KDIGO GN Guideline update – Evidence summary

Steroid-resistant nephrotic syndrome in children

Immunosuppressive therapy to treat steroid-resistant nephrotic syndrome

PICO question
In children with steroid-resistant nephrotic syndrome, what immunosuppressive therapy compared to no placebo or other immunosuppressive medication improves efficacy outcomes (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, relapse) and reduce adverse effects (infection, and malignancy)?

Search strategy and selection
All randomized control trials (RCTs) and quasi-RCTs, in which different immunosuppressive agents were used in the treatment of children (aged three months to 18 years) with idiopathic SRNS, were searched using Medline, EMBASE, and CENTRAL in 2004, 2006, 2010 and 2016. The Cochrane Kidney and Transplant Specialized Register was searched for all randomized control trials (RCTs) examining immunosuppressive therapy in children with steroid-resistant nephrotic syndrome up to April 2018.

Search results
The initial 2004 version of the review, 1744 relevant citations identified, one RCT was excluded, and nine RCTs were included in the review. Two updates have been published (2006 and 2010), and the 2016 review update identified 46 reports from the Cochrane Kidney and Transplant Specialized Register. Overall the 2016 update included 19 primary studies (42 reports) with 820 children. Three reports were on-going studies. The April 2018 search update identified 23 reports, seven (18 reports) new RCTs were included, two reports of RCTs previously included the 2016 Cochrane review were found, and three studies (3 reports) were excluded because they were not RCTs, or included the wrong population. Overall a total of 24 studies were included (1041 participants) and three ongoing studies identified. There were 15 comparisons. Most comparisons only included one to three studies with few patients.

Summary of the main findings

Immunosuppression compared with no treatment/placebo or steroids

- Cyclosporin compared with placebo or no treatment may increase complete remission (RR 7.66, 95%CI 1.06 to 55.34; 4 studies, 49 children). We are uncertain on infection due to very serious imprecision and very serious study limitations. Other critical and important outcomes were not reported in RCTs. Children with FSGS in these studies are presented in the forest plots, however, there was little or no effect on complete remission.
- For complete remission oral cyclophosphamide compared with steroids or placebo may have little or no effect (RR 1.05, 95%CI 0.61 to 1.87, 2 studies, 84 children). We are uncertain whether oral cyclophosphamide compared with steroids alone or placebo increases or decreases all-cause mortality because of very low certainty of the evidence and other critical and important outcomes were not reported in RCTs.
• We are uncertain whether azathioprine compared with placebo increases or decreases complete remission (RR 0.94, 95%CI 0.15 to 5.84; 1 study, 30 participants). Other critical and important outcomes were not examined in the RCT.

Calcineurin inhibitors versus other immunosuppression
• Calcineurin inhibitors compared with IV cyclophosphamide may increase complete remission at 3 to 6 months (RR 3.43, 95%CI 1.84 to 6.41; 2 studies, 15 children), it may have little or no effect on all-cause mortality (RR 0.33, 95%CI 0.01 to 7.92; 1 study, 131 children). We are uncertain whether cyclosporin compared with placebo or no treatment increases or decreases infection due to very serious study limitations and very serious imprecision. Other critical and important outcomes were not reported in RCTs.

Calcineurin inhibitors versus other immunosuppression
• Compared with mycophenolate mofetil with dexamethasone, cyclosporin may have little or no effect on complete remission at 6 months (RR 1.14, 95%CI 0.64 to 2.03) and 12 months (RR 0.80, 95%CI 0.45 to 1.42), based on 41 children from one RCT.

Tacrolimus versus cyclosporin
• Treatment with tacrolimus compared with cyclosporin may have little or no effect on complete remission at 6 months (RR 1.14, 95%CI 0.64 to 2.03) and 12 months (RR 0.80, 95%CI 0.45 to 1.42), based on data from 41 children in one RCT. The effect on infection (including sepsis or pneumonia) and annual GFR loss could not be determined due to very low certainty of the evidence. No studies were found that looked at all-cause mortality, end-stage kidney disease, ≥50% GFR loss, or malignancy.

Mycophenolate mofetil versus cyclophosphamide
• One small RCT (11 children) examined mycophenolate mofetil with cyclophosphamide and found that mycophenolate mofetil may have little or no effect on complete remission at 6 months (RR 0.90, 95%CI 0.36 to 2.24) and at 12 months (RR 1.20, 95%CI 0.41 to 3.51).

Leflunomide versus other immunosuppressive therapy
• One small RCT (12 children) compared leflunomide with mycophenolate mofetil and found it may have little or no effect on complete remission at 6 months (RR 1.61, 95%CI 0.51 to 2.80), and at 12 months (RR 1.19, 95%CI 0.51 to 2.80).
• One small RCT (12 children), compared leflunomide with cyclophosphamide and found it may have little or no effect on complete remission at 6 months (RR 1.46, 95%CI 0.82 to 2.61) and 12 months (RR 1.19, 95%CI 0.51 to 2.80). Other critical and important outcomes were not examined.
• No studies comparing leflunomide with another immunosuppressive therapy were found that looked at all-cause mortality, end-stage kidney disease, ≥50% GFR loss, infection, malignancy, or annual GFR loss.
**Intravenous cyclophosphamide versus oral cyclophosphamide**

- Intravenous compared with oral cyclophosphamide may have little or no difference on complete remission (RR 1.68, 95%CI 0.79 to 3.58) and infection (RR 1.41, 95%CI 0.05 to 41.41; 2 studies, 46 children). Other critical and important outcomes were not examined in RCTs.

**Intravenous cyclophosphamide versus oral cyclophosphamide plus IV dexamethasone (1 study, 46 children)**

- IV cyclophosphamide compared to oral cyclophosphamide plus IV dexamethasone may have little or no effect on complete remission (RR 1.13, 95%CI 0.65 to 1.96) and sustained remission/steroid sensitive relapses (RR 1.13, 95%CI 0.65 to 1.96). It may also have little or no effect on bacterial infections (RR 0.66, 95%CI 0.27 to 1.26) and urinary tract infections (RR 4.44, 95%CI 0.22 to 88.04), and corticosteroid-related adverse effects including; steroid encephalopathy (RR 0.30, 95%CI 0.01 to 6.94), cataract/glaucoma (RR 1.77, 95%CI 0.17 to 18.26), Cushingoid features (RR 0.78, 95%CI 0.52 to 1.17). However, it probably decreases hypertension (RR 0.04, 95%CI 0.00 to 0.68) and hypokalemia (RR 0.06, 95%CI 0.00 to 0.98).

**Chlorambucil versus indomethacin**

- We are uncertain whether chlorambucil compared with indomethacin increases or decreases end-stage kidney disease or complete remission due to the very low certainty of the evidence because of study limitations and imprecision in the effect estimates. Other critical and important outcomes were not examined in this small RCT (30 children).

**Effect modifiers**

The following effect modifiers were considered:

- Kidney function (GFR, proteinuria, presence of albuminuria)
- Relapse
- Primary vs. secondary forms of disease
- Genetic markers
- Gender

However, there was insufficient data from the RCTs to examine effect modifiers in children with steroid-resistant nephrotic syndrome.

**Studies from the 2012 KDIGO GN guideline evidence tables not included in 2018 evidence review.**

All RCTs included in the previous guideline evidence summary have been included in this evidence review, except for Hafeez et al. 2005 as this is not an RCT.