**Complications of nephrotic syndrome in children**

**Author:**

[Patrick Niaudet, MD](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/contributors)

**Section Editor:**

[Tej K Mattoo, MD, DCH, FRCP](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/contributors)

**Deputy Editor:**

[Melanie S Kim, MD](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/contributors)

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**INTRODUCTION**The nephrotic syndrome is caused by renal diseases that increase the permeability across the glomerular filtration barrier. It is classically characterized by four features, but the first two are used diagnostically because the last two may not be seen in all patients:

●Nephrotic range proteinuria – Urinary protein excretion greater than 50 mg/kg per day

●Hypoalbuminemia – Serum albumin concentration less than 3 g/dL (30 g/L)

●Edema

●Hyperlipidemia

Complications in children result from abnormalities directly related to the nephrotic syndrome and secondarily from therapy used for its treatment.

The five major complications directly related to the underlying nephrotic syndrome in children will be reviewed here:

●Infection

●Thromboembolism

●Renal insufficiency

●Anasarca

●Hypovolemia

The clinical manifestations, diagnosis, etiology, and treatment, including complications due to therapy in children with nephrotic syndrome, are discussed separately. (See ["Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children"](https://www.uptodate.com/contents/etiology-clinical-manifestations-and-diagnosis-of-nephrotic-syndrome-in-children?search=nephrotic+syndrome+children&topicRef=6102&source=see_link) and ["Treatment of idiopathic nephrotic syndrome in children"](https://www.uptodate.com/contents/treatment-of-idiopathic-nephrotic-syndrome-in-children?search=nephrotic+syndrome+children&topicRef=6102&source=see_link).)

**INFECTION**Children with nephrotic syndrome are at increased risk of infection. The following factors may contribute to this problem:

●Reduced serum concentrations of immunoglobulin G (IgG) [[1](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/1)]

●Impaired ability to make specific antibodies [[2](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/2)]

●Decreased levels of the alternative complement pathway factors B and D [[3-5](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/3-5)]

●Immunosuppressive therapy

The frequency and types of infection were evaluated in an observational study from India of 60 children with nephrotic syndrome who were not receiving glucocorticoid therapy [[6](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/6)]. There were 57 episodes of infection, which included:

●Upper respiratory infection – 16 episodes

●Urinary tract infection – 13 episodes

●Peritonitis – 9 episodes

●Pneumonia – 8 episodes

●Severe acute gastroenteritis – 6 episodes

●Empyema – 3 episodes

**Bacterial infection** — Children with nephrotic syndrome are at increased risk of developing serious bacterial infection, especially with encapsulated bacteria. This may be due in part to the loss of opsonizing factors, which may specifically increase susceptibility to encapsulated bacterial infection [[3,5](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/3,5)]. In addition, ascites and pleural effusions provide a natural culture media for bacterial growth. Thus, as noted in the above study, pneumonia, empyema, and peritonitis are infections seen in children with nephrotic syndrome [[6](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/6)].

In a retrospective review, 24 episodes of peritonitis occurred in 351 children with nephrotic syndrome over a 10-year period from 1970 to 1980 [[7](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/7)]. *Streptococcus pneumoniae was* the most common infectious agent, seen in 12 patients, followed by *Escherichia coli*in six, and negative cultures in four. Peritoneal signs of irritation were present in all patients, including in 16 who were receiving corticosteroid therapy.

In a retrospective study, eight episodes of peritonitis in seven patients over a five-year period were reported in 268 patients with nephrotic syndrome that was initially diagnosed as steroid sensitive [[8](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/8)]. In three cases the causative microorganism was identified as *S. pneumoniae*, *Streptococcus hemolyticus*, and *alpha-hemolytic Streptococcus*.

Sepsis, meningitis, and cellulitis are other serious infections that can occur in children with nephrotic syndrome [[9,10](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/9,10)]. Although not as serious, urinary tract infections are common [[6,11](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/6,11)].

Prior to 1940, the mortality rate in children with nephrotic syndrome was 40 percent, primarily due to infection [[12](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/12)]. Although the mortality rate has been significantly reduced with the introduction of corticosteroid treatment and antibiotics [[13,14](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/13,14)], infection still remains a cause of death in children with nephrotic syndrome. This was illustrated in an International Study of Kidney Disease in Children report of 10 deaths in a group of 389 children with minimal change disease (MCD) who were seen between 1967 and 1976 and were followed for 5 to 15 years [[15](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/15)]. Six of the deaths were due to infection, five were from sepsis (peritonitis as the primary site of infection in two), and one was due to peritonitis with pancreatitis. *S. pneumoniae*was isolated in two cases and *E. coli* in two other cases.

Because children with nephrotic syndrome are at increased risk for serious complications and potentially death from pneumococcal infection, they should receive 23-valent polysaccharide (PPSV23) pneumococcal vaccine if not previously immunized. Pneumococcal vaccine is effective even in children receiving high doses of steroids and it is not associated with an increased risk of relapse [[16](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/16)]. (See ["Pneumococcal vaccination in children", section on 'Immunization of high-risk children and adolescents'](https://www.uptodate.com/contents/pneumococcal-vaccination-in-children?sectionName=IMMUNIZATION+OF+HIGH-RISK+CHILDREN+AND+ADOLESCENTS&search=nephrotic+syndrome+children&topicRef=6102&anchor=H1271588764&source=see_link#H1271588764).)

**Viral infections** — Viral infections, particularly varicella, may be observed in children with nephrotic syndrome, especially in those receiving immunosuppressive therapy. Varicella can cause significant morbidity and mortality in such patients [[17-19](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/17-19)]. Treatment including vaccination is discussed in greater detail separately. (See ["Treatment of varicella (chickenpox) infection", section on 'Immunocompromised hosts'](https://www.uptodate.com/contents/treatment-of-varicella-chickenpox-infection?sectionName=Immunocompromised+hosts&search=nephrotic+syndrome+children&topicRef=6102&anchor=H1944532770&source=see_link#H1944532770).)

Although live attenuated viral vaccines have been discouraged for use in children receiving immunosuppressive therapy, a prospective study reported that administration of live attenuated vaccines was immunogenic and safe in children with nephrotic syndrome receiving immunosuppressive therapy [[20](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/20)]. However, the children in this study, who were in remission, had reasonable cellular and humoral immunologic function as inclusion criteria for this study included CD4+ cell count > 500/mm3, normal lymphocyte blast transformation by phytohemagglutinin, and serum IgG levels > 300 mg/dL. Additional studies are needed to confirm the safety, response rate and identify factors that may impact on immunogenicity prior to routine administration of life attenuated viral vaccines in children with nephrotic syndrome who are receiving immunosuppressive therapy.

Vaccination in children with nephrotic syndrome may cause a relapse but the protection offered from vaccines greatly outweigh this risk, which is in fact minimal [[21](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/21)].

**THROMBOEMBOLISM**Several factors contribute to an increased risk of thromboembolic complications in children with nephrotic syndrome:

●Hemoconcentration

●Immobility, especially in patients with anasarca

●Infection

●The presence of central venous catheter

●A possible underlying genetic thrombophilic tendency

In addition to these abnormalities, the nephrotic syndrome is associated with a hypercoagulable state due to thrombocytosis, and hemostatic abnormalities including decreased levels of antithrombin III, free protein S, and plasminogen (due to urinary losses), increased levels of procoagulant proteins (fibrinogen, and factors V and VIII), and increased platelet activation. (See ["Hypercoagulability in nephrotic syndrome", section on 'Pathogenesis'](https://www.uptodate.com/contents/hypercoagulability-in-nephrotic-syndrome?sectionName=PATHOGENESIS&search=nephrotic+syndrome+children&topicRef=6102&anchor=H6&source=see_link#H6).)

The reported incidence of thromboembolic complications in nephrotic children is between 2 and 3 percent [[22,23](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/22,23)]. In a retrospective study of 326 children with nephrotic syndrome from any cause diagnosed between 1999 and 2006, 9 percent had one thromboembolic event (TEE), resulting in an overall incidence of 20.4 patients with TEEs per 1000 patient-years [[22](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/22)]. The median time to TEE was approximately 71 days after diagnosis of nephrotic syndrome. Deep venous thrombosis was the most common TEE and was associated with the use of a central venous catheter. Multivariate analysis demonstrated that the risk of TEE was greater in children older than 12 years of age, and increased with increasing urinary protein excretion.

However, the true incidence of TEE may be higher, as many TEEs are asymptomatic. This was illustrated in a case series of 16 children with steroid-dependent minimal change disease [[24](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/24)]. Evaluation by ventilation-perfusion scans showed defects consistent with pulmonary embolism in 7 patients, residual changes in 10, and normal findings in only 9. In another study using dual energy computed tomography (CT) pulmonary angiography, 28 percent of children with nephrotic syndrome without respiratory symptoms had subclinical pulmonary embolism [[25](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/25)].

Both arterial and venous thromboses have been reported in children with nephrotic syndrome, although venous thrombosis complication accounted for most of the cases. [[22](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/22)]. The most common sites include the cerebral vein, pulmonary artery, renal vein, deep leg veins, inferior vena cava, and femoral/iliac artery [[26-29](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/26-29)]. Other reported sites include the cerebral and meningeal arteries, and mesenteric and hepatic veins [[26,30,31](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/26,30,31)].

Thromboembolic complications in children with nephrotic syndrome may be associated with significant morbidity, including cerebral venous thrombosis, pulmonary embolism, and renal vein thrombosis.

●Pulmonary embolism − As mentioned above, many pulmonary emboli are silent in children with nephrotic syndrome [[24](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/24)]. However, there are several case reports of significant morbidity from pulmonary embolism [[32-34](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/32-34)]. Pulmonary embolism should be suspected in patients with pulmonary or cardiovascular symptoms and can be confirmed by angiography or radioisotope scanning [[35](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/35)].

●Renal vein thrombosis − Infants with congenital nephrotic syndrome are at increased risk for renal vein thrombosis. Otherwise, renal vein thrombosis is rare in children with nephrotic syndrome, especially in comparison with adults. However, some children develop acute complete venous occlusion, which is characterized clinically by the sudden onset of macroscopic hematuria, flank pain and/or tenderness, and, in children with bilateral disease, acute renal failure. In such cases, Doppler ultrasonography shows an increase in kidney size and the absence of blood flow in the renal vein. (See ["Hypercoagulability in nephrotic syndrome", section on 'Pathogenesis'](https://www.uptodate.com/contents/hypercoagulability-in-nephrotic-syndrome?sectionName=PATHOGENESIS&search=nephrotic+syndrome+children&topicRef=6102&anchor=H6&source=see_link#H6).)

Prophylactic anticoagulation is not recommended unless the patient has had a TEE or has a high risk of thrombosis with albumin concentration of less than 2 g/dL (20 g/L), a fibrinogen level of more than 6 g/L, or an antithrombin III level less than 70 percent of normal. (See ["Symptomatic management of nephrotic syndrome in children", section on 'Hypercoagulability'](https://www.uptodate.com/contents/symptomatic-management-of-nephrotic-syndrome-in-children?sectionName=HYPERCOAGULABILITY&search=nephrotic+syndrome+children&topicRef=6102&anchor=H6&source=see_link#H6).)

**RENAL INSUFFICIENCY**At presentation, children with nephrotic syndrome can have reduced glomerular filtration rate (GFR) because of one or more of the following mechanisms [[36](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/36)]:

●Hypovolemia − Children with nephrotic syndrome, especially those with minimal change disease, can have a transient decrease in GFR due to hypovolemia that returns to normal after repletion of their vascular volume [[37-39](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/37-39)].

●Acute kidney injury (AKI) in children, although uncommon, may occur as a complication of infection, acute tubular necrosis (secondary to significant hypovolemia), allergic interstitial nephritis (due to antibiotics or nonsteroidal antiinflammatory drugs), drug toxicity, such as calcineurin-inhibitors ([cyclosporine](https://www.uptodate.com/contents/cyclosporine-ciclosporin-pediatric-drug-information?search=nephrotic+syndrome+children&topicRef=6102&source=see_link) or [tacrolimus](https://www.uptodate.com/contents/tacrolimus-pediatric-drug-information?search=nephrotic+syndrome+children&topicRef=6102&source=see_link), which are often used in children with steroid-dependent nephrotic syndrome) or angiotensin-converting enzyme (ACE) inhibitors [[38,40](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/38,40)]. AKI occurs more frequently in patients who are hospitalized. In a report from the Midwest Pediatric Nephrology Consortium, almost 60 percent of children hospitalized developed AKI [[40](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/40)]. Associated factors included steroid-resistant nephrotic syndrome, infection, and exposure to nephrotoxic medication.

●Underlying glomerular pathology − In children with nephrotic syndrome, primary renal disease (eg, primary membranoproliferative glomerulonephritis [[37](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/37)]) or secondary renal disease (eg, postinfectious glomerulonephritis or lupus nephritis) can present with renal insufficiency due to glomerular injury. (See ["Focal segmental glomerulosclerosis: Treatment of primary focal segmental glomerulosclerosis", section on 'Severity of renal dysfunction'](https://www.uptodate.com/contents/focal-segmental-glomerulosclerosis-treatment-of-primary-focal-segmental-glomerulosclerosis?sectionName=Severity+of+renal+dysfunction&search=nephrotic+syndrome+children&topicRef=6102&anchor=H5&source=see_link#H5) and ["Poststreptococcal glomerulonephritis"](https://www.uptodate.com/contents/poststreptococcal-glomerulonephritis?search=nephrotic+syndrome+children&topicRef=6102&source=see_link) and ["Diagnosis and classification of renal disease in systemic lupus erythematosus"](https://www.uptodate.com/contents/diagnosis-and-classification-of-renal-disease-in-systemic-lupus-erythematosus?search=nephrotic+syndrome+children&topicRef=6102&source=see_link).)

Minimal change disease (MCD), which is the most common form of nephrotic syndrome in children, particularly in those younger than age six years, may present with mild elevations in serum creatinine, but substantial declines in GFR are uncommon. In one study, a decrease in GFR appeared to correlate with an increased degree of fusion of the foot processes [[41](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/41)]. (See ["Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children"](https://www.uptodate.com/contents/etiology-clinical-manifestations-and-diagnosis-of-nephrotic-syndrome-in-children?search=nephrotic+syndrome+children&topicRef=6102&source=see_link) and ["Acute kidney injury (AKI) in minimal change disease and other forms of nephrotic syndrome"](https://www.uptodate.com/contents/acute-kidney-injury-aki-in-minimal-change-disease-and-other-forms-of-nephrotic-syndrome?search=nephrotic+syndrome+children&topicRef=6102&source=see_link).)

Progression to chronic or end-stage renal failure can occur in some patients, especially those who with steroid-resistant nephrotic syndrome. (See ["Treatment of idiopathic nephrotic syndrome in children", section on 'Outcome based upon response'](https://www.uptodate.com/contents/treatment-of-idiopathic-nephrotic-syndrome-in-children?sectionName=Outcome+based+upon+response&search=nephrotic+syndrome+children&topicRef=6102&anchor=H174702423&source=see_link#H174702423).)

**ANASARCA**Anasarca (generalized and massive edema) can be associated with the following complications:

●Inability to walk because of severe scrotal or vulvar edema

●Respiratory distress from large pleural effusions, and/or massive ascites, which can impair diaphragmatic movement

●Tissue breakdown and cellulitis

In some circumstances, patients with anasarca can be treated with salt-poor albumin with [furosemide](https://www.uptodate.com/contents/furosemide-pediatric-drug-information?search=nephrotic+syndrome+children&topicRef=6102&source=see_link) to improve their edema [[42](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/42)]. (See ["Symptomatic management of nephrotic syndrome in children"](https://www.uptodate.com/contents/symptomatic-management-of-nephrotic-syndrome-in-children?search=nephrotic+syndrome+children&topicRef=6102&source=see_link).)

**HYPOVOLEMIA**Despite the marked increase in extracellular fluid volume, some children with nephrotic syndrome, primarily those with minimal change disease (MCD), present with or develop signs of a decrease in effective circulating volume such as tachycardia, peripheral vasoconstriction, oliguria, decreased glomerular filtration rate, and elevation of plasma renin aldosterone [[39](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/39)]. Hypovolemia typically occurs early at onset of nephrosis or during a relapse. In such children, a further insult such as diuretic therapy, sepsis, or diarrhea can lead to hypotension and, rarely, shock [[43](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/43)].

**GROWTH**Growth can be adversely affected in patients with persistent nephrotic syndrome or as a complication of long-term steroid therapy in patients with steroid-dependent nephrotic syndrome. (See ["Treatment of idiopathic nephrotic syndrome in children", section on 'Steroid side effects'](https://www.uptodate.com/contents/treatment-of-idiopathic-nephrotic-syndrome-in-children?sectionName=Steroid+side+effects&search=nephrotic+syndrome+children&topicRef=6102&anchor=H13&source=see_link#H13) and ["Causes of short stature", section on 'Glucocorticoid therapy'](https://www.uptodate.com/contents/causes-of-short-stature?sectionName=Glucocorticoid+therapy&search=nephrotic+syndrome+children&topicRef=6102&anchor=H543524649&source=see_link#H543524649).)

**OTHER POTENTIAL COMPLICATIONS**Other potential complications that may occur in children with nephrotic syndrome include:

●Persistent hyperlipidemia increases the risk of early atherosclerosis. Dyslipidemia also increases the risks of progressive renal disease and thromboembolism [[44](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/44)]. (See ["Overview of risk factors for development of atherosclerosis and early cardiovascular disease in childhood", section on 'Chronic kidney disease'](https://www.uptodate.com/contents/overview-of-risk-factors-for-development-of-atherosclerosis-and-early-cardiovascular-disease-in-childhood?sectionName=Chronic+kidney+disease&search=nephrotic+syndrome+children&topicRef=6102&anchor=H3181068732&source=see_link#H3181068732).)

●Anemia – Patients with persistent nephrotic syndrome may develop anemia due to urinary losses of iron, transferrin, erythropoietin, transcobalamin, and/or metals such as copper [[45](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/45)].

●Abnormal endocrine tests and possible function – Patients with nephrotic syndrome may have low total T4 and T3 levels but normal serum free T4 and T3 and thyrotropin (TSH) concentrations, and as a result are usually clinically euthyroid. In addition, serum calcidiol (25-hydroxyvitamin D) and calcitriol concentrations may be reduced [[46](https://www.uptodate.com/contents/complications-of-nephrotic-syndrome-in-children/abstract/46)], but the physiologic serum free calcitriol concentration is normal. (See ["Endocrine dysfunction in the nephrotic syndrome", section on 'Thyroid function tests'](https://www.uptodate.com/contents/endocrine-dysfunction-in-the-nephrotic-syndrome?sectionName=THYROID+FUNCTION+TESTS&search=nephrotic+syndrome+children&topicRef=6102&anchor=H2&source=see_link#H2) and ["Endocrine dysfunction in the nephrotic syndrome", section on 'Vitamin D and calcium metabolism'](https://www.uptodate.com/contents/endocrine-dysfunction-in-the-nephrotic-syndrome?sectionName=VITAMIN+D+AND+CALCIUM+METABOLISM&search=nephrotic+syndrome+children&topicRef=6102&anchor=H6&source=see_link#H6).)

**SOCIETY GUIDELINE LINKS**Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See ["Society guideline links: Nephrotic syndrome in children"](https://www.uptodate.com/contents/society-guideline-links-nephrotic-syndrome-in-children?search=nephrotic+syndrome+children&topicRef=6102&source=see_link).)

**SUMMARY**Complications result from abnormalities directly related to the nephrotic syndrome. They include the following:

●Infection − Children with nephrotic syndrome have increased susceptibility to encapsulated bacterial infection, particularly peritonitis because of defects in humoral immunity. Although antibiotics have reduced the mortality rate of nephrotic syndrome due to infection, infection still remains a cause of death in children with nephrotic syndrome. (See ['Infection'](https://www.uptodate.com/index.html#H2) above.)

●Anasarca − Anasarca (generalized and massive edema) can cause respiratory distress (eg, large pleural effusions and/or massive ascites) and skin breakdown with an increased risk of cellulitis, and increases the risk of bacterial peritonitis. (See ['Anasarca'](https://www.uptodate.com/index.html#H7) above and ['Bacterial infection'](https://www.uptodate.com/index.html#H3) above.)

●Thrombosis − Children with nephrotic syndrome are at increased risk for thrombosis due primarily to hypercoagulability from thrombocytosis and hemostatic abnormalities. Arterial and venous thromboses occur and involve a variety of different sites. (See ['Thromboembolism'](https://www.uptodate.com/index.html#H5) above.)

●Renal insufficiency − Children with nephrotic syndrome can have transient impaired renal function at presentation because of hypovolemia, or persistent renal insufficiency because of glomerular injury from the underlying disease process. (See ['Renal insufficiency'](https://www.uptodate.com/index.html#H6) above.)

●Hypovolemia − Significant hypovolemia in children with nephrotic syndrome can be associated with hypotension, abdominal pain, and cold poorly perfused extremities. In rare and severe cases, shock can occur. (See ['Hypovolemia'](https://www.uptodate.com/index.html#H8) above.)

●Growth − Poor growth can be seen in patients with persistent nephrotic syndrome or in patients with steroid-dependent nephrotic syndrome who are treated with long-term steroid therapy.

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