすべていわゆるエビデンスレベルの高い臨床試験に基づくわけではなく，診断法や治療法は経験に基づくものも多い．ガイドラインは個々の医療者の経験を否定するものではなく，ガイドラインの記載内容を使用者自身が吟味し，自らの経験を加味し，目の前の患者にとって最善と考えられる選択がなされるべきである．

なお，本ガイドラインは医事紛争や医療訴訟における判断基準を示すものではない．

8 適応外使用について

薬物療法については適応外使用となる記載も含まれている．実際の使用にあたっては薬剤の特性，副作用を十分に理解し，慎重に用いる必要がある．また，適応外使用にあたっては小児腎臓病を専門とする医師との連携のうえで行うことが望ましい．

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1) Kikunaga K, et al. ; Japanese Pediatric Survey Holding Information of NEphrotic syndrome (JP-SHINE) study of the Japanese Study Group of Renal Disease in Children : High incidence of idiopathic nephrotic syndrome in East Asian children : a nationwide survey in Japan (JP-SHINE study). Clin Exp Nephrol 2017 ; 21 : 651-657.
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CQ・推奨一覧

CQ1	小児特発性ネフローゼ症候群の初発時治療において，プレドニゾロンは 8 週間治療（ISKDC 法）と 12 週間以上治療（長期漸減法）のどちらが推奨されるか	推奨グレード	一致率
	小児特発性ネフローゼ症候群の初発時治療は，8 週間治療（ISKDC 法）を選択することを推奨する	1B	100%

CQ2	小児頻回再発型・ステロイド依存性ネフローゼ症候群に対して免疫抑制薬は推奨されるか	推奨グレード	一致率
	小児頻回再発型・ステロイド依存性ネフローゼ症候群では，種々のステロイドの副作用が出現するため，免疫抑制薬の導入を推奨する	1B	94%
1.	シクロスポリンを投与することを推奨する	1B	100%
2.	シクロホスファミドを投与することを推奨する	1B	94%
3.	ミゾリビンを投与することを提案する（適応外使用）	2C	100%
4.	ミコフェノール酸モフェチルを投与することを提案する（適応外使用）	2C	100%
5.	タクロリムスを投与することを提案する（適応外使用）	2C	88%

CQ3	小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対しリツキシマブ治療は推奨されるか	推奨グレード	一致率
	小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対して，リツキシマブを寛解維持のために投与することを提案する	2B	82%

CQ4	小児ステロイド抵抗性ネフローゼ症候群に対して免疫抑制薬は推奨されるか	推奨グレード	一致率
1.	小児ステロイド抵抗性ネフローゼ症候群に対しては，ステロイドにシクロスポリンを併用することを推奨する	1B	100%
2.	ステロイドパルス療法とシクロスポリンの併用は寛解導入に有効な可能性があり，使用することを提案する	2C	94%
3.	タクロリムスは美容的な副作用などによりシクロスポリンを使用できないステロイド抵抗性ネフローゼ症候群に対する寛解導入の選択肢として提案する（適応外使用）	2B	88%
4.	ミコフェノール酸モフェチルは副作用などによりカルシニューリン阻害薬など他の免疫抑制薬を使用できないステロイド抵抗性ネフローゼ症候群に対する寛解導入の選択肢として提案する（適応外使用）	2C	94%
5.	シクロホスファミドの経口投与は小児ステロイド抵抗性ネフローゼ症候群の寛解導入療法として使用しないことを推奨する	1B	100%

CQ・文献検索式

▶主に用いたデータベースは，PubMed，医中誌 Web，The Cochrane Library で，検索対象期間は原則 2017 年 12 月までである．さらに，必要に応じて検索外の追加を行い，適宜必要と考えられる文献を選択した．原則査読のある論文を選択し，言語は英語と日本語とした．

CQ1：小児特発性ネフローゼ症候群の初発時治療において，プレドニゾロンは 8 週間治療（ISKDC 法）と 12 週間以上治療（長期漸減法）のどちらが推奨されるか

✦ **PubMed**（2018 年 5 月 20 日検索）

#1 "Nephrotic Syndrome"[TW]
#2 child*[TW] OR infant*[TW] OR boy*[TW] OR girl*[TW] OR pediatric*[TW] OR paediatric*[TW]
#3 #1 AND #2
#4 "Adrenal Cortex Hormones"[MH] OR "Adrenal Cortex Hormones" [PA]
#5 Prednisolone[TW]
#6 Prednisone[TW]
#7 #4 OR #5 OR #6
#8 #3 AND #7
#9 #8 AND (systematic[SB] OR Meta-Analysis[PT])
検索結果 54 件（システマティックレビュー）
#10 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic [mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))
#11 #8 AND #10
#12 ISKDC[TIAB]
#13 #8 AND #12
#14 #11 OR #13
検索結果 239 件（ランダム化比較試験）

✦ **医中誌 Web**（2018 年 6 月 2 日検索）

#1 （ネフローゼ /TH）and（SH= 薬物療法）
#2 （副腎皮質ホルモン /TH）and（SH= 治療的利用）
#3 #1 and #2
#4 （Prednisone/TH or プレドニゾン /AL）
#5 （Prednisolone/TH or プレドニゾロン /AL）
#6 初期治療 /AL
#7 長期漸減 /AL
#8 （国際法 /TH or 国際法 /AL）
#9 ISKDC/AL
#10 #4 or #5 or #6 or #7 or #8 or #9
#11 #1 and #10
#12 #3 or #11
#13 （#12）and（PT= 会議録除く CK= ヒト）

#14 （#13）and（CK= 新生児，乳児（1 ～ 23 ヶ月），幼児（2 ～ 5），小児（6 ～ 12），青年期（13 ～ 18））
#15 （小児 /TH or 小児 /AL）
#16 #13 and #15
#17 #14 or #16
#18 （#17）and（PT= 原著論文，総説）
#19 （#17）and（RD= メタアナリシス，ランダム化比較試験，準ランダム化比較試験，比較研究，診療ガイドライン）
#20 #18 or #19
#21 （#20）and（DT=1900:2017）
検索結果 260 件

✦ **The Cochrane Library**（2018 年 8 月 22 日検索）

#1 MeSH descriptor: [Nephrotic Syndrome] this term only
#2 MeSH descriptor: [Nephrosis, Lipoid] this term only
#3 nephrotic syndrome
#4 lipoid nephrosis
#5 #1 or #2 or #3 or #4
#6 child* or infant* or boy* or girl* or pediatric* or paediatric* or adolescen*
#7 #5 and #6
#8 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#9 Prednisolone:ti,ab,kw
#10 Prednisone:ti,ab,kw
#11 ISKDC
#12 #8 or #9 or #10 or #11
#13 #7 and #12
#14 pubmed:an
#15 #13 not #14 with Publication year from 1900 to 2017, in Trials
検索結果 96 件（Cochrane Controlled Trials Register：CENTRAL）
#16 #13 not #14 with Cochrane Library publication date from Jan 1900 to Dec 2017, in Cochrane Reviews and Cochrane Protocols
検索結果 12 件（The Cochrane Database of Systematic Review：CDSR）

CQ2：小児頻回再発型・ステロイド依存性ネフローゼ症候群に対して免疫抑制薬は推奨されるか

✦ **PubMed**（2018 年 5 月 19 日検索）

#1 "Nephrotic Syndrome"[TW]
#2 "steroid dependent"[TIAB]
#3 frequent*[TIAB] AND relaps*[TIAB]
#4 SDNS[TIAB] OR FRNS[TIAB]
#5 #2 OR #3 OR #4
#6 #1 AND #5
#7 "Immunosuppressive Agents"[MH] OR "Immunosuppressive Agents" [PA]
#8 cyclosporin*[TW]
#9 tacrolimus[TW]
#10 "Cyclophosphamide"[MH] OR cyclophosphamide[TW]
#11 mizoribine[TW]
#12 "Mycophenolic Acid"[MH] OR mycophenol*[TW]
#13 rituximab[TW]
#14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #6 AND #14

#16　child*[TW] OR infant*[TW] OR boy*[TW] OR girl*[TW] OR pediatric*[TW] OR paediatric*[TW] OR adolescen*[TW]
#17　#15 AND #16
#18　#17 AND (systematic[SB] OR Meta-Analysis[PT])) AND 0001[PDAT] : 2017[PDAT]
検索結果 17 件（システマティックレビュー）
#19　(("Epidemiologic Studies"[MH]) OR "Clinical Trials as Topic"[MH]) OR "Clinical Trial"[Publication Type]
#20　#17 AND #19
#21　#20 AND 0001[PDAT] : 2017[PDAT]
検索結果 262 件

✦ **医中誌 Web**（2018 年 6 月 2 日検索）
#1　免疫抑制療法 /TH or 免疫抑制剤 /TH
#2　ステロイド依存 /AL
#3　頻回 /AL and（再発 /TH or 再発 /AL）
#4　#2 or #3
#5　（ネフローゼ症候群 /TH）and（SH= 治療 , 薬物療法）
#6　#4 and #5
#7　（Ciclosporin/TH or シクロスポリン /AL）
#8　（Tacrolimus/TH or タクロリムス /AL）
#9　("Mycophenolate Mofetil"/TH or ミコフェノール酸モフェチル /AL）
#10　（Cyclophosphamide/TH or シクロフォスファミド /AL）
#11　（Mizoribine/TH or ミゾリビン /AL）
#12　（Rituximab/TH or リツキシマブ /AL）
#13　#1 or #7 or #8 or #9 or #10 or #11 or #12
#14　#5 and #13
#15　#6 or #14
#16　（#15）and（PT= 会議録除く CK= ヒト）
#17　（#16）and（CK= 新生児 , 乳児（1 ～ 23 ヶ月）, 幼児（2 ～ 5）, 小児（6 ～ 12）, 青年期（13 ～ 18））
#18　（小児 /TH or 小児 /AL）
#19　#16 and #18
#20　#17 or #19
#21　（#20）and（PT= 原著論文 , 総説）
#22　（#20）and（RD= メタアナリシス , ランダム化比較試験 , 準ランダム化比較試験 , 比較研究 , 診療ガイドライン）
#23　#21 or #22
#24　（#23）and（DT=1900:2017）
検索結果 286 件

✦ **The Cochrane Library**（2018 年 8 月 22 日検索）
#1　MeSH descriptor: [Nephrotic Syndrome] this term only
#2　MeSH descriptor: [Nephrosis, Lipoid] this term only
#3　nephrotic syndrome
#4　lipoid nephrosis
#5　#1 or #2 or #3 or #4
#6　child* or infant* or boy* or girl* or pediatric* or paediatric* or adolescen*
#7　#5 and #6
#8　steroid dependent
#9　frequent*
#10　relaps*
#11　SDNS

#12　FRNS
#13　#8 or #9 or #10 or #11 or #12
#14　MeSH descriptor: [Immunosuppressive Agents] explode all trees
#15　cyclosporin*
#16　tacrolimus
#17　MeSH descriptor: [Cyclophosphamide] explode all trees
#18　cyclophosphamide
#19　mizoribine
#20　#14 or #15 or #16 or #17 or #18 or #19
#21　#7 and #13 and #20
#22　pubmed:an
#23　#21 not #22
#24　#21 not #22 with Cochrane Library publication date between Jan 1900 and Dec 2017, in Cochrane Reviews, Cochrane Protocols
検索結果 16 件（The Cochrane Database of Systematic Review：CDSR）
#25　#21 not #22 with Publication year from 1900 to 2017, in Trials
検索結果 38 件（The Cochrane Controlled Trials Register：CCTR）

CQ3：小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対しリツキシマブ治療は推奨されるか

✦ **PubMed**（2018 年 5 月 20 日検索）
#1　"Nephrotic Syndrome"[TW]
#2　dependent[TIAB]
#3　frequent*[TIAB] AND relaps*[TIAB]
#4　SSNS[TIAB] OR FRNS[TIAB] OR SDNS[TIAB]
#5　refractory[TIAB]
#6　sensitive[TIAB]
#7　#2 OR #3 OR #4 OR #5 OR #6
#8　#1 AND #7
#9　"Rituximab*[TW] OR rituxan[TIAB]
#10　#8 AND #9
#11　#10 AND（child*[TW] OR infant*[TW] OR boy*[TW] OR girl*[TW] OR pediatric*[TW] OR paediatric*[TW] OR adolescen*[TW]）
#12　#11 AND 0001[PDAT] : 2017[PDAT]
検索結果 121 件

✦ **医中誌 Web**（2018 年 6 月 2 日検索）
#1　（ネフローゼ症候群 /TH or ネフローゼ症候群 /AL）
#2　（Rituximab/TH or リツキシマブ /AL）
#3　リツキサン /AL
#4　rituxan/AL
#5　#2 or #3 or #4
#6　#1 and #5
#7　（#6）and（PT= 会議録除く CK= ヒト）
#8　（#7）and（CK= 新生児 , 乳児（1 ～ 23 ヶ月）, 幼児（2 ～ 5）, 小児（6 ～ 12）, 青年期（13 ～ 18））
#9　（小児 /TH or 小児 /AL）
#10　#7 and #9
#11　#8 or #10

#12　（#11）and（DT=1900:2017）
検索結果 111 件

✦ **The Cochrane Library**（2018 年 8 月 22 日検索）
#1　MeSH descriptor: [Nephrotic Syndrome] this term only
#2　MeSH descriptor: [Nephrosis, Lipoid] this term only
#3　nephrotic syndrome
#4　lipoid nephrosis
#5　#1 or #2 or #3 or #4
#6　child* or infant* or boy* or girl* or pediatric* or paediatric* or adolescen*
#7　#5 and #6
#8　dependent
#9　frequent*
#10　relaps*
#11　SDNS
#12　FRNS
#13　SSNS
#14　refractory
#15　sensitive
#16　#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17　Rituximab
#18　MeSH descriptor: [Rituximab] explode all trees
#19　#17 or #18
#20　#7 and #16 and #19
#21　#7 and #16 and #19 with Cochrane Library publication date between Jan 1900 and Dec 2017, in Cochrane Reviews, Cochrane Protocols
検索結果 5 件（The Cochrane Database of Systematic Review：CDSR）
#22　#7 and #16 and #19 with Publication year from 1900 to 2017, in Trials
検索結果 24 件（The Cochrane Controlled Trials Register：CCTR）

CQ4：小児ステロイド抵抗性ネフローゼ症候群に対して免疫抑制薬は推奨されるか

✦ **PubMed**（2018 年 5 月 20 日検索）
#1　"Nephrotic Syndrome"[TW]
#2　resistant[TIAB]
#3　SRNS[TIAB]
#4　refract*[TIAB]
#5　#2 OR #3 OR #4
#6　#1 AND #5
#8　"Glomerulosclerosis, Focal Segmental"[MH]
#9　FGS[TIAB]
#10　FSGS[TIAB]
#11　"segmental glomerulosclerosis"[TW]
#12　"glomerular diseases"[TIAB]
#13　"glomerular disease"[TIAB]
#16　#8 OR #9 OR #10 OR #11 OR #12 OR #13
#17　#6 OR #16
#18　"Immunosuppressive Agents"[MH] OR "Immunosuppressive Agents"[PA]
#19　cyclosporin*[TW]

#20　tacrolimus[TW]
#21　"Cyclophosphamide"[MH] OR cyclophosphamide[TW]
#22　"Mycophenolic Acid"[MH] OR mycophenol*[TW]
#23　#18 OR #19 OR #20 OR #21 OR #22
#24　#17 AND #23
#25　child*[TW] OR infant*[TW] OR boy*[TW] OR girl*[TW] OR pediatric*[TW] OR paediatric*[TW] OR adolescen*[TW]
#26　#24 AND #25
#27　#26 AND（systematic[SB] OR Meta-Analysis[PT]）
#28　#27 AND 0001[PDAT] : 2017[PDAT]
検索結果 28 件（システマティックレビュー）
#31　"Epidemiologic Studies"[MH] OR "Clinical Trials as Topic"[MH] OR "Clinical Trial"[Publication Type]
#33　#26 AND #31
#34　#8 OR #9 OR #10 OR #11
#35　#34 AND #23 AND #25
#36　#31 AND #35
#37　#36 AND 0001[PDAT] : 2017[PDAT]
検索結果 236 件

✦ **医中誌 Web**（2018 年 6 月 2 日検索）
#1　（ネフローゼ症候群 /TH or ネフローゼ症候群 /AL）
#2　（糸球体硬化症 - 巣状分節性 /TH or 巣状分節性糸球体硬化症 /AL）
#3　抵抗性 /AL
#4　SNS/AL
#5　#3 or #4
#6　#1 and #5
#7　#2 or #6
#8　ネフローゼ症候群 - ステロイド抵抗性特発性 /TH
#9　#7 or #8
#10　（ネフローゼ症候群 /TH）and（SH= 薬物療法）
#11　#9 and #10
#12　免疫抑制療法 /TH or 免疫抑制剤 /TH
#13　#9 and #12
#14　（(※Methylprednisolone/TH and ※" パルス療法（薬物療法）"/TH）or ステロイドパルス療法 /AL）
#15　（Ciclosporin/TH or シクロスポリン /AL）
#16　（Cyclophosphamide/TH or シクロフォスファミド /AL）
#17　（Tacrolimus/TH or タクロリムス /AL）
#18　("Angiotensin-Converting Enzyme Inhibitors"/TH or アンギオテンシン変換酵素阻害薬 /AL）
#19　("Angiotensin Receptor Antagonists"/TH or アンジオテンシン受容体拮抗薬 /AL）
#20　（Rituximab/TH or リツキシマブ /AL）
#21　("Mycophenolate Mofetil"/TH or ミコフェノール酸モフェチル /AL）
#22　（血漿交換 /TH or 血漿交換 /AL）
#23　（血液成分除去法 /TH or 血液成分除去法 /AL）
#24　アフェレシス /AL
#25　("LDL Lipoproteins"/TH or LDL/AL）
#26　#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
#27　#11 and #26
#28　#11 or #13 or #27
#29　（#28）and（PT= 会議録除く CK= ヒト）

#30 （#29）and（CK= 新生児 , 乳児（1 ～ 23 ヶ月）, 幼児（2 ～ 5）, 小児（6 ～ 12）, 青年期（13 ～ 18））
#31 （小児 /TH or 小児 /AL）
#32 #29 and #31
#33 #30 or #32
#34 （#33）and（PT= 原著論文 , 総説）
#35 （#33）and（RD= メタアナリシス , ランダム化比較試験 , 準ランダム化比較試験 , 比較研究 , 診療ガイドライン）
#36 #34 or #35
#37 （#36）and（DT=1900:2017）
検索結果 185 件

✦ **The Cochrane Library**（2018 年 8 月 22 日検索）

#1 MeSH descriptor: [Nephrotic Syndrome] explode all trees
#2 Nephrotic Syndrome
#3 MeSH descriptor: [Nephrosis, Lipoid] this term only
#4 lipoid nephrosis
#5 #1 or #2 or #3 or #4
#6 resistant
#7 SRNS
#8 refract*
#9 #6 or #7 or #8
#10 #5 and #9
#11 MeSH descriptor: [Glomerulosclerosis, Focal Segmental] explode all trees
#12 FGS
#13 FSGS
#14 segmental glomerulosclerosis
#15 glomerular diseases
#16 glomerular disease
#17 #11 or #12 or #13 or #14 or #15 or #16
#18 #10 or #17
#19 MeSH descriptor: [Immunosuppressive Agents] explode all trees
#20 cyclosporin*
#21 tacrolimus
#22 MeSH descriptor: [Cyclophosphamide] explode all trees
#23 Cyclophosphamide
#24 MeSH descriptor: [Mycophenolic Acid] explode all trees
#25 mycophenol*
#26 #19 or #20 or #21 or #22 or #23 or #24 or #25
#27 #18 and #26
#28 pubmed:an
#29 #27 not #28
#30 #27 not #28 with Cochrane Library publication date between Jan 1900 and Dec 2017, in Cochrane Reviews, Cochrane Protocols
検索結果 14 件（The Cochrane Database of Systematic Review：CDSR）
#31 #27 not #28 with Publication year from 1900 to 2017, in Trials
検索結果 82 件（The Cochrane Controlled Trials Register：CCTR）

Chapter I: General

1. Disease Concept and Etiology

[Summary]

- Nephrotic syndrome refers generically to a set of pathologic conditions characterized by severe proteinuria, hypoalbuminemia, and generalized edema due to glomerular capillary disorder.
- Approximately 90% of cases of pediatric nephrotic syndrome are classified as idiopathic nephrotic syndrome (primary nephrotic syndrome).

Nephrotic syndrome refers generically to a set of pathologic conditions characterized by severe proteinuria and hypoalbuminemia due to glomerular capillary disorder, resulting in generalized edema. While it was reported to occur at a rate of 2 in 100,000 children per year in Western countries [1], its incidence in Japan was about 3 times higher at an incidence of 6.5 in 100,000 children per year, according to an epidemiological survey in 2013 [2] (refer to p. 23, "4. Epidemiology").

In addition, as the primary disease, idiopathic nephrotic syndrome of an unknown cause (primary nephrotic syndrome) accounts for approximately 90% of children with nephrotic syndrome (approximately 60% of adults at age ≥20 years) (Figure 1) [a], and approximately 80% of these cases are of the minimal-change-disease [b,c] (refer to p. 18 "3. Kidney biopsy"). The diseases covered by this 2020 guideline will be pediatric idiopathic nephrotic syndrome of the minimal-change-disease, focal segmental glomerulosclerosis, and diffuse mesangial proliferation, and hereditary focal segmental glomerulosclerosis, which has recently been reported with increasing detection, will be described as an important disease to differentiate from the other types.

Although the etiology of glomerular capillary disorder in pediatric idiopathic nephrotic syndrome is considered to involve I) T cell functional impairment, II) humoral factors (circulating factors), and III) genetic abnormalities (in podocyte constituents, mainly slit membrane), no definite factor has been identified.

I) The discussion about T cell functional impairment dates back to 1974 when Shalhoub proposed the "theory of lymphocyte functional impairment" [3]. This theory was proposed on the basis of suggestions from some events, including the following: 1) Steroids and calcineurin inhibitors are effective in patients with the minimal-change-disease. 2) The minimal-change-disease can remit with the contraction of measles and malaria, which reduce cellular immunity. 3) Complication of the minimal-change-disease as a tumor-associated symptom in patients with malignant lymphoma or other diseases that can cause T cell functional impairment.

II) Involvement of humoral factors has been assumed from the results of studies in steroid-resistant nephrotic syndrome. 1. Nephrotic syndrome develops in mice receiving a serum from a patient with steroid-resistant nephrotic syndrome [4]. 2. Some patients with a relapse of nephrotic syndrome following kidney transplantation respond to plasma exchange [5], and when the graft is immediately excised from a patient with a relapse of nephrotic syndrome in the transplanted kidney and re-transplanted to another patient, the nephrotic syndrome remits [6]. Although humoral factor candidates have been reported, including hemopexin, vascular permeability factor (VPF), vascular endothelial growth factor (VEGF), active oxygen, soluble urokinase receptor (suPAR), interleukin-13 and -8, tumor necrosis factor alpha (TNFα), and cardiotrophin-like cytokine factor 1 (CLC-1) [7-18], no reproducible results have so far been obtained and the essential natures of humoral factors and immunological abnormalities that can express them remain unclear.

III) As for genetic abnormalities, Tryggvason et al. discovered the causal gene for Congenital nephrotic syndrome - Finnish type in 1998 [19] (*NPHS1* gene abnormality), driving research on genes associated with podocyte constituent proteins. Thereafter, analyses of genes for familial steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis have identified more than 50 genetic abnormalities in slit membrane components, podocyte actin backbone constituents, glomerular basement membrane and podocyte - glomerular basement membrane junction components, and components involved in the negative charge of the podocyte membrane (refer to p. 30 "6 Genetic testing"). These findings have shown that podocyte disorders are important to the

mechanism of protein leakage in nephrotic syndrome; however, single-gene abnormalities account for only a small percentage of cases of idiopathic nephrotic syndrome (approximately 30% in steroid-resistant nephrotic syndrome) and rare in steroid-sensitive idiopathic nephrotic syndrome. Based on the involvement of immune abnormalities in the etiology and the racial differences in the incidence of the disease, the HLA gene has so far been suggested to be involved in disease susceptibility in steroid-sensitive nephrotic syndrome [20,21]. A recent large-scale genome-wide association analysis (GWAS) suggested an association with *HLA-DQA1* and *PLCG2* [22] in South Asians and European and American Caucasians, and with *HLA-DR/DQ* in Japanese [23].

Chapter I: General

2. Definitions

[Summary]

The diagnostic criteria for pediatric idiopathic nephrotic syndrome will be based on the definition by the International Study of Kidney Disease in Children (ISKDC) [1].

I) Persistent severe proteinuria (nocturnal urine collection ≥40 mg/hr/m^2 or early morning urine protein-creatinine ratio ≥2.0 g/gCr)
and
II) Hypoalbuminemia (serum albumin ≤2.5 g/dL)

The condition that concurrently meets the above requirements I) and II) in the absence of definite causal disease is defined as pediatric idiopathic nephrotic syndrome (primary nephrotic syndrome).

The definition of pediatric idiopathic nephrotic syndrome is shown above. The definitions for the other terms are shown in Table 1 below. For reference, the diagnostic criteria for adults is shown in Table 2 [a].

Table 1 Definitions of terms concerning pediatric idiopathic nephrotic syndrome

Nephrotic syndrome	Persistent severe proteinuria (C40 mg/h/m2 in pooled night urine or early morning urine protein creatinine ratio ≥2.0 g/gCr) and hypoalbuminemia (serum albumin ≤2.5 g/dL)
Primary nephrotic syndrome	Nephrotic syndrome with primary glomerulonephritis
Idiopathic nephrotic syndrome	Primary nephrotic syndrome of unknown cause
Secondary nephrotic syndrome	Including nephrotic syndrome from an evident causal disease and nephrotic syndrome due to genetic abnormalities.
Complete remission	Negative protein on dipstick testing of early morning urine for 3 consecutive days, or early morning urine protein creatinine ratio < 0.2 g/gCr for 3 consecutive days
Incomplete remission	≥1+ protein on dipstick testing of early morning urine or early morning urine protein creatinine ratio ≥0.2 g/gCr, and serum albumin >2.5 g/dL
Relapse	≥3+ protein on dipstick testing of early morning urine (urine protein-creatinine ratio ≥2.0 g/gCr)for 3 consecutive days
Steroid-sensitive nephrotic syndrome	Disease with complete remission within 4 weeks following the start of daily prednisolone therapy
Frequently-relapsing nephrotic syndrome	Two or more relapses within 6 months after initial remission, or 4 or more relapses within any 12 consecutive months
Steroid-dependent nephrotic syndrome	Two consecutive relapses during prednisolone tapering or within 14 days after discontinuation of prednisolone
Steroid-resistant nephrotic syndrome	Absence of complete remission after at least 4 weeks of daily prednisolone therapy
Refractory nephrotic syndrome*1	Steroid sensitive nephrotic syndrome with continuing frequent relapses or steroid-dependent despite of standard immunosuppressant therapy*2, and, thus requiring continuation of steroid therapy (refractory frequently-relapsing and steroid-dependent nephrotic syndrome); or steroid resistant nephrotic syndrome without complete remission despite of standard immunosuppressant therapy*2(refractory steroid-resistant nephrotic syndrome)

*1The Ministry of Health and Welfare Study Group for the Designated Disease Nephrotic Syndrome defines "refractory nephrotic syndrome" in adults as "cases in which complete remission or incomplete remission cannot be achieved with various treatments during a 6-month treatment period." In this 2020 guideline, which targets children, treatment-resistant frequently-relapsing and steroid-dependent nephrotic syndrome and steroid-resistant nephrotic syndrome are defined together as "refractory nephrotic syndrome."

*2While the definition may be changed according to the approval status of immunosuppressive agent indications in the future, "frequently-relapsing and steroid-dependent" and "steroid-resistant" are defined as "refractory" in cases where the condition is difficult to control with the use of cyclosporine and cyclophosphamide, and where remission cannot be induced even with a combination therapy with cyclosporine and steroid pulse therapy, respectively, as of November 2019.

Table 2 Diagnostic criteria for adult nephrotic syndrome

1. Proteinuria: A level of ≥3.5 g/day persists.
(the same applies in cases of spot urine check showing a urinary protein/creatinine ratio of ≥3.5 g/gCr)
2. Hypoalbuminemia: Serum albumin level ≤3.0 g/dL. A total serum protein content of ≤6.0 g/dL also serves for reference.
3. Edema

4. Dyslipidemia (hyper-LDL-cholesterolemia)

Notes: 1) Of note, both the above-described findings of urine protein content and hypoalbuminemia (hypoproteinemia) are an essential requirements for the diagnosis of this syndrome.
2) Edema is not an essential condition for this syndrome but is an important finding.
3) Dyslipidemia is not an essential condition for this syndrome.
4) Oval fat bodies serve for reference in the diagnosis of this syndrome.

(Source: 1. Disease concept, definition, constituting illness, and pathophysiology. Evidence-based Clinical Practice Guideline for Nephrotic Syndrome 2017, edited by the Study Group on refractory Kidney Diseases in the MHLW Grant-in-Aid for Scientific Research Project for Research on Policies for Refractory Diseases (Refractory Disease Policy Research Project), Tokyo, Tokyo Igakusha. co.jp., 2017: 1-5.)

India and Japan in 2015 [6,7], and the description in the 2015 Cochrane review was substantially modified [8].
Including these three new randomized controlled studies, a meta-analysis of high quality was conducted, demonstrating that there was no difference in the risk of frequent relapses between the ISKDC regimen and the long-term tapering regimen. The long-term tapering regimen is considered to have been over-evaluated in the study with a high risk of biasing; it was concluded that there was no benefit from an extension of the duration of prednisolone treatment to 3 months or longer in the treatment at the time of first episode [8]. Accordingly, this 2020 guideline will recommend that 8-week treatment (ISKDC regimen) be chosen in the treatment of pediatric idiopathic nephrotic syndrome at the time of first episode. Strictly speaking, the 8-12 week treatment is recommended since the analysis in the Cochrane review compared 8-12 weeks and 12 weeks or longer; however, we recommend the 8-week treatment as in the randomized controlled study conducted in Japan [7]. It is necessary to continue to compile evidence, and we would like to monitor the results from similar randomized controlled studies (e.g., PREDNOS Study [8]) and the trends in guidelines available outside Japan.

♦2. Treatments of relapses

For steroid treatment at the time of relapse, no new evidence has been compiled. We propose the modified ISKDC regimen or the long-term tapering regimen in this 2020 guideline, as in the previous Guideline 2013.

Examples of treatment
At the time of relapse Modified ISKDC regimen Example of prednisolone therapy
I) 60 mg/m^2/day or 2 mg/kg/day (up to 60 mg/day) in 1-3 divided doses, consecutive days, at least until 3 days after confirmation of the disappearance of urine protein, but not exceeding 4 weeks.
II) 60 mg/m^2/day or 2 mg/kg/day (up to 60 mg/day), single dose, morning, alternate days, 2 weeks
III) 30 mg/m^2/day or 1 mg/kg/day (up to 30 mg/day), single dose, morning, alternate days, 2 weeks
IV) 15 mg/m^2/day or 0.5 mg/kg/day (up to 15 mg/day), single dose, morning, alternate days, 2 weeks

*The tapering methods of II) to IV) are largely dependent on the attending physician's discretion, and the long-term tapering regimen may be chosen as appropriate. Body surface areas and body weights will be calculated using height-based standard body weights (refer to Tables 1-A and 1-B on pages 42-45, "1. General description of treatments").

The KDIGO Guideline proposes the ISKDC regimen (prednisolone administered at 60 mg/m^2/day for consecutive days and +40 mg/m^2/day for alternate-day administration for 4 weeks until 3 days after negative urine protein testing) for the non-frequently-relapsing type, and the long-term tapering regimen for the frequently-relapsing and steroid-dependent type [a]. In Japan, there is no discretion according to therapeutic responsiveness, and the modified ISKDC regimen with the duration of alternate-day administration extended to 6 weeks as described above and the long-term tapering regimen involving longer duration of long-term alternate-day administration are common. We have decided to propose the same in this 2020 guideline.
In the Cochrane review, a report from Sri Lanka (meeting minutes) was reviewed, concluding that long-term dose tapering on alternate days for 7 months was more effective than the 2-month ISKDC regimen [8]. This is the only available randomized controlled study; a further randomized controlled study is desired to determine the rationale for the long-term tapering regimen during relapses.

♦3. Others

For steroid dose tapering, daily dose reduction is recommended in the "Evidence-based Clinical Practice Guideline for Nephrotic Syndrome 2017" [b]; however, in children, dose reductions should be performed by alternate-day administration to prevent growth disorders caused by steroids. While

no report is available for nephrotic syndrome patients, two studies have reported that growth disorders in patients undergoing kidney transplantation were ameliorated by switching the steroid regimen from daily administration to alternate-day administration [9,10]. In patients with confirmed epiphyseal closure (at 17 years of age for boys, 15 years for girls), there is no longer concern about growth disorder; therefore, daily tapering may be considered with the disease control status or patient transfer to a medical institution for adults in mind.
For daily administration of steroid, the Japanese Guideline states that the daily dose should be in three divided doses [c], whereas in the KDIGO Guideline, the daily dose should be administered in one portion [a]. It has been reported that there was no difference in efficacy of treatment at the time of relapse between single dose and 3 divided doses, and that the incidence of steroid side effects was lower with single dose [11]. On the other hand, no controlled study has compared treatments at first episode. Based on the above facts, this 2020 guideline describes daily dosing as one to three divided doses. To minimize the incidence of steroid side effects after alternate-day dose reduction, it is desirable that the daily dose be given in a single dose as conventional.
It is disputable whether steroid doses should be based on body surface area (mg/m^2) or body weight (mg/kg). With regard to the influence of this difference on treatment and prognosis, one study reported that a better relapse suppression effect was obtained when the dose is determined on the basis of body surface area to increase exposure [12], and a randomized controlled study reported that there was no difference in relapse rate [13]. As of December 2018, no clinical study was available with a high accuracy that permits a determination of superiority/inferiority; therefore, this 2020 guideline mentions both cases.
Since considerable intestinal edema poses a concern about poor absorption of oral steroid, the "Evidence-based Clinical Practice Guideline for Nephrotic Syndrome 2017" states that intravenous administration may be considered [b]. However, since no studies have compared oral medications and intravenous drugs, efficacy differences are unclear. If oral medication is difficult due to vomiting and abdominal pain associated with intestinal edema in children, we consider that intravenous steroid may be used temporarily at the same dose.
The 2015 Cochrane review newly included a description of daily administration of low-dose steroid to prevent relapses with common cold in patients with frequently-relapsing nephrotic syndrome at a high risk of relapse [8]. More than one randomized controlled study has been reported, including studies of remission maintenance by alternate-day administration of prednisolone at 0.1-0.75 mg/kg to maintain remission in frequently-relapsing and steroid-dependent nephrotic syndrome [14-16], and one study in patients with a history of the frequently-relapsing type who had been withdrawn from prednisolone for 3 months [17]. The relapse risk was reported to have been decreased significantly by switching the regimen to daily administration of low-dose prednisolone for 5-7 consecutive days. We consider that these results deserve noting in clinical practice for pediatric idiopathic nephrotic syndrome in Japan in the future.
Finally, an investigation by the Japanese Study Group of Kidney Disease in Children (JSKDC) suggested that in the treatment of first episode of pediatric idiopathic nephrotic syndrome, a length of time of 9 days or more taken from treatment initiation to remission and first relapse within 6 months were risk factors for frequently-relapsing nephrotic syndrome [18]. To demonstrate the accuracy of this result, another demonstrative cohort is required, and this is an issue to be investigated in the future.

Chapter II: Treatments

2. Specifics

B. Treatment of frequently-relapsing and steroid-dependent nephrotic syndrome

CQ 2
Are immunosuppressive agents recommended for children with frequently-relapsing and steroid-dependent nephrotic syndrome?

Recommendation statements:
- Since various side effects develop with the use of steroid in children with frequently-relapsing and steroid-dependent nephrotic syndrome, use of an immunosuppressive agent is recommended. Recommended grade 1B (agreement ratio 94%)

1. Administration of cyclosporine is recommended. Recommendation grade 1B (agreement ratio 100%)
2. Administration of cyclophosphamide is recommended. Recommendation grade 1B (agreement ratio 94%)
3. We propose administration of mizoribine (off-label use). Recommendation grade 2C (agreement ratio 100%)
4. We propose administration of mycophenolate mofetil (off-label use). Recommendation grade 2C (agreement ratio 100%)
5. We propose administration of tacrolimus (off-label use). Recommendation grade 2C (agreement ratio 88%)

Treatment examples
1. Example of cyclosporine treatment
Reference: Started at 2.5-5 mg/kg/day in two divided doses. Doses will be adjusted to reach the following blood concentrations:
For management by trough level*1: 80-100 ng/mL for 6 months and then 60-80 ng/mL.
For management by C2 value*2: 600-700 ng/mL for 6 months and then 450-550 ng/mL.
For long-term administration, a kidney biopsy should be performed, even in the absence of renal dysfunction, to examine for chronic nephrotoxicity (refer to p. 18 "3. Kidney biopsy").

2. Example of cyclophosphamide treatment
Reference: Administered at 2-2.5 mg/kg/day (up to 100 mg) in a single portion for 8-12 weeks.
The cumulative dose should not exceed 300 mg/kg, and doses should be administered in one course only.

3. Example of mizoribine treatment (off-label use)
Reference: Administered at 7-10 mg/kg/day in a single portion (high dose). Doses will be adjusted to reach the following blood concentrations: Peak blood concentration (C2 value*2 or C3 value*3): ≥3.0 μg/mL.

4. Example of mycophenolate mofetil treatment (off-label use)
Reference: Administered when the standard immunosuppressive agent cannot be used due to side effects.
1,000-1,200 mg/m^2/day (or 24-36 mg/kg/day, up to 2 g/day) in two divided doses.

5. Example of tacrolimus treatment (off-label use)
Reference: Administered when the standard immunosuppressive agent cannot be used due to side effects.

Started at 0.1 mg/kg/day in two divided doses. Doses will be adjusted to reach the following blood concentrations: Trough range*1: 5-7 ng/mL for 6 months and then 3-5 ng/mL.

Note 1: Body weights will be calculated using height-based standard body weights (refer to Tables 1-A and 1-B on pages 42-45, "1. General description of treatments") (the same applies for body surface areas).
Note 2: It is desirable that the above-described treatment be performed in collaboration with a pediatric nephrologist. In particular, drugs to be used off-label are desirably administered by a pediatric nephrologist.
*1Predose blood concentration
*2Blood concentration at 2 hours post dose
*3Blood concentration at 3 hours post dose

Evidence summary
The efficacy of cyclophosphamide for children with frequently-relapsing nephrotic syndrome has been reported in some randomized controlled studies; however, other studies reported that the effect was limited. Cyclosporine was shown to be as effective as cyclophosphamide in the only available randomized controlled study in children with frequently-relapsing and steroid-dependent nephrotic syndrome with cyclophosphamide as the comparator. Although mizoribine was not shown to be effective for children with frequently-relapsing and steroid-dependent nephrotic syndrome in a randomized controlled study to compare usual doses with placebo, a retrospective study suggested its efficacy at high doses. Mycophenolate mofetil was shown to produce side effects within the acceptable range, although its relapse-suppressing effect was slightly lower than that of cyclosporine, in a randomized controlled study in children with frequently-relapsing and steroid-dependent nephrotic syndrome with cyclosporine as the comparator. Tacrolimus was studied in a non-randomized controlled study and retrospective study in children with frequently-relapsing and steroid-dependent nephrotic syndrome with mycophenolate mofetil as the comparator, and was shown to be as effective as mycophenolate mofetil in the suppression of relapses.

Commentary
♦1. General

In children with frequently-relapsing and steroid-dependent nephrotic syndrome, a broad range of steroid side effects develop, such as growth disorder, obesity, diabetes mellitus, cataract, glaucoma, hypertension, osteoporosis, and femoral head necrosis; therefore, we recommend that immunosuppressive agents be used. The Cochrane review shows that cyclophosphamide, chlorambucil, cyclosporine, and levamisole are significantly effective, and that mycophenolate mofetil may be effective but there is a limited range of data comparing the aforementioned four drugs [1]. The KDIGO guideline [2] recommends six drugs consisting of the above five and tacrolimus. According to a nation-wide survey in an MHLW Grant-in-Aid for Scientific Research project, cyclosporine, mizoribine, and cyclophosphamide are the most commonly used immunosuppressive agents used as first-line drugs for pediatric frequently-relapsing and steroid-dependent nephrotic syndrome in Japan, listed in this descending order, and facilities with cyclosporine as the first-line drug accounted for more than 50% [3]. Of these three drugs, cyclosporine and cyclophosphamide have strong evidence for efficacy. The Cochrane review reported that cyclosporine and cyclophosphamide were equally effective [1]. Mizoribine has been suggested to be effective at a high dose (off-label use), although evidence is lacking. In addition, this also constitutes off-label use in Japan,mycophenolate mofetil and tacrolimus may be mentioned as therapeutic options for cases difficult to treat with standard immunosuppressive agents.
In the presence of nephrotic syndrome relapse, oliguria and hypertension can develop, and the risks of cyclosporine-induced acute nephrotoxicity, posterior reversible encephalopathy syndrome (PRES), cyclophosphamide-induced hemorrhagic cystitis, and other events are considered to increase; therefore, it is safe to newly start any immunosuppressive agent after remission by steroid therapy. Since administration of immunosuppressive agents for children with frequently-relapsing and

steroid-dependent nephrotic syndrome is usually performed in combination with a steroid, the statement in this section has been prepared on the assumption of combination with a steroid. While cyclophosphamide is the only drug that has been reported to be effective in a randomized controlled study comparing a treatment group and a non-treatment group, we have investigated the efficacy and recommendation grades by mutual comparisons of individual drugs. Bearing in mind the above-described frequency of use and recommended grades, cyclosporine, cyclophosphamide, mizoribine, mycophenolate mofetil, and tacrolimus are described in this order. In actual settings, drugs should be chosen in view of their effects, side effects, and the patient's condition. In recent years, evidence for rituximab has been increasing in volume remarkably.
For details, refer to "CQ3" on page 59 "2 Specifics" "C. Treatment of refractory frequently-relapsing and steroid-dependent nephrotic syndrome".

♦2. Specifics

1. Cyclosporine
Cyclosporine is highly effective against pediatric frequently-relapsing and steroid-dependent nephrotic syndrome, allowing steroids to be tapered and discontinued in most patients [4-10]. In a randomized controlled study in children with frequently-relapsing and steroid-dependent nephrotic syndrome, the remission maintenance rate at 9 months after the start of intervention was similar between a group receiving cyclosporine at 6 mg/kg/day for 9 months (thereafter tapered and discontinued over a period of 3 months) and a group receiving cyclophosphamide at 2.5 mg/kg/day for 8 weeks [11]. The Cochrane review reported that cyclosporine and cyclophosphamide were equally effective [1]. Based on the fact that the efficacy of cyclophosphamide for children with frequently-relapsing nephrotic syndrome has been demonstrated in some randomized control studies, the recommendation grade for cyclosporine has been determined as 1B.
Cyclosporine doses are adjusted while monitoring its blood concentrations. In a Japanese multicenter prospective randomized controlled study of Sandimmun® in 44 children with frequently-relapsing nephrotic syndrome, higher remission maintenance effect was shown in the dose-adjustment group (blood trough level 80-100 ng/mL for 6 months and at 60-80 ng/mL for 18 months) than in the dose-fixation group (2.5 mg/kg/day for 24 months) (50% vs. 15%, p=0.006) [8]. Thereafter, a multicenter clinical study of Neoral®, a newly developed microemulsified preparation of cyclosporine [12], in 62 children with frequently-relapsing nephrotic syndrome patients was conducted with dose adjustments based on the above-described trough levels, showing that the drug was similarly effective and highly safe (2-year relapse-free rate 58%, incidence of nephrotoxicity 8.6%) [9].
The area under the time-concentration curve (AUC0-4) of cyclosporine in patients with pediatric idiopathic nephrotic syndrome has been reported to be most strongly correlated with C2 (blood concentration at 2 hours post dose), as in the kidney transplantation patients [13,14]. With this background, a multicenter, prospective, randomized, controlled trial was conducted in Japan in 93 children with frequently-relapsing nephrotic syndrome to compare two different target C2 levels: a higher C2 group (target C2 600-700 ng/mL for the first 6 months, followed by 450-550 ng/mL for the next 18 months) and a lower C2 group (target C2 450-550 ng/mL for the first 6 months, followed by 300-400 ng/mL for the next 18 months). As a result, no significant difference in the proportion of remission maintenance at 24 months was found, but the frequent relapse inhibition rate during the study period was significantly higher in the higher C2 group, and the incidence of nephrosis relapse was significantly lower. There was also no significant difference in the incidence of adverse events [15].

Points to note for use
The greatest concern about cyclosporine side effects is chronic nephrotoxicity, and its risk increased as administration is continued for 2 years or more [16,17]. Since it is impossible to diagnose cyclosporine-induced chronic nephrotoxicity merely by urinalysis and blood tests, a kidney biopsy should be performed to examine for nephrotoxicity [18] in case of long-term administration as appropriate, and long-term administration should be avoided whenever possible (refer to p. 18 "3.

Kidney biopsy").
On the other hand, a problem arises from relapses following treatment discontinuation in many patients (cyclosporine dependence) [4-7,19]. In the above-described randomized controlled study with cyclophosphamide as the comparator, in which cyclosporine was discontinued at 1 year post dose, the 2-year remission maintenance rate was significantly higher with cyclophosphamide [11]. It has also been reported that in patients who responded to cyclosporine, sensitivity decreased during the clinical course and relapses occurred frequently [20], and that the drug had become ineffective at the restart of administration following the discontinuation [4]. According to a follow-up survey following the end of the above-described multicenter clinical study of Neoral® [9], 84.7% of the subjects experienced a relapse, and 59.2% suffered frequent relapses within 2 years after the end of cyclosporine treatment, and the risk of post-discontinuation relapse was high in the group of subjects with any relapse during cyclosporine treatment [19]. In addition, a follow-up report at 10 years after the end of the main study showed that these relapses were also noted in the transition from puberty to adulthood [21].
Other characteristics include high incidences of cosmetic side effects such as hypertrichosis and gingival swelling [4-7,9,10]. In addition, infections, hypertension, and PRES can occur as complications [4-10]; sufficient information on side effects should be provided during use. Regarding the timing of oral medication, better absorption has been suggested with prepprandial medication (15-30 minutes before meals) than with postprandial medication. Since many drugs influence the metabolism of macrolide antibiotics, concomitant medications should be used carefully. In addition, grapefruit juice should be avoided as it inhibits metabolism of cyclosporine and causes increased blood concentrations of the drug.

2. Cyclophosphamide
Cyclophosphamide has long been demonstrated to be effective against frequently-relapsing nephrotic syndrome in children by a randomized controlled study [22], and the Cochrane review showed that the drug significantly lowered the risk of relapse at 6 to 12 months compared with prednisolone monotherapy (RR 0.47, 95% CI 0.33-0.66; I^2=0%) [1] In a randomized controlled study in pediatric frequently-relapsing nephrotic syndrome, cyclophosphamide was shown to be significantly more effective at a dose of 3 mg/kg/day in an 8-week dosing group than in a 2-week dosing group [23]. However, a German nonrandomized controlled study [24] reported that 12-week administration (cumulative dose 168 mg/kg) was more effective than 8-week administration (cumulative dose 112 mg/kg) for steroid dependent nephrotic syndrome at a dose of 2 mg/kg/day, whereas a Japanese randomized controlled study [25] showed that no difference was found between 8-week administration at a dose of 2 mg/kg/day and 12-week administration, with the effect being limited in both cases. Based on a comprehensive evaluation of these reports, the recommendation grade was set at 1B.

Points to note for use
Important side effects of cyclophosphamide include gonadal dysfunction, especially azoospermia in boys, of which the risk is particularly higher in those of pubertal age (Tanner stage 2 or greater, corresponding to a testicular weight of 3 mL or more in boys) [26]. In addition, a meta-analysis reported that the risk of azoospermia increases in boys when the cumulative dose of cyclophosphamide exceeds 300 mg/kg. In men, a cumulative dose of 168 mg/kg is said to be safe, and the KDIGO guideline describes the cyclophosphamide regimen for pediatric frequently-relapsing and steroid-dependent nephrotic syndrome as 2 mg/kg for 8-12 weeks (maximum cumulative dose 168 mg/kg) [2]. In this 2020 guideline, the cumulative dose should not exceed 300 mg/kg, and doses should be administered in one course only. The risk of female infertility has been documented to be lower than the risk of male infertility, and meta-analyses reported that a cumulative dose up to 200 mg/kg was safe [26] and that female infertility at post-pubertal age developed at cumulative doses of 300 mg/kg and higher [27].
Other common side effects include myelosuppression, particularly leukopenia with an incidence of 32% [26]. It is therefore desirable that blood tests should be performed periodically every 1 to 2 weeks to monitor white blood cell (WBC) counts, and onset of leukopenia warrants cyclophosphamide dose reduction or suspension (e.g., dose reduction at a WBC count of ≤4,000/μL, suspension at a WBC

count of ≤3,000/μL). Other important side effects to note include infections, alopecia, hemorrhagic cystitis, hepatic dysfunction, interstitial pneumonia, and inappropriate antidiuretic hormone secretion. Before use of cyclophosphamide, sufficient information on side effects should be given to patients and their families in advance.
Cyclophosphamide treatment has been reported to be less effective in young patients [28-32], steroid-dependent patients [25,26,30,33-35], and patients with focal segmental glomerulosclerosis [36,37].

3. Mizoribine
Mizoribine is a metabolic antagonist developed in Japan. In Japan, a double-blind placebo-controlled multicenter randomized controlled study compared mizoribine and placebo administered at a dose of 4 mg/kg/day for 48 weeks in pediatric frequently-relapsing and steroid-dependent nephrotic syndrome, showing no significant difference in relapse rate between the mizoribine group and placebo group [38]. Therefore, mizoribine therapy for children with frequently-relapsing and steroid-dependent nephrotic syndrome is not also recommended in the Cochrane review [1].
A number of studies of high doses of mizoribine for children with frequently-relapsing and steroid-dependent nephrotic syndrome were reported one after another [39-42]. A retrospective cohort study to compare standard doses and high doses (7-10 mg/kg/day) showed that the high doses were more effective, with significantly decreased frequency of relapse in patients with a peak blood mizoribine concentration of 3.0 μg/mL or higher [43]. Thus, mizoribine was suggested to be effective at high doses of 7-10 mg/kg/day; however, no reports with strong evidence exist, so the recommendation grade was set at 2C.

Points to note for use
Although attention should be paid to hyperuricemia as a side effect, other side effects are relatively infrequent, which makes this drug advantageous over other products. Since this drug is excreted mainly via the kidneys, dose reductions are desired when the patient has renal dysfunction. In addition, it should be noted that mizoribine is indicated for "nephrotic syndromes that are difficult to treat with steroid alone (excluding frequently-relapsing and steroid-dependent cases)", and that the daily adult dose is specified as 150 mg/day in the package insert.

4. Mycophenolate mofetil
Mycophenolate mofetil is a purine metabolism antagonist with a mechanism of action similar to that of mizoribine, and has been used for immunosuppressive therapy following organ transplantation. Mycophenolate mofetil has been shown to be highly tolerable regarding side effects in two randomized comparative studies for children with frequently-relapsing and steroid-dependent nephrotic syndrome, although its remission maintenance effect was lower than cyclosporine [44,45]. In the Children's Nephrotic Syndrome Consensus Conference (CNSCC) (USA) [46] and the KDIGO guideline [2], 1-year treatment with mycophenolate mofetil is described as an immunosuppressive therapy for frequently-relapsing and steroid-dependent nephrotic syndrome. This treatment is considered to warrant consideration as a treatment for patients with frequently-relapsing and steroid-dependent nephrotic syndrome who do not permit the use of standard immunosuppressive agents because of side effects, although it represents off-label use in Japan. Since it is necessary to evaluate its efficacy and safety by adequate randomized controlled studies etc., 2C was selected as the recommendation grade in this 2020 guideline. As of December 2018, a randomized controlled study with cyclophosphamide as a comparator (ClinicalTrials. Gov NCT01092962) has been completed outside Japan, with results expected to be reported soon.
In many previous studies, mycophenolate mofetil doses were set on the basis of body surface area (1,200 mg/m^2/day)[45,47-52]. In the present guideline, the regimens and doses recommended in the CNSCC [46] and KDIGO guideline [2] have been adopted. Since the absorption of mycophenolate mofetil is widely variable among individuals, it is desirable that blood concentrations of mycophenolate be monitored. It has been reported that the tendency to relapse is high when the pre-dose concentration is less than 2.0 μg/mL [45,51].

Points to note for use
Major side effects produced by mycophenolate mofetil consist of gastrointestinal symptoms and myelosuppression. Because of teratogenicity, females in and after puberty need to receive instructions for contraception [53]. In addition, the high risk of relapse after discontinuation of treatment poses a problem [54]. The CNSCC [46] and KDIGO [2] guidelines recommend that treatment be continued 1 year or longer; however, the efficacy or safety of long-term treatment are unclear.

5. Tacrolimus
Tacrolimus is a cyclosporine-like calcineurin inhibitor, being the first-line drug over cyclosporine for immunosuppression in kidney transplantation as of December 2018. It is advantageous over cyclosporine with lower incidences of cosmetic side effects such as hypertrichosis and gingival hypertrophy; in the CNSCC [46] and KDIGO [2] guidelines, it is positioned as an immunosuppressive agent for children with frequently-relapsing and steroid-resistant nephrotic syndrome, like cyclosporine and mycophenolate mofetil. For tacrolimus, no randomized controlled study has been reported to compare it with cyclosporine or other immunosuppressive agents. In a nonrandomized prospective study in 72 patients with pediatric frequently-relapsing and steroid-dependent nephrotic syndrome, tacrolimus and mycophenolate mofetil were shown to be similarly effective in remission maintenance [55]. A retrospective cohort study reported that tacrolimus was more effective than mycophenolate mofetil in relapse suppression, but produced adverse events such as infections and pancreatitis [56]. Since it is necessary to evaluate its efficacy and safety by adequate randomized comparative studies etc., 2C was selected as the recommendation grade in this 2020 guideline. As of December 2018, one multicenter open-label randomized controlled study of tacrolimus and cyclosporine in patients with pediatric frequently-relapsing and steroid-dependent nephrotic syndrome was ongoing (JSKDC06, UMIN ID UMIN000004204); a report of its results is awaited. Tacrolimus is a drug for which the dose is adjusted while monitoring its blood concentrations. In and outside Japan, tacrolimus therapy represents off-label use for frequently-relapsing and steroid-dependent nephrotic syndrome, with no safe and effective regimen established. In many previous studies, blood trough levels were adjusted to 5-10 ng/mL on the basis of clinical research on kidney transplantation [55,57-61], and the efficacy and safety of long-term treatment are unknown. For this reason, the tacrolimus regimen and doses in this 2020 guideline have been set in the same manner as with the KDIGO guideline [2] and the protocol of the aforementioned JSKDC06.

Points to note for use
With regard to tacrolimus side effects, the development of diabetes mellitus is important; special caution should be exercised when using tacrolimus in patients with a family history of diabetes mellitus and patients with any glucose tolerance impairment risk factor (e.g., obesity) [57]. As described above, infections and pancreatitis have also been reported.[56] In addition, tacrolimus has been reported to cause renal interstitial fibrosis as with cyclosporine; long-term treatment should be avoided if possible. With regard to renal interstitial fibrosis, a study reported that there was a significant correlation with high trough levels of tacrolimus [61].

C Q3
Is rituximab treatment recommended for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome?

Recommendation statements:

- We propose that rituximab be administered for remission maintenance in childhood-onset, refractory frequently-relapsing and steroid-dependent nephrotic syndrome. Recommendation grade 2B (agreement ratio 82%)

Treatment examples
Rituximab is administered by intravenous drip infusion at a rituximab dose of 375 mg/m^2/dose at 1-week intervals in a total of 1-4 doses. However, the single maximum dose should be up to 500 mg.

Evidence summary
Rituximab is administered for the purpose of remission maintenance in refractory nephrotic syndrome characterized by onset of idiopathic nephrotic syndrome with steroid sensitivity in childhood and the inability to maintain remission with conventional treatment (e.g., steroid, immunosuppressive agents) and hence the development of frequent relapses or steroid dependence. Caution should be exercised on side effects both in the acute and chronic phases, indications should be determined carefully, and treatment should be administered by a physician with adequate knowledge and experience. No established method of after-treatment is available.

Commentary
Rituximab is a monoclonal antibody against CD20 differentiated antigens expressed on B-cell surfaces. Some cohort studies [2-8], including a placebo-controlled randomized controlled study in Japan [1], and other randomized controlled studies [9,10] have suggested that rituximab is effective for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome. We propose using rituximab for the purpose of remission maintenance in refractory frequently-relapsing and steroid-dependent nephrotic syndrome. Since there are many points to note for use, a warning statement is provided in the package insert that treatment should be administered by a physician with adequate knowledge and experience. In actual settings, it is desirable that the treatment be administered by a physician specializing in renal disease in children.
As a result of an investigator-initiated trial in Japan [1], the indication of rituximab for refractory frequently-relapsing and steroid-dependent nephrotic syndrome was approved for the first time in the world. The median relapse-free time, the primary efficacy endpoint, was significantly longer in the rituximab group (24 subjects, age at registration 11.5 years, mean duration of illness 7.9 years) than in the placebo group (24 subjects, age at registration 13.6 years, mean duration of illness 8.0 years) (rituximab group 267.0 days, placebo group 101.0 days; hazard ratio [HR] 0.27, 95% CI 0.14-0.53, p<0.0001). Time to treatment failure was significantly longer in the rituximab group (HR 0.27, 95% CI 0.14-0.53, p=0.0005), and time to a frequently-relapsing and steroid-dependent state also lengthened significantly in the rituximab group (HR 0.17, 95% CI 0.06-0.46, p=0.0001). The relapse rate was significantly lower in the rituximab group than in the placebo group (HR 0.37, 95% CI 0.23-0.59, p<0.0001), and the mean steroid dose was found to be significantly lower at 9.12 mg/m^2/day in the rituximab group than in the placebo group at 20.85 mg/m^2/day (p<0.0001). There

was no significant difference in the frequency of adverse events between the two groups. Based on the above results, rituximab was concluded to be effective and safe for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome. Outside Japan, a placebo-controlled randomized controlled study in patients (2-18 years) with cyclosporine-dependent refractory frequently-relapsing and steroid-dependent nephrotic syndrome (ClinicalTrials.gov NCT01268033) and a randomized controlled study to compare the efficacies and safeties of rituximab and tacrolimus in patients (3-16 years) with steroid-dependent nephrotic syndrome (ClinicalTrials.gov NCT 02438982) were conducted; although both studies have completed patient registration, study results have not been published. In an open-label randomized controlled study of rituximab (administered at 375 mg/m^2/dose in 1-2 doses) compared with the standard treatment (steroid + calcineurin inhibitor) in 54 patients with refractory frequently-relapsing and steroid-dependent nephrotic syndrome (dependent on steroid and calcineurin inhibitors) [9], the 3-month relapse rate was significantly lower in the rituximab group (18.5%) than in the standard treatment group (48%) (p=0.029), and the 3-month steroid and calcineurin inhibitor discontinuation rate was significantly higher in the rituximab group (62.95%) than in the standard treatment group (3.7%) (p<0.001).
According to the package insert, rituximab is administered by intravenous drip infusion at a rituximab dose of 375 mg/m^2/dose at 1-week intervals in a total of 1-4 doses. However, no study of high quality is available to compare dosing frequencies, effects, and safety results. Since previous studies were conducted with rituximab administered at 375 mg/m^2/dose in 1-4 doses (at 1-week intervals) [1-13], this 2020 guideline describes the dosing frequency as 1-4 doses. In an observational study to examine long-term prognosis in 37 patients receiving 1 to 4 doses of rituximab, relapse-free time at 12 months after initial dosing was significantly shorter in the group of patients receiving 1-2 initial doses than in the group of patients receiving 3-4 initial doses (p<0.05) [11]. Although no association was reported between remission for 2 years or longer and the number of initial doses, this study involved repeated doses of rituximab in 19 of the 37 subjects, in which 20 (69%) of the 29 subjects followed for 2 years or longer maintained remission for 2 years, and 14 (48%) of the 29 subjects discontinued immunosuppressive therapy [11].
Side-effect characteristics of rituximab include infusion reactions typically occurring within 24 hours after intravenous infusion (with manifestations including fever, vomiting, chills, nausea, headache, pain, itching, rash, bronchospasm, cough, weakness, and angioedema). Infusion reactions have been reported also in patients with refractory frequently-relapsing and steroid-dependent nephrotic syndrome [1,6-12]. The package insert states that pretreatment with antipyretic sedatives, antihistamine drugs, and steroids should be administered to prevent infusion reactions [6,9,12]. Neutropenia and agranulocytosis, among other side effects of rituximab, are known to occur not only with early onset but also with late onset. Of 114 patients with childhood-onset refractory nephrotic syndrome receiving rituximab (213 doses), 11 experienced agranulocytosis 54-161 days (median 66 days) after administration of rituximab, of whom 9 were treated for infections [13]. After administration of rituximab, blood tests, including CD19 measurement, should be performed periodically and the patient's condition should be closely monitored. Also, depletion, or a decrease, of peripheral B cells can lead to onset of bacterial or viral infections, for which caution is required, particularly in children. In Japan, onset of atypical *Pneumocystis jirovecii* pneumonia after rituximab therapy was reported in a patient with refractory steroid-resistant nephrotic syndrome [14]. Attempts have been made to investigate the use of a sulfamethoxazole/trimethoprim (ST) mixture during the period of peripheral B-cell depletion for prophylaxis of pneumocystis infection [6,11,12]; however, there are distinct opinions about its necessity. Another adverse event is hypogammaglobulinemia. It is desirable that IgG values and peripheral lymphocyte subsets be checked to confirm the absence of an asymptomatic immunodeficient state prior to administration of rituximab. Following administration, IgG values should also be checked periodically, with globulin replacement and other treatments performed as required.
Known side effects (including death) of rituximab include progressive multifocal leukoencephalopathy [a] and fulminant hepatitis associated with hepatitis B carrier reactivation [15]. Patients with generalized erythematosus who have manifested progressive multifocal leukoencephalopathy have markedly decreased immune function due to concomitant use of an immunosuppressive agent, and a risk from long-term depletion of B cells is suggested. Responding

to this situation, the FDA issued a strict warning against the off-label use of rituximab [a]. Fatal fulminant hepatitis, after hepatitis B virus reactivation in carriers, has also been reported in some patients with malignant lymphoma; hepatitis B virus antibody and liver function should be assessed before initiation of rituximab therapy [15]. Since serious adverse events, such as pulmonary fibrosis (fatal) [16], immune ulcerative colitis [17], and fulminant viral myocarditis [18], have been reported in patients with refractory frequently-relapsing and steroid-dependent nephrotic syndrome, indications should be determined carefully, and attention should also be paid to long-term side effects.
There is no established standard treatment to be administered after rituximab. Long-term results (media length of observation period 59 months) for 51 patients with refractory frequently-relapsing and steroid-dependent nephrotic syndrome receiving rituximab in four doses weekly showed that 48 patients (94%) experienced a relapse, with a 50% relapse-free time of 261 days. The remaining three did not experience a relapse during the observation period [19]. In an observational study in 30 patients with refractory steroid-dependent nephrotic syndrome to evaluate prognosis after repeated doses of rituximab following 1-4 doses of rituximab and depletion of CD19 for 15 months, approximately two-thirds of patients maintained long-term remission without oral immunosuppressive agents even after a recovery of CD19, and cotrimazole (20 mg/kg, 3 doses a week, off-label use) was administered to prevent pneumocystis infection, with no serious adverse events, during the CD19 depletion period [12]. Given serious adverse events like those described above, it should be noted, however, that still more careful investigation is needed to determine the acceptability of repeated administration of rituximab.
According to a pilot study aiming to reduce the total number of rituximab doses with administration of mycophenolate mofetil (MMF) as an after-treatment following rituximab, and to extend relapse-free time [20], the mean number of relapses following rituximab administration was significantly smaller in a group receiving a combination of single rituximab dose and mycophenolate mofetil than in a group receiving a single dose of rituximab (without mycophenolate mofetil). With no serious adverse events noted, mycophenolate mofetil was considered to be useful as an after-treatment following rituximab. Based on this pilot study, a multicenter double-blind placebo-controlled randomized controlled study is ongoing in Japan to assess the efficacy and safety of mycophenolate mofetil as a remission maintenance therapy following rituximab treatment in children with refractory frequently-relapsing and steroid-dependent nephrotic syndrome, and its results are awaited (JSKDC07, UMIN ID UMIN000014347). With regard to immunosuppressive agents for after-treatment, a prospective nonrandomized study to compare cyclosporine and mycophenolate mofetil in a few cases [21] is available, but evidence is insufficient to allow their comparison.

2. Specifics

D. Treatment of steroid-resistant nephrotic syndrome

CQ 4
Are immunosuppressive agents recommended for pediatric steroid-resistant nephrotic syndrome?

Recommendation statements:
1. A combination of steroid with cyclosporine for pediatric steroid-resistant nephrotic syndrome is recommended. Recommendation grade 1B (agreement ratio 100%)

2. We propose using a combination of steroid pulse therapy and cyclosporine, since it is likely to be effective for remission induction. Recommendation grade 2C (agreement ratio 94%)

3. We propose tacrolimus as a therapeutic option for remission induction for steroid-resistant nephrotic syndrome where cyclosporine cannot be used because of aesthetic side effects and for other reasons. (Off-label use) Recommendation grade 2B (agreement ratio 88%)

4. We propose mycophenolate mofetil as a therapeutic option for remission induction for steroid-resistant nephrotic syndrome where other immunosuppressive agents such as calcineurin inhibitors cannot be used because of side effects and for other reasons. (off-label use) Recommendation grade 2C (agreement ratio 94%)

5. We recommend that oral cyclophosphamide is not used for remission induction therapy for pediatric steroid-resistant nephrotic syndrome. Recommendation grade 1B (agreement ratio 100%)

Treatment examples
1. Example of cyclosporine treatment
- The dose should be started at 2.5-5 mg/kg/day in two divided doses and adjusted to reach the following trough levels:
  Trough range 100-150 ng/mL (to Month 3)
  Trough range 80-100 ng/mL (Month 4 to Month 12)
  Trough range 60-80 ng/mL (Month 13 and thereafter)
- If incomplete remission or higher outcome is not obtained in 4-6 months after cyclosporine administration, the treatment policy should be reconsidered.
- If incomplete/complete remission is achieved in 4-6 months after cyclosporine administration, treatment should be continued for 1-2 years.
- Since a combination therapy with low-dose steroid (prednisolone 0.5-1.0 mg/kg alternate-day administration) raises the remission rate, a combination with low-dose steroid should be considered.

2. Example of steroid pulse therapy
- Steroid pulse therapy will be performed with methylprednisolone administered intravenously at 20-30 mg/kg/dose (up to 1 g) once daily for 3 consecutive days in one cycle.
- Steroid pulse therapy can elevate blood cyclosporine concentrations; during steroid pulse therapy, cyclosporine cessation should be considered.

3. Example of tacrolimus treatment (off-label use)
- Tacrolimus is started at 0.1 mg/kg/day in two divided doses, and the dose is adjusted while monitoring its blood concentrations.

4. Example of mycophenolate mofetil treatment (off-label use)
- Mycophenolate mofetil is administered at 1,000-1,200 mg/m^2/day (or 24-36 mg/kg/day, up to 2 g/day) in two divided doses.

Note 1: Body weights will be calculated using height-based standard body weights (refer to Tables 1-A and 1-B on pages 42-45, “1. General description of treatments”) (the same applies for body surface areas).
Note 2: Immunosuppressive therapy performed in a nephrotic condition necessitates adequate caution against serious complications and side effects, such as infections and hypertension; it is desirable that steroid-resistant nephrotic syndrome be treated by physicians specializing in pediatric renal disease.

Evidence summary
In a meta-analysis to assess the effects of coadministered immunosuppressive agents in patients with steroid-resistant nephrotic syndrome in children, coadministered cyclosporine and tacrolimus was shown to be significantly superior to other immunosuppressive agents such as mycophenolate mofetil and cyclophosphamide in terms of induction of complete remission. However, these meta-analyses included many reports with small sample sizes, and all reports evaluated short-term prognosis only. Six randomized controlled studies of cyclosporine are available, including one controlled study to compare it with placebo and oral cyclophosphamide, which showed a significant remission induction effect; we considered that this finding provided strong evidence for short-term remission induction effect. In a randomized controlled study, tacrolimus has been reported to be as effective as cyclosporine, to produce a significantly lower incidence of cosmetic side effects, and to be more effective than cyclophosphamide pulse therapy. For steroid pulse therapy, no randomized controlled study has been conducted in children with steroid-resistant nephrotic syndrome patients, with only a few observational studies published. In a non-randomized controlled study, a combination of steroid pulse therapy and cyclosporine has been reported to produce high remission rates for focal segmental glomerulosclerosis. Although three randomized controlled studies investigated oral administration of cyclophosphamide, none of them demonstrated a remission induction effect. One randomized controlled study is available in which mycophenolate mofetil and cyclosporine were compared in terms of remission induction effect in patients, including adults, with steroid-resistant focal segmental glomerulosclerosis (dexamethasone coadministered in the mycophenolate mofetil group), and showed no difference in remission induction. However, that study included adult patients and was judged to have insufficient evidence; we have decided to propose mycophenolate mofetil as an optional treatment in cases where calcineurin inhibitors cannot be used.

Commentary
As of December 2018, three immunosuppressive agents were covered by health insurance for the treatment of steroid-resistant nephrotic syndrome in Japan: cyclosporine, mizoribine, and cyclophosphamide. In 2017, two meta-analysis studies were reported assessing the effect of concomitant immunosuppressive agents in children with steroid-resistant nephrotic syndrome [1,2]. In a meta-analysis of 18 randomized controlled studies in steroid-resistant nephrotic syndrome [1] and a meta-analysis of seven randomized controlled studies in 373 patients with steroid-resistant focal segmental glomerulosclerosis [2], calcineurin inhibitors (cyclosporine, tacrolimus) were shown to be significantly superior to other immunosuppressive agents such as mycophenolate mofetil and cyclophosphamide in terms of induction of complete remission. While these meta-analyses included many reports with small sample sizes, and all reports evaluated short-term prognosis only, we recommend cyclosporine, which has good evidence for its efficacy for first-line treatment of steroid-resistant nephrotic syndrome.

1. Calcineurin inhibitors (cyclosporine, tacrolimus [off-label use])
A combination of steroid with cyclosporine for steroid-resistant nephrotic syndrome is recommended.

Tacrolimus is considered to be a therapeutic option for cases of steroid-resistant nephrotic syndrome where cyclosporine cannot be used because of cosmetic side effects such as hypertrichosis and gingival hypertrophy [3].
Randomized controlled studies of cyclosporine in children with pediatric steroid-resistant nephrotic syndrome reported that the incomplete/complete remission rate at 12 months after treatment initiation was 60% in 1993 [4], 100% at 6 months in 1996 [5], and 80% at 6 months in 2009; high remission induction rates were noted in all these studies [6]. In a Japanese non-randomized controlled study in 35 patients with pediatric steroid-resistant nephrotic syndrome, the regimen was changed due to histopathological findings in the kidney as follows: Twenty-eight patients with minimal-change-disease or mesangial proliferation received cyclosporine (trough level at 120-150 ng/mL for 3 months, at 80-100 ng/mL for 9 months, followed by recommended treatment at 60-80 ng/mL for 12 months) + prednisolone (1 mg/kg/day in three divided doses on consecutive days for 4 weeks, 1 mg/kg/dose alternate-day administration Week 5 to Month 12), whereas 7 patients with focal segmental glomerulosclerosis received the two drugs described above in combination with steroid pulse therapy in five courses (Weeks 1, 2, 5, 9, and 13); as a result, high remission rates of 82.1% and 85.7%, respectively, were obtained [6].
Although no timing has been established for determining the effect of cyclosporine on steroid-resistant nephrotic syndrome, the incidence of proteinuria decreased at 4.4±1.8 weeks [5], and a randomized controlled study conducted in 2009 reported that the time to incomplete or complete remission was 8-12 weeks [7]. In an observational study conducted in 2005, the mean time to incomplete/complete remission was 9.9±3.4 weeks (range 2-16 weeks) [8]. A Japanese prospective study of 5-year prognosis in 35 patients with steroid-resistant nephrotic syndrome reported that 5-year prognosis can be roughly predicted by therapeutic responsiveness at 4 months after treatment initiation [9]. In other randomized controlled studies, cyclosporine efficacy was often evaluated at 6 months after treatment initiation; if incomplete remission or higher remission is not observed within 4 to 6 months of treatment, it seems necessary to reconsider the treatment policy concerning the timing of determination of cyclosporine efficacy.
Cyclosporine doses are adjusted while monitoring its blood concentrations. Some papers have reported a target trough level of 100-200 ng/mL [10-13]. When cyclosporine is administered at a trough level of 100 ng/mL for 2 years, approximately 50% of the recipients experience nephrotoxicity [14]; therefore, in view of the initial dose in kidney transplantation, this 2020 guideline has set a trough level at 100-150 ng/mL for 3 months until remission and at 60-80 ng/mL for the 2nd year and beyond in case of treatment for 1 year or longer. While management of pediatric steroid-resistant nephrotic syndrome by C2 (blood concentration at 2 hours post dose) has not yet been established, the $AUC_{0\text{-}4}$ (area under the concentration curve) of cyclosporine was reported to be correlated with C2 [15]. A study of C2 controls was conducted in pediatric frequently-relapsing and steroid-dependent nephrotic syndrome and adult steroid-resistant nephrotic syndrome (a randomized controlled study of cyclosporine C2 dose adjustments, UMIN Study ID: C000000008) [16,17]; it is hoped that evidence will be compiled for C2 controls in pediatric steroid-resistant nephrotic syndrome.
Many side effects are known to be associated with cyclosporine, including nephrotoxicity, hypertension, susceptibility to infection, gingival hypertrophy, and hypertrichosis. In the development of posterior reversible encephalopathy syndrome (PRES), in particular, edema (or nephrotic state) has been suggested as a risk factor, and steroid resistance was reported in 5 of 7 patients with nephrotic syndrome who suffered PRES [18], thereby warranting careful observation and appropriate actions.
While some studies have reported tacrolimus efficacy in a few cases [19-24], there is no randomized controlled study in a large number of cases. In a small-scale randomized controlled study in 41 children with steroid-resistant nephrotic syndrome, tacrolimus was compared with cyclosporine, showing that the remission rate (remission and incomplete remission) was similar between the cyclosporine group (86%) and the tacrolimus group (75%) [19]. In that study, no significant difference in the incidence of nephrotoxicity, hypertension, or diabetes mellitus was found, with hypertrichosis and gingival hypertrophy noted at significantly lower incidences in the tacrolimus group [25]. In a randomized controlled study in 131 patients with steroid-resistant nephrotic syndrome, the complete remission and partial remission (urine protein reduction of 50% or more) rate with

cyclophosphamide pulse therapy was significantly higher in the tacrolimus group (82.5%) than in the cyclophosphamide pulse therapy group (45.9%) [26]. In a study in 60 patients with steroid-resistant nephrotic syndrome patients at 1 year or older and 18 years or younger who achieved remission with the use of tacrolimus, a tacrolimus group and a group with a switch from tacrolimus to mycophenolate mofetil for remission maintenance therapy were compared. At 12 months, the complete remission / incomplete remission maintenance rate did not differ significantly between the two groups (54.8% vs. 41.1%); however, the complete remission / incomplete remission rate including the steroid-sensitive, non-frequent relapse state at 12 months, was significantly higher in the tacrolimus group (90.3% vs. 44.8%) [25].
The regimen recommended by the KDIGO guideline [a] is 0.05-0.1 mg/kg/day (in two divided doses) with a target trough level of 5-10 ng/mL. However, this regimen is based on a clinical study in kidney transplantation; the efficacy and safety of long-term use in steroid-resistant nephrotic syndrome are unclear.
The optimum length of dosing of calcineurin inhibitors is unknown. In steroid-resistant nephrotic syndrome, relapses have been found to occur at high ratios of 10% to 76% after discontinuation of cyclosporine and tacrolimus [8,9,16,27]. Two randomized controlled studies in children have reported that relapses frequently occurred after discontinuation of treatment for 6 or 12 months [5,7]. Therefore, it is a common practice to continue the treatment for more than 12 months to suppress relapses; however, since nephrotoxicity poses a concern, investigation of long-term remission maintenance ratios and renal prognosis need to be investigated in the future.
Necessity of steroid medication is unknown because of the absence of a study comparing calcineurin inhibitor monotherapy and a combination of calcineurin inhibitor with low-dose steroid. However, coadministration of steroid has been performed in the majority of clinical studies, and is proposed in the KDIGO guideline [a]; therefore, we consider coadministration at the lowest dose for maintaining remission.

2. Steroid pulse therapy
We propose using a combination of steroid pulse therapy and cyclosporine for steroid-resistant nephrotic syndrome, since it is likely to be effective in remission induction. Evidence is lacking to determine whether steroid pulse monotherapy is effective in remission induction, and no definite conclusion can be reached. During methylprednisolone treatment, cyclosporine discontinuation should be considered.
Although no randomized controlled study has been reported to compare steroid pulse therapy + cyclosporine and cyclosporine in pediatric steroid-resistant nephrotic syndrome, it has been reported that 8 of 10 patients with focal segmental glomerulosclerosis receiving a combination of steroid pulse therapy + cyclosporine + prednisolone achieved remission within 8 weeks after treatment initiation [27]. Observational studies reported from Japan include a study in which 10 children with cyclophosphamide- and cyclosporine-resistant, pediatric steroid-resistant nephrotic syndrome (focal segmental glomerulosclerosis) were treated by steroid pulse therapy (methylprednisolone 30 mg/kg/dose, up to 1 g/dose, 3 days of each cycle) in 14 cycles. One of the 10 patients discontinued the treatment because of peritonitis. Of the remaining 9 patients, 4 achieved complete remission, 3 achieved incomplete remission, and 2 did not achieve remission; steroid pulse therapy was shown to allow remission to be induced in pediatric patients with cyclophosphamide- or cyclosporine-resistant pediatric steroid-resistant nephrotic syndrome [28]. Judging from the above, a treatment consisting of cyclosporine medication and steroid pulse therapy is likely to produce high remission rates. As of December 2018, a randomized controlled study to compare a cyclosporine + prednisolone + steroid pulse therapy combination and cyclosporine + prednisolone combination was ongoing in Japan (UMIN Study ID C000000007).
A randomized controlled study has not been conducted on steroid pulse monotherapy for steroid-resistant nephrotic syndrome in children, with only a few observational studies available. According to Yorgin et al., 11 children with pediatric steroid-resistant nephrotic syndrome (mean age 3.6±1.5 years) received a steroid pulse therapy (methylprednisolone 30 mg/kg/dose, up to 1 g/dose) in a mean total of 24.8±10.5 doses, and 9 of the 11 patients achieved complete remission [29]. In addition, since adverse events were observed with moderate severity and infrequently, they reported that the

steroid pulse therapy was safe and effective in inducing remission in young children with pediatric steroid-resistant nephrotic syndrome [29]. Furthermore, a study in 16 children with pediatric steroid-resistant nephrotic syndrome (median age 3.8 years) reported that 10 of the 16 subjects receiving methylprednisolone at 15 mg/kg/day for 3 or 5 days achieved remission [30]. The 6 non-responders later achieved clinical remission with the use of an immunosuppressive agent (cyclophosphamide for 3 subjects, cyclosporine for 2 subjects, tacrolimus for 1 subject) [30].
As described above, steroid pulse therapy may be effective in remission induction in pediatric steroid-resistant nephrotic syndrome; however, the evidence level is not high because of the low sample size and the absence of randomized controlled study. The results from the randomized controlled study completed at the end of 2018 in Japan (JSKDC02 Study) are awaited.
During steroid pulse therapy, side effects such as hypertension, hyperglycemia, bradycardia, thrombosis, and PRES can occur; monitoring of the patient's condition is required.

3. Cyclophosphamide
We recommend that oral cyclophosphamide is not used for remission induction therapy for pediatric steroid-resistant nephrotic syndrome. With regard to cyclophosphamide pulse therapy, evidence is so scanty that no definite conclusion can be reached.
The following three randomized controlled studies of cyclophosphamide treatment for pediatric steroid-resistant nephrotic syndrome are available [31-33]. First, in two randomized controlled studies comparing a combination of cyclophosphamide and steroid with steroid monotherapy, no significant differences in remission rate or adverse events were found [31,32]. Thereafter, a randomized study to compare oral cyclosporine medication and cyclophosphamide pulse therapy was conducted in children with first-onset pediatric steroid-resistant nephrotic syndrome (histologically classified as the minimal-change-disease, focal segmental glomerulosclerosis, diffuse mesangial proliferation [33]. The proportion of complete and incomplete remission at 12 weeks after treatment initiation was significantly higher in the cyclosporine group (60%) than in the cyclophosphamide pulse therapy group (17%) ($p<0.05$). In that study, the proportion of complete remission at Week 24 did not differ significantly between the cyclosporine group (13%) and the cyclophosphamide pulse therapy group (5%); however, the proportion of incomplete remission was significantly higher in the cyclosporine group (46%) than in the cyclophosphamide pulse therapy group (11%); the incidence of adverse events was similar between the two groups [33]. In a randomized controlled study in 131 patients with steroid-resistant nephrotic syndrome to compare cyclophosphamide pulse therapy and oral tacrolimus therapy the complete remission and partial remission (urine protein reduction of 50% or more) rate was significantly higher in the tacrolimus group (82.5%) than in the cyclophosphamide pulse therapy group (45.9%) [26]. Based on the above facts, it can be concluded that oral cyclophosphamide administration is ineffective for steroid-resistant nephrotic syndrome.

4. Mycophenolate mofetil (off-label use)
We propose mycophenolate mofetil as a therapeutic option for steroid-resistant nephrotic syndrome where other immunosuppressive agents such as calcineurin inhibitors cannot be used because of side effects and for other reasons.
A series of case studies of mycophenolate mofetil for steroid-resistant nephrotic syndrome (off-label use) reported a few cases, with the reported remission rates not always being high [34-36]. In the KDIGO guideline [a], mycophenolate mofetil is recommended for patients who are resistant to calcineurin inhibitors and steroids. This is rationalized as follows: In a controlled study in 138 patients with steroid-resistant nephrotic syndrome (focal segmental glomerulosclerosis) at 2 to 40 years of age (including 93 patients younger than 18 years and 33 patients with urinary protein <2 g/day), urinary protein reductions were compared between the cyclosporine (5-6 mg/kg/day) group and the mycophenolate mofetil (25-36 mg/kg/day, up to 2 g/day) + dexamethasone [0.9 mg/kg/day, 2 days after the start of the week (every week, Weeks 1-8, Weeks 10-26 at 2-week intervals, Weeks 30-50 at 4-week intervals)] group, and the remission rate at 12 months after study initiation was 46% in the cyclosporine combination group and 33% in the mycophenolate mofetil + dexamethasone combination group; although the remission rates were low, there was no significant difference

between the two groups [37]. In addition, no significant difference in the frequency of complications of infections, gastrointestinal symptoms, neurological complications, or hypertension was noted between the two groups [37]. As for prognosis, 14% of the subjects in the cyclosporine combination group and 11% of the subjects in the mycophenolate mofetil + dexamethasone combination group, respectively, at Week 78 were dead or suffering renal failure; a combination of steroid and mycophenolate mofetil was less effective than cyclosporine in suppressing renal function impairment.

5. Treatment of post-remission relapse of nephrotic syndrome
Nephrotic syndrome often relapses after remission (complete remission or incomplete remission) in pediatric steroid-resistant nephrotic syndrome. Patients who have once achieved remission induction are likely to be steroid-sensitive; therefore, it is considered appropriate to administer prednisolone to treat nephrotic syndrome relapses (refer to p. 47 "2. Specifics" "A. Treatments of steroid-sensitive nephrotic syndrome", "2. Treatments of relapses").

Chapter II: Treatments

2. Specifics

E. Supplementary treatment of steroid-resistant nephrotic syndrome

[Summary]
- For supplementary treatment of steroid-resistant nephrotic syndrome, renin-angiotensin system inhibitors are effective in reducing the incidence of proteinuria but do not improve renal prognosis. Caution should be exercised on acute kidney injury when using such inhibitors in the presence of endovascular dehydration.
- Plasma exchange and LDL apheresis (LDL-A) are effective when performed early after onset of the disease.
- Although it constitutes an off-label use, rituximab may be used more effectively in combination with steroid pulse therapy or cyclosporine rather than monotherapy. (An investigator-initiated clinical trial of steroid pulse therapy and rituximab in refractory steroid-resistant nephrotic syndrome is ongoing [JSKDC11 Study]).

♦Commentary

Steroid-resistant nephrotic syndrome accounts for 10% to 20% of cases of pediatric idiopathic nephrotic syndrome. Steroid pulse therapy and immunosuppressive agent medication are administered for steroid-resistant nephrotic syndrome excluding nephrosis due to genetic abnormalities and secondary nephrosis (the minimal-change-disease and focal segmental glomerulosclerosis are targeted in this 2020 guideline), and various supplementary treatments are administered for cases of refractory steroid-resistant nephrotic syndrome. Their treatments are described below. First, some renin-angiotensin system inhibitors, plasma exchange, and LDL adsorption therapy (up to 12 times in 3 months for focal segmental glomerulosclerosis that does not respond to conventional drugs, and the serum cholesterol level does not decrease under 250 mg/dL) are described, with mention of rituximab in off-label use as of December 2018, when this 2020 guideline was in preparation.

1. Renin-angiotensin system inhibitors
Intrarenal angiotensin II constricts the efferent and afferent arterioles via angiotensin type 1 receptor to raise intraglomerular pressure. Therefore, renin-angiotensin system inhibitors suppress vasoconstriction and lower glomerular filtration pressure to reduce the incidence of proteinuria. In chronic nephritis, podocyte apoptosis is known to be induced by increased expression of angiotensin 1 receptor in podocytes and increased production of angiotensin II by podocytes, and renin-angiotensin system inhibitors are said to protect podocytes.
One study reported that proteinuria was suppressed, and renal function was improved in IgA nephropathy and other conditions [1]. There are two studies of the efficacy or renin-angiotensin system inhibitors in pediatric steroid-resistant nephrotic syndrome in children: a study of enalapril by Bagga et al. in 2004 [2] and a study of fosinopril by Yi et al. in 2006 [3]. Although both drugs are effective in reducing proteinuria, they do not improve renal prognosis. In the use in adult focal segmental glomerulosclerosis, it is effective in reducing proteinuria, but it is difficult to induce complete remission; one study reported that the proportion of cases with progression to renal failure did not decrease [4]. In adult nephrotic syndrome without hypertension, evidence for utility is lacking. Based on the above facts, it can be considered that it is better not to use a renin-angiotensin system inhibitor alone, but to use in combination with other treatments. When using a renin-angiotensin system inhibitor for nephrotic syndrome, it should always be kept in mind that use of such drugs in this situation to dilate the efferent arteriole can induce acute kidney injury, since circulating blood volume may have decreased and hence renal blood flow may have lowered in the acute phase of

nephrosis, and the afferent arterioles have been constricted by cyclosporine already in use.

2. Plasma exchange (PE)
Plasma exchange (PE) began to be used to remove humoral factors, which are considered to be the etiology of focal segmental glomerulosclerosis, a common primary disease in steroid-resistant nephrotic syndrome [5]. Remission induction rates have been variably reported at 25%, 57%, and 72% [6-8]. One report has suggested that PE would be more useful when applied early in the course of the disease with any pathological changes [6]; however, PE commencement is unavoidably after kidney biopsy because of the indication for focal segmental glomerulosclerosis. The priming volume required is lower than in low-density lipoprotein apheresis (LDL-A) as described below, PE can be used in low-weight children. Although an albumin preparation is often used as the displacing liquid, it has been suggested that humoral factor activity inhibitors are also removed when removing humoral factors; some authors consider that fresh frozen plasma should be used as the displacing liquid.

3. LDL apheresis (LDL-A)
LDL-A is a treatment of Japanese origin that has been used since 1988 to induce early remission of the nephrotic state in focal segmental glomerulosclerosis by rapidly removing low-density lipoprotein (LDL) [9]. It has been reported to ameliorate lipid-induced nephropathies caused by LDL, oxidized LDL and lipid-induced excessive stimulation of macrophages, and to improve steroid sensitivity after adsorption and removal of humoral factors and LDL [10]. It was reported that when the proteinuria selectivity index (SI) was 0.05±0.02, complete remission occurred, the responsiveness was low at 0.25±0.04, and that very mild urinary tubular interstitial lesions were an efficacy marker, suggesting that early intervention is effective [11]. In the investigation of efficacy (short-term results) during a 2-year observation period in a prospective observational survey on the long-term effects of LDL apheresis on drug-resistant nephrotic syndrome started in Japan in 2007 (POLARIS Study), daily urinary protein contents were evaluated in 53 patients [age 18-87 years: mean 55.8±18.1 (SD)] out of 58 patients undergoing LDL-A for steroid-resistant nephrotic syndrome [cyclosporine (CYA) +/−, 24 patients / 27 patients; steroid pulse therapy +/−, 4 patients / 47 patients]. Of the 44 followable patients, 25% achieved complete remission, 22.7% achieved incomplete remission I (urinary protein <1 g/day), 25.0% achieved incomplete remission II (<3.5 g /day), and 27.3% failed to respond (≥3.5g/day) [12].
For precautions for clinical use, because of the priming volume issue, a body weight of 30 kg or more is suggested to ensure safe LDL-A in children. During oral medication of angiotensin converting enzyme inhibitor (ACE-I), blood bradykinin levels increased to the extent that causes anaphylactoid reactions; therefore, caution should be exercised on the timing of implementation and the control of hypotension and blood coagulation.
A regimen in accordance with the above-described indication criteria is available in which LDL-A is not used alone, but used in combination with steroid or cyclosporine; for example, the drug may be administered twice weekly for 3 weeks, and then once weekly for 6 weeks (according to the clinical course), to have a total of 12 doses [11].

4. Rituximab
Although a clinical study has been reported on rituximab for refractory steroid-resistant nephrotic syndrome, it constitutes off-label use as of December 2018, when this 2020 guideline was in preparation. An investigator-initiated clinical trial seeking approval for additional indications is ongoing in Japan (JSKDC11 Study), and its results are awaited. It is desirable that when using rituximab, it should be carefully administered after ruling out secondary nephrotic syndrome by a kidney biopsy, and confirming the absence of genetic abnormalities. For research into rituximab for refractory steroid-resistant nephrotic syndrome, evidence is available from 11 case series and one open-label randomized controlled study as of December 2018. Regarding comparison of remission rates, Kamei et al. reported used rituximab for 10 patients with refractory steroid-resistant nephrotic syndrome at his facility, reporting that complete remission was achieved in 70% of the subjects,

incomplete remission in 10%, and the treatment was ineffective in 20% [13]. Fujinaga et al. reported that 6 patients receiving rituximab treatment for refractory steroid-resistant nephrotic syndrome all achieved complete remission with regard to 5-year long-term prognosis (mean 158 days), followed by a total of 17 relapses in 5 patients [14]. It is likely that the effect may be variable depending on whether rituximab is used early after onset of the disease, timing of post-dose assessments, and choice of combination therapy; it is difficult to simply compare their results with the data on the proportion of complete remission reported from outside Japan. In fact, a randomized controlled study by Maganasco et al. determined efficacy 3 months after administration of rituximab and reported that the remission rate in the rituximab group was 18.8%, a level distinct from the rate reported in Japan [17]. In a questionnaire-based survey on the use of rituximab at 141 facilities in Japan conducted by Ito et al. in 2010, 19 patients received rituximab for refractory steroid-resistant nephrotic syndrome, of whom 9 patients achieved complete remission, 6 others achieved incomplete remission, and the remaining 7 did not respond [15].
A systematic review showed that the remission rate was 46.4% [16]. The review included the above-described open-label randomized controlled study reporting a remission rate of 18.8% [17], hence necessitating special caution in interpreting its results. Unlike steroid-sensitive nephrotic syndrome, refractory steroid-resistant nephrotic syndrome may include hereditary nephrotic syndrome, and past studies may have failed to strictly exclude such cases. Therefore, efficacy higher than that reported previously can be expected in patients for whom hereditary nephrotic syndrome is ruled out.

Remark 1
Remarks
Coenzyme Q10
Coenzyme Q10 deficiency is a mitochondrial disease that can progress to secondary nephrotic syndrome due to genetic abnormalities. Possible drug therapies for secondary nephrotic syndrome are described below. Progression of nephrotic syndrome can be suppressed by administering coenzyme Q10 at a high dose of 5-50 mg/kg/day for primary coenzyme Q10 deficiency [1,2].
Although the evidence level is not high, early administration will be useful. To this end, early diagnosis is important. While the timing of onset and symptoms are variable, treatment should be administered with attention paid to the existence of extrarenal symptoms and the timing of onset of steroid-resistant nephrotic syndrome.
For details of differences in symptoms and time of onset due to genetic abnormalities, please refer to the review by Otsuka [3].

2. Specifics

F. Long-term drug treatment for pediatric idiopathic nephrotic syndrome

[Summary]
1. It is acceptable to shift the method of remission induction from the international method (ISKDC regimen) to the same regimen used with adults after reaching the adult transition period or final height.

2. Although long-term administration of cyclosporine is unavoidable, attention should be paid to duration of use and blood concentrations, and the patient should be monitored for nephrotoxicity by performing a kidney biopsy as appropriate (refer to p. 18 “3. Kidney biopsy”).

3. Cyclophosphamide should only be used in 1 course, with the cumulative dose (should not exceed 300 mg/kg) in mind (refer to p. 50 “2. Specifics” “B. Treatment of frequently-relapsing and steroid-dependent nephrotic syndrome”).

4. When combining a steroid and more than one immunosuppressive agent, they should be used with a good understanding of their natures and side effects, and it is desirable that relapses during the growth period be minimized.

♦Commentary

In patients with childhood-onset idiopathic nephrotic syndrome who experience frequent relapses and steroid dependence, relapses are seen, not infrequently, during adulthood as well; long-term use of an immunosuppressive agent is often required [1,2].
Because of these features of the disease, caution should be exercised not to be too fearful about relapses from a short-term viewpoint, and to prevent life-long side effects from developing due to excessive treatment to avoid relapses. It is important that the long-term period of suffering is navigated safely; not only the attending physician, but also the patient’s family should understand the long-term treatment.
For long-term management of nephrotic syndrome, there is no high-quality evidence, such as randomized controlled studies. For example, clinical studies are conducted to investigate the short-term efficacy of each drug. Even if a long-term follow-up study is performed as part of such a clinical study, no more than long-term results under extremely limited conditions are obtained, and it is often difficult to apply the results to actual patients. When the disease is managed over a long period of time, the attending physician should understand the nature of each drug well in view of the clinical course and other circumstances of each patient and administer the treatment, while taking into account concomitant use of more than one drug, at his/her discretion [1,2].
Such management aims to minimize limitations from nephrotic syndrome and allow the patient to live a life similar to that of other healthy children, so as to reach adulthood with no physical, mental, or social disabilities. Specific goals will be to reduce hospitalizations and excessive limitations and to minimize the long-term use of steroids.
Upon first remission, the patient should be instructed that periodical testing for qualitative urinalysis at home is important to the early detection of relapses of nephrotic syndrome. If a relapse is noted after the development of edema, the likelihood of hospitalization required until remission will increase. At many facilities, ambulatory steroid treatment is administered upon relapse, which necessitates special caution against epidemic infections, i.e., chicken pox and measles. If contracted during immunosuppressive therapy, such infections can be fatal; therefore, history of vaccination and history of such infections should be checked, and in the absence of history of either, vaccination

should be administered as soon as possible. Under appropriate conditions, live vaccination can be performed safely during immunosuppressive therapy, which is to be investigated in the future [3].
It seems that if steroid medication is discontinued, with no relapses, after the start of an immunosuppressive agent, the immunosuppressive agent will be tapered and discontinued in 1 to 2 years at many facilities, and continuing the same immunosuppressive agent, in view of safety, until the final height is reached during the growth period will be considered. If a relapse occurs after discontinuation of the immunosuppressive agent, frequent relapse and steroid dependence can develop; repeated use of steroid during the growth period significantly influences the final height [4-6].
Therapeutic outcomes for steroid-resistant nephrotic syndrome have been improved by combining various immunosuppressive agents [7]; if such approach fails to achieve remission for a long time, renal failure is likely to occur eventually. If the therapeutic response is weak even with potent immunosuppressive therapy, it is important that the immunosuppressive therapy be discontinued and shifted to a kidney replacement therapy, so as to prevent the development of side effects only with no desired effect. The off-label use of immunosuppressive agents and biological products can induce unforeseeable adverse events, and can also interfere with clinical studies to seek an approval for additional indications; therefore, their use should be considered carefully. When off-label use is applied after taking specified procedures, it can be useful as it provides basic data for future clinical studies and additional indications.

1. Steroids
It seems acceptable to shift the method of remission induction from the international method (ISKDC regimen) to the same regimen as with adult use as appropriate after reaching the adult transition period or final height [8]. In a questionnaire-based survey of the board members of the Japanese Society for Pediatric Nephrology in 2010, opinions were variable: I) at post-pubertal age; change to the same regimen as the adult regimen (15 members, 30%), II) at post-pubertal age; daily administration at 40 mg or lower, followed by alternate-day administration (23 members, 46%), and III) post-pubertal age; same as the ISKDC regimen (14 members, 28%) [9]. No evidence exists showing respective advantages and disadvantages. Provided that remission can be induced by steroid administration and is shown to have no influence on subsequent relapses, the maximum dose of the steroid used to induce remission seems to be variable as appropriate. Not only for long-term management, but also in cases where a relapse occurs in a patient with femoral head necrosis, treatment is quite difficult because no drugs, other than steroid, are available for actual use to induce remission. It is necessary to minimize the steroid dose and treatment duration, and then to prevent relapses by immunosuppressive agent treatment, and risks should also be taken into account. Use of steroid during the long-term clinical course often requires a difficult choice for each patient; its acceptability should be determined after assessing what should be given the first priority according to the status of occurrence of side effects and other factors.

2. Cyclosporine
While many reports stated that long-term use is acceptable, it is necessary to pay special attention to the duration of use and blood concentrations, and to check for nephrotoxicity by kidney biopsy as appropriate [10-25]. Although some experts suggest that the course of nephrotic syndrome tends to be prolonged after introduction of cyclosporine, investigation is to be conducted to determine whether this is true. If cyclosporine is unavoidably administered for a long time, it is advisable that its blood concentration be kept lower than the target blood concentration recommended for initial treatment, as far as a reasonable effect is expected. Regarding the timing of blood sampling, blood concentrations show a higher correlation with AUC in terms of the value obtained 2 hours after oral medication just before a meal than the trough level [26]; however, caution should be exerted on the method of measurement. The trend is changing from enzyme immunoassay (EIA) to chemiluminescence immunoassay (CLIA), with data available to show lower values with CLIA [27-29]. Since EIA has been the mainstream method reported previously, adjusting the blood concentration using CLIA may pose a concern regarding increased nephrotoxicity; it is desirable that the method of measurement and conversion formula be confirmed at each facility.

3. Cyclophosphamide
Gonadal dysfunction has been shown to present a concern [30,31]; cyclophosphamide should only be used for 1 course during the clinical course, with the cumulative dose (should not exceed 300 mg/kg) in mind.

4. Mizoribine
Although it is not highly effective against frequently-relapsing and steroid-dependent nephrotic syndrome, mizoribine is expected to be somewhat effective against less severe nephrotic syndrome. Therefore, it is necessary to raise the blood concentration to about 3 μg/mL during 2 or 3 hours post dose [32]; a dose higher than the doses specified in the package insert (off-label use) is often required. Further assessments, including evidence for safety and long-term use, are awaited.

5. Rituximab
Although rituximab is effective for remission maintenance in childhood-onset refractory nephrotic syndrome (cases where frequent relapse or steroid dependence develops as remission cannot be maintained with conventional treatment), evidence for its long-term use is insufficient. Some rare but life-threatening side effects have been reported; indications should be determined carefully, and it is desirable that treatment be administered at a specialized facility.

6. Mycophenolate mofetil
Efficacy has been suggested in patients with frequently-relapsing and steroid-dependent nephrotic syndrome, including refractory cases [33,34]; in Western countries, mycophenolate mofetil is used for immunosuppressive therapy for the disease. In Japan, however, this represents off-label use, and hence may be considered only when standard immunosuppressive agents cannot be used for any reason.

7. Tacrolimus
A potential surrogate for cyclosporine to be discontinued due to cosmetic adverse reactions and for other reasons. In Japan, however, it represents off-label use, and no evidence is available of a safe and effective regimen for long-term use.