PO1643

DEFINE: Physicians – An International Delphi Survey to Identify Consensus in the Care of Patients with Focal Segmental Glomerulosclerosis/Idiopathic Nephrotic Syndrome

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Background

- Focal segmental glomerulosclerosis (FSGS) is a histopathologic pattern of podocyte injury that is often characterized by the presence of nephrotic syndrome
  - In pediatric patients, steroid-resistant nephrotic syndrome (SRNS) is an indication for kidney biopsy and most commonly associated with FSGS histologically
- There are currently no US Food and Drug Administration or European Medicines Agency-approved medications specifically for patients with FSGS

Rationale

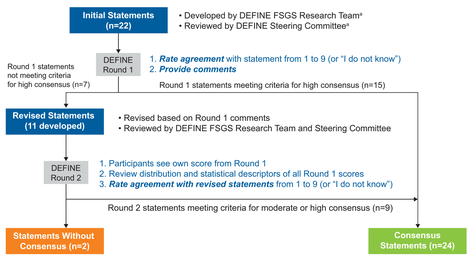
- The extent to which practicing physicians agree with and apply clinical practice guidelines (eg, Kidney Disease: Improving Global Outcomes [KDIGO] or International Pediatric Nephrology Association [IPNA])[1-3] for the management of patients with FSGS and pediatric SRNS is unknown
- The ***De**lphi **F**ocal Segmental Glomerulosclerosis (FSGS) & **I**gA **N**ephropathy (IgAN) **E**xperts: Physicians (DEFINE: Physicians)* project aimed to characterize physicians' consensus opinions on pathophysiology, diagnosis, and optimal management of FSGS/SRNS or IgAN
- Consensus opinions on the diagnosis and optimal management of IgAN are presented in the companion poster (PO1641, abstract #3604214)

Methods

- *DEFINE: Physicians* was an online 2-round Delphi survey that recruited nephrologists from Canada, France, Germany, Italy, Spain, the United Kingdom, and the United States
- Nephrologists scored 22 statements on FSGS/SRNS using a 1-9 Likert scale (1=strongly disagree; 9=strongly agree) with an additional option of "I do not know"
  - Free-text responses were also collected from participants who rated their agreement ≤6
- Consensus was defined as a median and mean agreement score of ≥7 and ≥75% of participants scoring agreement (ie, score 7-9)
  - Statements with ≥90% agreement were considered to have high consensus among the participants
  - Statements with 75% to 89% agreement were considered to have moderate consensus among the participants
- Statements not achieving high consensus in Round 1 were revised based on the free-text response and retested in Round 2 (**Figure 1**)

Results

Figure 1. Overview of *DEFINE: Physicians'* methodology and study results



[a]The DEFINE Steering Committee and FSGS Research Team are groups of experts on the treatment of FSGS and are the authors of this poster.

Survey participants

- Characteristics of the 207 nephrologists participating in Round 1 of the survey (November 17, 2020-January 14, 2021) are presented in **Table 1**
  - Round 2 of the survey (March 29, 2021-April 13, 2021) was completed by 80% of adult nephrologists and 64% of pediatric nephrologists from Round 1

Table 1. Key characteristics of participants

Characteristic	Nephrologists	
	Adult n=157	Pediatric n=50
Experience as a practicing nephrologist in years, median (range)	18 (5-49)	17 (5-40)
No. of patients with FSGS in the last 2 years,[a] median (IQR)	20 (10-40)	30 (12-60)
Practice setting, n (%)		
Academic center or academic hospital	70 (45)	34 (68)
Nonacademic	87 (55)	16 (32)
Country of practice, n (%)		
United States	69 (44)	26 (52)
Italy	19 (12)	4 (8)
Germany	14 (9)	7 (14)
United Kingdom	15 (10)	5 (10)
France	17 (11)	2 (4)
Spain	13 (8)	5 (10)
Canada	10 (6)	1 (2)
Participants referencing ≥1 clinical guideline when treating patients,[b] n (%)	144 (92)	47 (94)
KDIGO	138 (88)	33 (66)
IPNA	7 (4)	27 (54)

FSGS, focal segmental glomerulosclerosis; IPNA, International Pediatric Nephrology Association; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes.
[a]Refers to patients diagnosed or treated.
[b]Participants were able to select multiple guidelines.

Statements with high consensus in Round 1

- Criteria for high consensus were met for 15 of the 22 (68%) statements in Round 1 (**Table 2**)
  - All 4 pathophysiology statements and 11 of 18 diagnosis- and treatment-focused statements had high consensus

Table 2. Statements with high consensus in Round 1

		Statements rated by all participants	Agreement in Round 1
Pathophysiology	1	Persistently elevated proteinuria is a major adverse prognostic marker in FSGS and IgAN.	97%
Pathophysiology	2	Damage to podocytes and other glomerular cells are amplified by activation of angiotensin and/or endothelin pathways, contributing to high levels of proteinuria and greater risk for progressive kidney injury.	92%
Pathophysiology	3	Persistent proteinuria causes tubulointerstitial injury by inducing and amplifying inflammation, fibrosis, and kidney scarring, thereby driving further disease progression.	98%
Pathophysiology	4	A close correlation exists between the level of proteinuria and the risk of kidney failure; the higher the proteinuria the higher the risk of kidney failure.	96%
Diagnosis	5	FSGS is a disease characterized by physiological and histological evidence of glomerular injury in a typical pattern of lesions. Due to diverse etiologies and pathogenic mechanisms underlying the FSGS lesion, the disease can be broadly subdivided into four forms: primary FSGS, secondary FSGS, genetic FSGS, and FSGS of undetermined cause.	94%
		Statements rated by adult nephrologists only	
Diagnosis	7	Patients with nonnephrotic proteinuria and those with nephrotic-range proteinuria but without hypoalbuminemia require optimized supportive therapy with the goal of reducing proteinuria as much as possible.	96%
Diagnosis	8	Patients with nephrotic syndrome (proteinuria >3.5 g/day and serum albumin <30 g/L) exhibit the highest severity of the disease and require a more aggressive therapeutic approach.	97%
Treatment	11	For persistent proteinuria, ACE-I/ARBs are used as the basis of optimized supportive maintenance therapy.	99%
Treatment	12	In patients with nephrotic syndrome who do not tolerate or are resistant to corticosteroids (proteinuria >3.5 g/day with <50% reduction from baseline despite 16 weeks of steroid use), CNIs may be considered.	97%
Monitoring/follow-up	19	In both FSGS and IgAN, the goal of therapy is to reduce proteinuria as much as safely possible in order to preserve kidney function as evidenced by stable or improved GFR.	98%
		Statements rated by pediatric nephrologists only	
Diagnosis	9	In children, the risk for kidney failure is highly dependent on the response to therapy; patients responsive to steroids are at low risk, patients without complete remission with steroids but responsive to CNIs are at intermediate risk, and patients without remission in response to steroids or CNIs are at highest risk.	96%
Treatment	15	In children with NS, oral prednisolone is the standard-of-care initial treatment. Absence of remission after 4 (up to 8) weeks of prednisolone treatment suggests a diagnosis of SRNS.	98%
Treatment	16	In children with infrequently relapsing NS, frequently relapsing, and/or steroid-dependent NS, corticosteroids are repeated to treat a relapse.	94%
Treatment	18	Treatment options for pediatric patients with steroid-resistant NS are cyclosporine or tacrolimus and RAAS blockade (ACE-I or ARB).	96%
Monitoring/follow-up	21	The goal of therapy is to reduce proteinuria as much as safely possible in order to preserve kidney function as evidenced by stable or improved GFR.	96%

Pathophysiology; Diagnosis; Treatment; Monitoring/follow-up; High consensus (≥90% agreement); Moderate consensus (75-89% agreement); No consensus (<75% agreement)

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; IgAN, IgA nephropathy; NS, nephrotic syndrome; RAAS, renin-angiotensin-aldosterone system; SRNS, steroid-resistant nephrotic syndrome..

Statements with moderate consensus in Round 1

- Moderate consensus was reached for 5 of 22 (23%) statements (**Table 3**)

Table 3. Statements with moderate consensus in Round 1 that were updated and retested in Round 2

		Statements rated by adult nephrologists	Agreement in Round 1	Revised Statement	Agreement in Round 2
Treatment	10	In primary FSGS, immunosuppression is used as initial therapy.	82%	In patients with primary FSGS and well-controlled blood pressure, corticosteroids are used as first-line therapy to induce remission.	88%
Treatment	13	In cases of relapse for steroid-sensitive FSGS (proteinuria >3.5 g/d and serum albumin <30 g/L), a repeat course of corticosteroids is used.	89%	In steroid-sensitive FSGS (proteinuria >3.5 g/d and serum albumin <30 g/L), infrequent relapse is treated with a repeat course of corticosteroids.	87%
Treatment	14	Use of corticosteroids in patients with genetic forms of FSGS is largely ineffective and should be avoided.	82%	In adult patients with a documented genetic cause of FSGS, corticosteroids are ineffective.	86%
Monitoring/follow-up	20	During the initial phase of treatment, monitor the patient every 1-3 months. If the patient has persistent proteinuria, monitor every 4-6 months. If the patient becomes nephrotic again, monitor more frequently.	88%	In the initial phase of treatment, monitor the patient at least monthly.	90%
				For patients in remission, monitor every 3-6 months thereafter.	90%
		Statements rated by pediatric nephrologists			
Monitoring/follow-up	22	In children with NS, monitor proteinuria every few days using a dipstick at home. Once in complete remission, monitor proteinuria every 1-4 weeks using a dipstick at home (for up to 2 years).	84%	In children with FSGS/steroid-resistant NS, monitor proteinuria at diagnosis and at least every 3 months using laboratory testing.	66%
				In children with NS, monitor proteinuria daily during induction therapy using a dipstick at home.	88%
				In children with NS in complete remission, monitor proteinuria every 1-4 weeks, or daily if a respiratory infection occurs, using a dipstick at home for up to 2 years.	91%

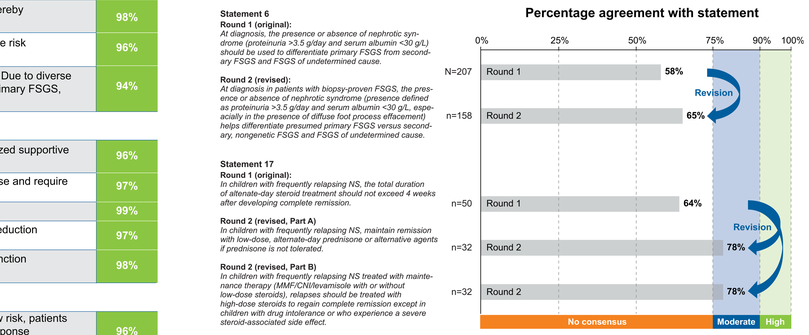
Pathophysiology; Diagnosis; Treatment; Monitoring/follow-up; High consensus (≥90% agreement); Moderate consensus (75-89% agreement); No consensus (<75% agreement)

FSGS, focal segmental glomerulosclerosis; NS, nephrotic syndrome. Based on McNemar's test, the differences in percentage of agreement between Round 1 and Round 2 statements were not statistically significant.

Statements not meeting criteria for moderate or high consensus in Round 1

- Of the 22 statements in Round 1, there were 2 statements that did not meet criteria for moderate or high consensus (**Figure 2**)

Figure 2. Scoring of statements without consensus and revisions



CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; MMF, mycophenolate mofetil; NS, nephrotic syndrome.

Discussion

- Most statements reached high levels of consensus and were aligned with the 2021 KDIGO guideline, suggesting that understanding of pathophysiology and optimal management of adults and children with FSGS is relatively homogeneous
- There was relatively less consensus on how best to differentiate primary FSGS from secondary FSGS, nongenetic FSGS, and FSGS of undetermined cause, as well as on the optimal frequency and method of proteinuria monitoring in children with FSGS/SRNS
  - These are new definitions of FSGS[3] and the lack of consensus observed highlights the controversial nature of this new classification
- *DEFINE: Physicians* demonstrated consensus that it is important to reduce proteinuria as much as possible
  - Neither the 2012 nor the 2021 KDIGO guidelines explicitly state this as a treatment goal,[1,3] but the 2021 guideline notes as a general practice point that proteinuria remission is a desirable goal in FSGS

Conclusion

- High consensus was observed among participating adult and pediatric nephrologists regarding the importance of reducing proteinuria, indications for immunosuppressive treatments, and monitoring of proteinuria in adults
- Areas of less than moderate consensus included how best to differentiate forms of FSGS and proteinuria monitoring in children with SRNS, suggesting that these areas may require further research and education

References

1. International Society of Nephrology. *Kidney Int.* 2012;(suppl 2):139-274.
2. Trautmann A, et al. *Pediatr Nephrol.* 2020;35:1529-1561.
3. International Society of Nephrology. *Kidney Int.* 2021;100(suppl).S1-S276.

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Disclosures

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Contact Information

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