Childhood Nephrotic Syndrome

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Introduction

Objectives

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2. Participants will be able to approach the treatment of CNS in a cost effective and scientifically rational way.
3. Participants will know where to go to get more information on CNS.

Case Definition

Let's get started!

What kind of patients are we talking about anyway?

Nephrotic Syndrome Children over the age of 1 year

- Edema
- Urine Protein:Creatinine ratio (uPCR) >= 2000mg/g
- Urine Protein > 300mg/dL
- Dipstick Urine protein 3+
- Hypoalbuminemia (<= 2.5mg/L)

What is missing from the case definition?

Resources

Important resources to know

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- Lecture slides (http://github.com/forbajato/ChildNephroticSyndrome)

Epidemiology

Obligatory Epidemiology Slide

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

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- 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 cholorpheniramine 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?

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- What therapy should you start?

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- 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

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- 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

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3+ protein on dipstick for 3 consecutive days

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1-3 relapses in a 12 month period

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- Prednisone dose is the same initially, treat until protein free for 3 days (trace or less)

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- 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?

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- 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?

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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

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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

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- 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

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- Male gender
- Prolonged time to first remission

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- Infection with first relapse

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- 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

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- 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 (cyclophosphamide/chlorambucil)

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2. Calcinurin inhibitors (cyclosporine/tacrolimus)
3. Mycophenolate mofetil

Approach to therapy - Steroid sparing agents

Corticosteroid sparing agents

1. Alkylating Agents (cyclophosphamide/chlorambucil)
2. Calcinurin 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

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Others: Levamisole, Mizoribine, Azothioprine

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Cyclophosphamide (Cytoxan)

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- check weekly CBCs
- only given after remission achieved

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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

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- Keep 12 hour troughs 80-150ng/mL (67-125nmol/l)

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- 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

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- Frequently see relapse when stopping therapy (become "CNI" dependent)

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- Cost

Lesser established therapies

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- no levels needed

Mycophenolate mofetil

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Hogg, et. al. study

- Prospective study design

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- Enrollment - 33 kids (26 with FR SSNS)

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- 24 kids stayed in remission (75%)

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- 12 kids relapse free for 6 months post-treatment

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- 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)

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First received: February 26, 2010
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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

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- 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

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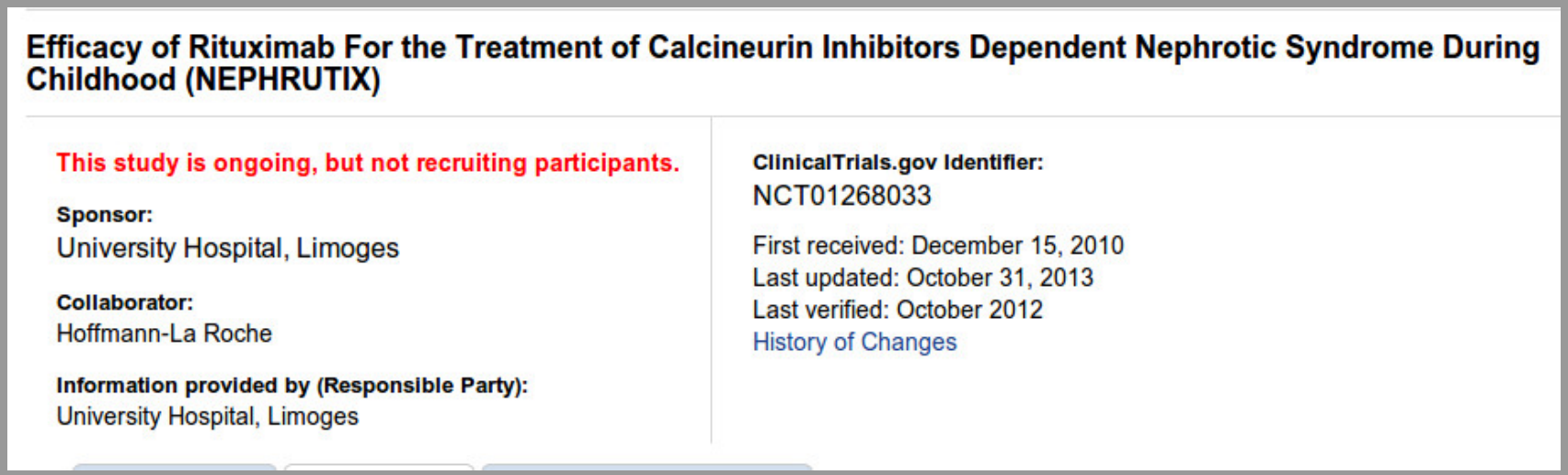

Efficacy of Rituximab For the Treatment of Calcineurin Inhibitors Dependent Nephrotic Syndrome During Childhood (NEPHRUTIX)

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

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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

Steroid Resistant Nephrotic Syndrome

Case - Xiao Han

Xiao Han - the case

Xiao Han

Xiao Han is a 6 year old boy who presented to clinic about two months ago with swelling around the lower legs and ankles for 3 days, uPCR of 5000mg/g, microscopic hematuria and a blood pressure of 120/80. He was started on 2mg/kg/day prednisone and has been monitoring urine proteins. He has been on the 2mg/kg/day for 4 weeks and is ready to start weaning but is still spilling protein (2-3+ every day).

Disease definition

What exactly is Steroid Resistant Nephrotic Syndrome?

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- ISKDC - 95% of SSNS respond after 4 weeks of daily
- ISKDC - Maybe you just need to treat longer or with higher doses
- KDIGO - non responsiveness after 4 weeks of 2mg/kg/day then 4 weeks of 1.5mg/kg/day

Steroid Resistant Nephrotic Syndrome

- 50% risk of ESRD within five years

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- thromboembolic events

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- 50% risk of ESRD within five years
- thromboembolic events
- hypertension
- peritonitis
- elevated lipids

Workup

In a patient with SRNS:

- Renal biopsy

Workup

In a patient with SRNS:

- Renal biopsy
- Evaluate GFR

Workup

In a patient with SRNS:

- Renal biopsy
- Evaluate GFR
- Quantify the protein leak

Calcineurin inhibitors

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- Tacrolimus has significantly less hypertrichosis and gingival hyperplasia
- Reduction in proteinuria in 4-6 weeks
- Remission in 8 - 12 weeks usually

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- Cyclosporine has the most evidence and experience
- Choudhry looked at tacrolimus vs. cyclosporine and found no efficacy difference
- Tacrolimus has significantly less hypertrichosis and gingival hyperplasia
- Reduction in proteinuria in 4-6 weeks
- Remission in 8 - 12 weeks usually
- Optimal duration is unknown

Steroids

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- Taper to the lowest dose that keeps the patient in remission

Steroids

- Taper to the lowest dose that keeps the patient in remission
- All studies done so far use CNI with low dose steroids, no RCT looking at CNI alone vs. CNI with steroids

Other meds

Renin-Angiotensin System blockade

- Dose response effect

Renin-Angiotensin System blockade

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- 33% have reduction in proteinuria with 0.2mg/kg/day (enalapril)

Renin-Angiotensin System blockade

- Dose response effect
- 33% have reduction in proteinuria with 0.2mg/kg/day (enalapril)
- 52% have reduction in proteinuria with 0.6mg/kg/day (enalapril)

High dose steroids

Steroid control arm of SRNS studies

Trial	Total N	Response (%)
ISKDC (1974)	13	46.2
Tarshish (1996)	21	57.1

- RCTs have shown up to 34% response to high dose steroids

High dose steroids

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Trial	Total N	Response (%)
ISKDC (1974)	13	46.2
Tarshish (1996)	21	57.1

- RCTs have shown up to 34% response to high dose steroids
- May be useful in kids who fail CNI therapy

MMF, Cytotoxic agents, Rituximab

Mycophenolate mofetil

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Cyclophosphamide - probably more harm than benefit

Rituximab - RCTs required

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Mycophenolate mofetil

- May be useful in kids who fail CNI therapy
- Usually added to steroid or CNI

Cyclophosphamide - probably more harm than benefit

Rituximab - RCTs required

Conclusion

Questions?

Thank you!