

Childhood Nephrotic Syndrome

Thomas C. Hicks, MD, MPH

November 9, 2013

- 1 Introduction
- 2 Steroid Sensitive Nephrotic Syndrome
- 3 Frequent Relapse/Steroid Dependent Therapy
- 4 Steroid Resistant Nephrotic Syndrome

Introduction
Steroid Sensitive Nephrotic Syndrome
Frequent Relapse/Steroid Dependent Therapy
Steroid Resistant Nephrotic Syndrome

Introduction

Steroid Sensitive Nephrotic Syndrome
Frequent Relapse/Steroid Dependent Therapy
Steroid Resistant Nephrotic Syndrome

Case Definition
Resources
Epidemiology

Introduction

Introduction

Steroid Sensitive Nephrotic Syndrome
Frequent Relapse/Steroid Dependent Therapy
Steroid Resistant Nephrotic Syndrome

Case Definition

Resources
Epidemiology

Case Definition

Introduction

Steroid Sensitive Nephrotic Syndrome
Frequent Relapse/Steroid Dependent Therapy
Steroid Resistant Nephrotic Syndrome

Case Definition

Resources
Epidemiology

Let's get started!



Thomas C. Hicks, MD, MPH

Childhood Nephrotic Syndrome



What kind of patients are we talking about anyway?

Nephrotic Syndrome Children over the age of 1 year

Edema

Urine Protein:Creatinine ratio (uPCR) $\geq 2000\text{mg/g}$

Urine Protein $> 300\text{mg/dL}$

Dipstick Urine protein 3+

Hypoalbuminemia ($\leq 2.5\text{mg/L}$)

What is missing from the case definition?

Introduction

Steroid Sensitive Nephrotic Syndrome
Frequent Relapse/Steroid Dependent Therapy
Steroid Resistant Nephrotic Syndrome

Case Definition

Resources

Epidemiology

Resources

Important resources to know

- ISKDC - International Study of Kidney Disease in Children

Important resources to know

- ISKDC - International Study of Kidney Disease in Children
- KDIGO - Kidney Disease: Improving Global Outcomes
(www.kdigo.org/home/glomerulonephritis-gn)

Introduction

Steroid Sensitive Nephrotic Syndrome
Frequent Relapse/Steroid Dependent Therapy
Steroid Resistant Nephrotic Syndrome

Case Definition

Resources

Epidemiology

Epidemiology

Obligatory Epidemiology Slide

- 1-3 (some reports as high as 7)/100,000 children under the age of 16

Obligatory Epidemiology Slide

- 1-3 (some reports as high as 7)/100,000 children under the age of 16
- Black and Hispanic kids in the US more likely to have steroid resistant disease

Obligatory Epidemiology Slide

- 1-3 (some reports as high as 7)/100,000 children under the age of 16
- Black and Hispanic kids in the US more likely to have steroid resistant disease
- Male to Female - from 2:1 to 3:2 in young children, equal in older kids (>8yo)

Obligatory Epidemiology Slide

- 1-3 (some reports as high as 7)/100,000 children under the age of 16
- Black and Hispanic kids in the US more likely to have steroid resistant disease
- Male to Female - from 2:1 to 3:2 in young children, equal in older kids (>8yo)
- Lower incidence of steroid sensitive nephrotic syndrome in African children

Obligatory Epidemiology Slide

- 1-3 (some reports as high as 7)/100,000 children under the age of 16
- Black and Hispanic kids in the US more likely to have steroid resistant disease
- Male to Female - from 2:1 to 3:2 in young children, equal in older kids (>8yo)
- Lower incidence of steroid sensitive nephrotic syndrome in African children
- Increased incidence (all types) in Asians (up to 6 times increase in some studies)

Steroid Sensitive Nephrotic Syndrome

Case - Xiao Ma

Xiao Ma - The case

Xiao Ma is a 3YO Asian male who presented to his local doc 3 days ago with puffy eyes. The local doc gave chlorpheniramine and sent him home. He comes back today with extension of the swelling to the feet and legs.

Xiao Ma - The discussion

- Most likely what time of day did he present initially?

Xiao Ma - The discussion

- Most likely what time of day did he present initially?
- What tests do you want to do?

Xiao Ma - The discussion

- Most likely what time of day did he present initially?
- What tests do you want to do?
- What therapy should you start?

Xiao Ma - The discussion

- Most likely what time of day did he present initially?
- What tests do you want to do?
- What therapy should you start?
- What is the most important predictor of outcome in Xiao Ma's case?

Initial Therapy

Initial approach to therapy for Childhood Nephrotic Syndrome

- Steroids are the mainstay

Initial approach to therapy for Childhood Nephrotic Syndrome

- Steroids are the mainstay
- Initial dose is 2mg/kg/day or 60mg/m²/day in single daily dose

Initial approach to therapy for Childhood Nephrotic Syndrome

- Steroids are the mainstay
- Initial dose is 2mg/kg/day or 60mg/m²/day in single daily dose
- Don't reduce the dose for at least 4 weeks, better to go for 6 weeks

Initial approach to therapy for Childhood Nephrotic Syndrome

- Steroids are the mainstay
- Initial dose is 2mg/kg/day or 60mg/m²/day in single daily dose
- Don't reduce the dose for at least 4 weeks, better to go for 6 weeks
- Follow up dose of 1.5mg/kg alternate days and tapered over 2 - 5 months

Why so long?

Hodson, et.al. did some meta-analysis of RCTs using steroid therapy regimens.

Objective	Result	Stats stuff
3 vs. 2 months	30% relapse reduction	RR 0.7 (0.58-.84)
6 vs. 3 months	reduction in 12-24m relapse	RR 0.57 (0.45-0.71)

Relapse

Relapse Therapy - The Return of Xiao Ma

Poor Xiao Ma got a cold. It has been 5 months since his original episode but now he has three plus protein in his urine by mom's home albustix. She calls the office for advice.

- What are you going to tell her?

Approach to Relapse Therapy in Childhood Nephrotic Syndrome

Relapse $\text{uPCR} \geq 2000\text{mg/g}$ (200mg/mmol)
3+ protein on dipstick for 3 consecutive days

Approach to Relapse Therapy in Childhood Nephrotic Syndrome

Relapse $\text{uPCR} \geq 2000\text{mg/g}$ (200mg/mmol)
3+ protein on dipstick for 3 consecutive days

Infrequent Relapse One relapse within 6 months of initial response
1-3 relapses in a 12 month period

Approach to Relapse Therapy in Childhood Nephrotic Syndrome

Relapse $\text{uPCR} \geq 2000\text{mg/g}$ (200mg/mmol)
3+ protein on dipstick for 3 consecutive days

Infrequent Relapse One relapse within 6 months of initial response
1-3 relapses in a 12 month period

- 80-90% of children will have a relapse, half of those will have an infrequently relapsing course

Approach to Relapse Therapy in Childhood Nephrotic Syndrome

Relapse $\text{uPCR} \geq 2000\text{mg/g}$ (200mg/mmol)
3+ protein on dipstick for 3 consecutive days

Infrequent Relapse One relapse within 6 months of initial response
1-3 relapses in a 12 month period

- 80-90% of children will have a relapse, half of those will have an infrequently relapsing course
- Prednisone dose is the same initially, treat until protein free for 3 days (trace or less)

Approach to Relapse Therapy in Childhood Nephrotic Syndrome

Relapse uPCR $\geq 2000\text{mg/g}$ (200mg/mmol)
3+ protein on dipstick for 3 consecutive days

Infrequent Relapse One relapse within 6 months of initial response
1-3 relapses in a 12 month period

- 80-90% of children will have a relapse, half of those will have an infrequently relapsing course
- Prednisone dose is the same initially, treat until protein free for 3 days (trace or less)
- After initial therapy give 1.5mg/kg every other day for 4 weeks minimum

On ward!



Frequent Relapse/Steroid Dependent Therapy

Case - Xiao Li

Xiao Li

Xiao Li has nephrotic syndrome and has had multiple relapses. Every time he responds to the steroids but then relapses whenever he is ill. “It just seems he is addicted to the steroids!”

- What do you suppose is his mother’s number one concern?

Xiao Li

Xiao Li has nephrotic syndrome and has had multiple relapses. Every time he responds to the steroids but then relapses whenever he is ill. “It just seems he is addicted to the steroids!”

- What do you suppose is his mother’s number one concern?
- Do you need to do any more workup? If so what tests do you want to run?

Xiao Li

Xiao Li has nephrotic syndrome and has had multiple relapses. Every time he responds to the steroids but then relapses whenever he is ill. “It just seems he is addicted to the steroids!”

- What do you suppose is his mother’s number one concern?
- Do you need to do any more workup? If so what tests do you want to run?
- What therapy can you offer this family?

Definitions

Frequent Relapse 2+ relapses within 6 months of initial response
4+ relapses within a 12 month period

Definitions

Frequent Relapse 2+ relapses within 6 months of initial response
4+ relapses within a 12 month period

Steroid dependence 2 consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy

Steroids

Steroid side effects



Figure: Cushing Syndrome

Steroid side effects

- Obesity

Steroid side effects

- Obesity
- Hypertension

Steroid side effects

- Obesity
- Hypertension
- Impaired linear growth

Steroid side effects

- Obesity
- Hypertension
- Impaired linear growth
- Cushing syndrome

Steroid side effects

- Obesity
- Hypertension
- Impaired linear growth
- Cushing syndrome
- Cataracts, etc.

Steroid side effects

- Obesity
- Hypertension
- Impaired linear growth
- Cushing syndrome
- Cataracts, etc.
- Impaired glucose tolerance

Steroid side effects

- Obesity
- Hypertension
- Impaired linear growth
- Cushing syndrome
- Cataracts, etc.
- Impaired glucose tolerance
- Reduced bone mineral density

Steroid side effects

- Obesity
- Hypertension
- Impaired linear growth
- Cushing syndrome
- Cataracts, etc.
- Impaired glucose tolerance
- Reduced bone mineral density
- Etc. (skin changes, behavior changes . . .)

Who is most likely to become a frequent relapser?

- Short time to first relapse

Who is most likely to become a frequent relapser?

- Short time to first relapse
- Number of relapses in first six months

Who is most likely to become a frequent relapser?

- Short time to first relapse
- Number of relapses in first six months
- Younger age

Who is most likely to become a frequent relapser?

- Short time to first relapse
- Number of relapses in first six months
- Younger age
- Male gender

Who is most likely to become a frequent relapser?

- Short time to first relapse
- Number of relapses in first six months
- Younger age
- Male gender
- Prolonged time to first remission

Who is most likely to become a frequent relapser?

- Short time to first relapse
- Number of relapses in first six months
- Younger age
- Male gender
- Prolonged time to first remission
- Infection with first relapse

Who is most likely to become a frequent relapser?

- Short time to first relapse
- Number of relapses in first six months
- Younger age
- Male gender
- Prolonged time to first remission
- Infection with first relapse
- Hematuria at presentation

Approach to therapy - Steroids

- Daily prednisone until remission for 3 days

Approach to therapy - Steroids

- Daily prednisone until remission for 3 days
- Alternate day prednisone for 3 months minimum

Approach to therapy - Steroids

- Daily prednisone until remission for 3 days
- Alternate day prednisone for 3 months minimum
- Daily prednisone at lowest dose possible for SD patients

Approach to therapy - Steroids

- Daily prednisone until remission for 3 days
- Alternate day prednisone for 3 months minimum
- Daily prednisone at lowest dose possible for SD patients
- Consider daily prednisone during times of URI or other infection in kids with FR or SD disease who are already on alternate day therapy

Approach to therapy - Steroid sparing agents

Corticosteroid sparing agents

- 1 Alkylating Agents (cyclosporine/chlorambucil)

Approach to therapy - Steroid sparing agents

Corticosteroid sparing agents

- 1 Alkylating Agents (cyclosporine/chlorambucil)
- 2 Calcineurin inhibitors (cyclosporine/tacrolimus)

Approach to therapy - Steroid sparing agents

Corticosteroid sparing agents

- 1 Alkylating Agents (cyclosporine/chlorambucil)
- 2 Calcineurin inhibitors (cyclosporine/tacrolimus)
- 3 Mycophenolate mofetil

Approach to therapy - Steroid sparing agents

Corticosteroid sparing agents

- 1 Alkylating Agents (cyclosporine/chlorambucil)
- 2 Calcineurin inhibitors (cyclosporine/tacrolimus)
- 3 Mycophenolate mofetil
- 4 Rituximab

Alkylating Agents

Cyclophosphamide/Chlorambucil

Cyclophosphamide (Cytoxan)

- 2mg/kg/day for 8-12 weeks

Chlorambucil

Others: Levamisole, Mizoribine, Azothioprine

Cyclophosphamide/Chlorambucil

Cyclophosphamide (Cytoxan)

- 2mg/kg/day for 8-12 weeks
- check weekly CBCs

Chlorambucil

Others: Levamisole, Mizoribine, Azothioprine

Cyclophosphamide/Chlorambucil

Cyclophosphamide (Cytoxan)

- 2mg/kg/day for 8-12 weeks
- check weekly CBCs
- only given after remission achieved

Chlorambucil

Others: Levamisole, Mizoribine, Azothioprine

Cyclophosphamide/Chlorambucil

Cyclophosphamide (Cytoxan)

- 2mg/kg/day for 8-12 weeks
- check weekly CBCs
- only given after remission achieved

Chlorambucil

- 0.1-0.2mg/kg/day for 8 weeks

Others: Levamisole, Mizoribine, Azothioprine

Calcineurin inhibitors

Calcineurin inhibitors

Cyclosporine

- 4-5mg/kg/d divided bid

Tacrolimus

Calcineurin inhibitors

Cyclosporine

- 4-5mg/kg/d divided bid
- Keep 12 hour troughs 80-150ng/mL (67-125nmol/l)

Tacrolimus

Calcineurin inhibitors

Cyclosporine

- 4-5mg/kg/d divided bid
- Keep 12 hour troughs 80-150ng/mL (67-125nmol/l)

Tacrolimus

- 0.1mg/kg/d divided bid

Calcineurin inhibitors

Cyclosporine

- 4-5mg/kg/d divided bid
- Keep 12 hour troughs 80-150ng/mL (67-125nmol/l)

Tacrolimus

- 0.1mg/kg/d divided bid
- Monitor troughs (5-10ng/mL, 6-12nmol/l)

Calcineurin inhibitors

Cyclosporine side effects

Side Effect	Prevalance
Hypertension	5-10%
Renal dysfunction	5-10%
Tubulointerstitial lesions	30-40% of patients after 12 months
Hypertrichosis	70%
Gum hypertrophy	30%

Using CNIs

Caveats

- Both cause renal dysfunction

Using CNIs

Caveats

- Both cause renal dysfunction
- Frequently see relapse when stopping therapy (become “CNI” dependent)

Using CNIs

Caveats

- Both cause renal dysfunction
- Frequently see relapse when stopping therapy (become “CNI” dependent)
- Cost

Lesser established therapies

Mycophenolate mofetil

Mycophenolate mofetil

- 1200mg/m²/d divided bid

Mycophenolate mofetil

Mycophenolate mofetil

- 1200mg/m²/d divided bid
- give for at least 12 months (longer OK)

Mycophenolate mofetil

Mycophenolate mofetil

- 1200mg/m²/d divided bid
- give for at least 12 months (longer OK)
- some abdominal pain and diarrhea, can cut dose in half

Mycophenolate mofetil

Mycophenolate mofetil

- 1200mg/m²/d divided bid
- give for at least 12 months (longer OK)
- some abdominal pain and diarrhea, can cut dose in half
- no levels needed

Mycophenolate mofetil

Mycophenolate mofetil

Hogg, et. al. study

- Prospective study design

Mycophenolate mofetil

Mycophenolate mofetil

Hogg, et. al. study

- Prospective study design
- Enrollment - 33 kids (26 with FR SSNS)

Mycophenolate mofetil

Mycophenolate mofetil

Hogg, et. al. study

- Prospective study design
- Enrollment - 33 kids (26 with FR SSNS)
- Gave MMF for 6 months

Mycophenolate mofetil

Mycophenolate mofetil

Hogg, et. al. study

- Prospective study design
- Enrollment - 33 kids (26 with FR SSNS)
- Gave MMF for 6 months
- 24 kids stayed in remission (75%)

Mycophenolate mofetil

Mycophenolate mofetil

Hogg, et. al. study

- Prospective study design
- Enrollment - 33 kids (26 with FR SSNS)
- Gave MMF for 6 months
- 24 kids stayed in remission (75%)
- 12 kids relapse free for 6 months post-treatment

Mycophenolate mofetil

Mycophenolate mofetil

Hogg, et. al. study

- Prospective study design
- Enrollment - 33 kids (26 with FR SSNS)
- Gave MMF for 6 months
- 24 kids stayed in remission (75%)
- 12 kids relapse free for 6 months post-treatment
- 8 of the 12 relapse free for up to 30 months follow up

Mycophenolate mofetil

Coming attractions: Clinicaltrials.gov

Cyclophosphamide Versus Mycophenolate Mofetil for the Treatment of Steroid-dependent Nephrotic Syndrome in Children (NEPHROMYCY)

This study is ongoing, but not recruiting participants.

Sponsor:

Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):

Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:

NCT01092962

First received: February 26, 2010

Last updated: September 2, 2013

Last verified: August 2013

[History of Changes](#)

- Compare efficacy of MMF vs. cyclophosphamide therapies

Mycophenolate mofetil

Coming attractions: Clinicaltrials.gov

Cyclophosphamide Versus Mycophenolate Mofetil for the Treatment of Steroid-dependent Nephrotic Syndrome in Children (NEPHROMYCY)

This study is ongoing, but not recruiting participants.

Sponsor:

Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):

Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:

NCT01092962

First received: February 26, 2010

Last updated: September 2, 2013

Last verified: August 2013

[History of Changes](#)

- Compare efficacy of MMF vs. cyclophosphamide therapies
- Looking forward to results in September, 2014

Monoclonals

Rituximab

- Anti-CD20 monoclonal

Monoclonals

Rituximab

- Anti-CD20 monoclonal
- 375mg/m²/dose, up to four weekly doses

Monoclonals

Rituximab

- Anti-CD20 monoclonal
- 375mg/m²/dose, up to four weekly doses
- Some studies with great results (anecdotal data of 80% remission rate)

Monoclonals

Rituximab

- Anti-CD20 monoclonal
- 375mg/m²/dose, up to four weekly doses
- Some studies with great results (anecdotal data of 80% remission rate)
- Ravani, et.al. showed significant reduction in relapse rate at 3 months a small, open label RCT

Monoclonals

Coming attractions: Clinicaltrials.gov

Efficacy of Rituximab For the Treatment of Calcineurin Inhibitors Dependent Nephrotic Syndrome During Childhood (NEPHRUTIX)

This study is ongoing, but not recruiting participants.

Sponsor:

University Hospital, Limoges

Collaborator:

Hoffmann-La Roche

Information provided by (Responsible Party):

University Hospital, Limoges

ClinicalTrials.gov Identifier:

NCT01268033

First received: December 15, 2010

Last updated: October 31, 2013

Last verified: October 2012

[History of Changes](#)

- Look at use of rituximab in the CNI “dependent” patients

Other considerations

Indications for biopsy

Renal biopsy can be helpful in evaluating prognosis, do a biopsy for

- late failure to respond to steroids following initial response

Indications for biopsy

Renal biopsy can be helpful in evaluating prognosis, do a biopsy for

- late failure to respond to steroids following initial response
- high index of suspicion of different underlying pathology

Indications for biopsy

Renal biopsy can be helpful in evaluating prognosis, do a biopsy for

- late failure to respond to steroids following initial response
- high index of suspicion of different underlying pathology
- decreasing renal function in child on CNI therapy

Immunizations

Steroid Resistant Nephrotic Syndrome