



SPNSG SPECTRUM

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Where Has the Spectrum Been Lately?

This issue of the SPNSG Spectrum is the first that you have received in the past few months. The reason for this "interlude" has been the relative lack of new information that we have had during that period of time and the time it takes to put together the newsletter. Henceforth, we are planning to produce the newsletter on a quarterly basis, but we are planning to supplement this primary means of communication with emails when we have "breaking news". In the present issue of the newsletter, we will bring you up to date with the current status of the NIH-sponsored IgA Nephropathy study that has been completed; the new MMF/IgA Nephropathy study which is now underway, and the NIH-sponsored study of Focal Segmental Glomerulosclerosis which should be ready for patient enrollment later this year. We will also provide you with some information regarding studies that have been or are about to be published. In addition, we are pleased to include reproductions of the three abstracts that have been accepted for presentation at the 2nd World Congress of Nephrology which will be held in June 2003.

If you have any questions about any of our studies that are ongoing or those that have been completed, please do not hesitate to contact us (by phone: 800.345.4426 or email: spnsg@lonestarhealth.com). We will be planning to produce the Spectrum each Spring, Summer, Fall and Winter. Although our colleagues in the North-east may not agree... this is the 2003 SPRING edition!

Sincerely,
Ron Hogg, MD



Recent - and Pending - SPNSG Publications

The last 6 months has been quite productive for SPNSG publications. A list of recent and pending publications is provided below. Thanks to all coordinators and investigators who participated in these studies.

1. Watkins SL, Alexander SR, Brewer ED, Hesley TM, West DJ, Chan ISF, Mendelman P, Bailey SM, Burns JL, Hogg RJ, from the Southwest Pediatric Nephrology Study Group: **Response to Recombinant Hepatitis B Vaccine in Children and Adolescents With Chronic Renal Failure**. American Journal Kidney Diseases, Aug 2002; 40:365-72
2. Furth SL, Hogg RJ, Tarver J, Moulton LH, Chan C, Fivush BA: **Varicella Vaccination in Children with Chronic Renal Failure. A report of the Southwest Pediatric Nephrology Study Group**. Pediatric Nephrology, Jan 2003; 18:33-38.
3. Furth SL, Arbus GS, Hogg RJ, Tarver J, Chan C, Fivush BA: **Varicella Vaccination in Children With Nephrotic Syndrome: A report of the Southwest Pediatric Nephrology Study Group**. Journal of Pediatrics, Feb 2003; 142:145-148.
4. Lande MB, Gullion C, Hogg RJ, Gauthier B, Shah B, Leonard MB, Bonilla-Felix M, Nash M, Roy S, Strife CF, Arbus G: **Long versus Standard Initial Steroid Therapy for Children with the Nephrotic Syndrome: A report from the Southwest Pediatric Nephrology Study Group**. Pediatric Nephrology – in press 2003.

If you wish to have a copy of any of these papers, please contact us at spnsg@lonestarhealth.com



News from the 2nd World Congress (Berlin, June 2003)

We have recently received feedback from the 2nd World Congress regarding SPNSG abstracts that were accepted for presentation. The abstracts are shown in this edition of the newsletter. Please note that the HUS data from the SPNSG Study (shown on this page) will also be presented by Phil Tarr, MD at the VTEC meeting in Edinburgh, Scotland. This will be held on the same day as the World Congress meeting! (Who's on first?) Each of the posters will list all participating investigators.

ASSESSMENT OF THE ACCURACY AND CONSISTENCY OF ROUTINE LABORATORY ASSAYS FOR SERUM AND URINE CREATININE CONCENTRATIONS COMPARED TO HPLC METHODOLOGY. R Hogg, L Fitzgibbons, K Hyland

Uncertainty about the accuracy and consistency of serum creatinine (SCr) levels has been the source of considerable concern since these measurements provide the basis for prediction equations that estimate glomerular filtration rate (GFR_{est}) in both children and adults. Over the past 6 years, the North American IgA Nephropathy Trial has collected serum samples from 90 patients with IgAN at 3 month intervals to evaluate the effect of alternate day prednisone or daily Omega 3 fatty acid supplements on GFR. The concern that non-creatinine chromogens would lead to spuriously high levels of creatinine prompted us to obtain more accurate measurements with high performance liquid chromatography (HPLC). Serum creatinine was determined using isocratic (succinic acid-mobile phase) ion-exchange HPLC with ultraviolet detection. This method is sensitive, free from drug interference, and the effect of non-creatinine chromogens in serum, and provides results which range from 97 to 102% of those obtained using stable isotope mass spectrometry – which is the definitive method for creatinine measurement. During the study, 593 serum samples were obtained and creatinine was measured in all serum by both the HPLC method and by a central commercial laboratory (Laboratory Corporation of America) that used an alkaline picric acid for the first 4 years of the study and an enzymatic calorimetric method in the final 2 years. Level of agreement was assessed with the Bland-Altman approach (Bland JM, Altman DG; Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* i 307-310, 1986). **RESULTS:**

	Grouped by HPLC Serum Creatinine Values			All measurements
	<1.0 (n=325)	1.0-1.5 (n=197)	≥ 1.6 (n=71)	
HPLC Mean SCr (\pm 1 SD)	0.67 \pm 0.17	1.16 \pm 0.16	2.01 \pm 0.35	1.00 \pm 0.48
Lab Mean SCr (\pm 1 SD)	0.77 \pm 0.21	1.25 \pm 0.23	2.12 \pm 0.37	1.09 \pm 0.49
Difference (Mean \pm 1 SD)	0.10 \pm 0.15	0.09 \pm 0.17	0.11 \pm 0.14	0.09 \pm 0.15
95% Confidence Interval	0.08-0.12	0.07-0.11	0.07-0.15	0.08-0.10

CONCLUSIONS: Although the SCr levels obtained by 2 standard laboratory methods were usually higher than the HPLC measurements, the difference between the levels was less than reported in other series. This was consistent at 3 different levels of serum creatinine. This difference is of greater concern in patients with lower SCr levels, where it often represents an error of = 10%. **(ACCEPTED FOR POSTER PRESENTATION 6/11/2003)**

Current Status of the NIH-Sponsored IgA Nephropathy Study

This study has now been completed in all respects except the unblinding of the therapeutic arms to which the patients were randomized and the data analysis! Nancy Nardelli and others in the central office along with the coordinators in participating centers have completed the final visits of the patients who were still in the study at the end of the period of follow-up and these data have all been submitted to Jeannette Lee, PhD in the Data Coordinating Center in Birmingham, AL. Over the course of the next two months the data will be analyzed and hopefully will be correlated with pathologic features that are being evaluated by Drs. Richard Sibley and Charles Jennette. Our goal is to complete the analysis and provide a report for the investigators prior to the submission of an abstract to the American Society of Nephrology, the deadline for which has now been pushed back to June 25, 2003. I would anticipate that we will have the abstract reasonably complete prior to the time of the World Congress in Berlin. We will of course share the information with all of the participating investigators as soon as we complete the analysis. We are also preparing individual reports on patients that will be sent back to the submitting institutions.



More News from the 2nd World Congress (Berlin, June 2003)

Title: MOLECULAR DETERMINANTS IN DIARRHEA-ASSOCIATED HEMOLYTIC UREMIC SYNDROME (D+ HUS). A REPORT OF THE SOUTHWEST PEDIATRIC NEPHROLOGY STUDY GROUP (SPNSG). Ronald J. Hogg ^{1*}, Sandra I. Watkins ² and Phillip I. Tarr ². ¹ Medical City Dallas Hospital, Dallas, TX, United States and ² Seattle, WA, United States

Abstract Body: HUS is a thrombotic microangiopathy characterized by hemolytic anemia, thrombocytopenia, and acute renal failure (ARF), and is most often precipitated by *Escherichia coli* O157:H7. Abnormalities in HUS include disseminated microvascular thrombi, composed largely of fibrin, and endothelial cell swelling. In this study, we studied 39 children with D+ HUS, to determine if changes in the coagulation (coag) system early in illness were associated with the course of the ensuing HUS, and if improvements in these abnormalities preceded hematologic resolution (HR) and nephrologic resolutions (NR). Daily blood (B) samples were obtained for the study at the same time as specimens for clinical purposes. Each patient remained in the study until 48 hours after both HR and NR or until 5% of the pts B volume was removed for research, whichever came first. NR was defined as urine output >0.5 mL/kg/hour if the child was oligoanuric; or a serum creatinine fall at least 0.2 mg/dl if the child was not oligoanuric. HR was defined as the first day the platelet count began a sustained rise. P conc of D-dimer, t-plasminogen activator antigen, plasminogen activator inhibitor-1 activity, and fragment₁₊₂ were determined. A time-dependent proportional hazard model was constructed to determine the odds ratio and accompanying p-values between the concentration of each factor at study entry and the length of the intervals between enrollment and both HR and NR. Our results showed that the concentration of circulating D-dimers (representing intravascular fibrin accretion) and of t-PA antigen (representing, paradoxically, fibrinolysis inhibition) are elevated early in the course of HUS, and remain elevated at later points in illness. These data lend support to the theory that thrombin formation, and, presumably, thrombus formation, play major roles in the pathogenesis of HUS. Moreover, these data support the concept that resolution of HUS requires attenuation of fibrinolysis inhibition. F₁₊₂ remained elevated throughout the illness, and did not attenuate by study exit, even though NR and HR resolutions had occurred. The persistent elevation of F₁₊₂ suggests some degree of continued vascular injury throughout the course of HUS. Our data might be useful early in HUS to identify pts who are likely to have prolonged or more severe courses. Specifically, the assessment of prothrombotic indices might identify groups in which aggressive therapy might be warranted. However, the development of new prognostic formulae would probably have to take into account a panel of factors, because the overlap of the values for individual factors between groups of pts appears to preclude univariate analyses. Treatment of HUS should remain supportive until the molecular mechanisms leading to HR and NR are better delineated.

(ACCEPTED FOR POSTER PRESENTATION—6/10/2003)

Progress Report on the MMF/IgA Nephropathy Study

We are pleased to report that this study has shown excellent progress over the past three months. We now have 16 centers that have IRB approval. These include the following: Cook Children's Medical Center, University of Tennessee, Schneider Children's Hospital, Cincinnati Children's Hospital, Kidney and Hypertension Center in Cincinnati, Duke University Medical Center, Erie County Medical Center, Mayo Clinic in Rochester, Marshfield Clinic, Rhode Island Hospital, Toronto General Hospital, University of Rochester, Nemours Children's Clinic in Orlando and Medical City Dallas Hospital.

To date, 6 patients have been enrolled into the study. Over the next few weeks, we will be forwarding information about the study to IgA Nephropathy patient networks and listserves around the country. As you know the patients and their parents are very interested in knowing more about the disease entity and particularly information as to how they might be able to combat the illness. We anticipate a number of these patients may contact the participating centers and of course we will be willing to provide the patients with general information about the condition and (as appropriate) we will provide information to you regarding patients if they indicate their interest and their permission to be contacted.

As many of you know, we have developed some excellent collateral materials to provide information about the study for both patients and their physicians. If you would like to have additional copies of the study overview brochure that we have developed, please let us know. In addition, if you have a patient who would like a copy of our patient handbook, we would be very pleased to send it to you for the patient. It is of course very important that we maintain the confidentiality of all of the patients who may be interested in receiving materials and so I would urge you not to send us patient information, unless you have written permission from the patient.



News from the 2nd World Congress (Berlin, June 2003) cont.

Title: MULTICENTER TRIAL OF MYCOPHENOLATE MOFETIL (MMF) IN CHILDREN WITH STEROID DEPENDENT (SD) OR FREQUENT RELAPSING (FR) NEPHROTIC SYNDROME (NS). REPORT OF THE SOUTHWEST PEDIATRIC NEPHROLOGY STUDY GROUP Ron Hogg^{1*}, Lisa Fitzgibbons¹, Joy Bruick¹, Martin Bunke², Bettina Ault³, Noosha Baqi⁴, Howard Trachtman⁵ and Rita Swinford⁶. ¹Medical City Dallas Hospital, Dallas, TX, United States; ²Roche Laboratories, Nutley, NJ, United States; ³University of Tennessee, Memphis, TN, United States; ⁴SUNY Brooklyn, Brooklyn, NY, United States; ⁵Schneider Childrens Hospital, New Hyde Park, NY, United States and ⁶UT Houston, Houston, TX, United States.

Abstract Body: Children with SDNS and FRNS often develop adverse effects (AE) from prednisone (P). Attempts to induce long-term remission in such patients (pts) with cytotoxic agents (e.g., cyclophosphamide) and calcineurin inhibitors (e.g., cyclosporin A) have had varying levels of success. Concerns about long-term AEs with these agents prompted us to evaluate MMF in pts <21 years with SDNS and FRNS. In this multicenter, prospective study, 14 centers enrolled 33 pts who were in remission at entry, fulfilled standard criteria for SDNS or FRNS, and had not received CsA, azathioprine, le-vamisole, FK506, or MMF. The pts received MMF in a liquid formulation (provided by Roche Labs) at a dose of 600mg/m² BID for 24 weeks. It was then tapered over 4 weeks and discontinued. A tapering dose of alternate day P was given during the first 3 months of MMF therapy. Pts were monitored for up to 6 months post MMF therapy. Urine protein was monitored at home by dipstick. Treatment failure was defined as a relapse of NS, i.e., presence of edema, or =2+ proteinuria for =3 days, **plus** central lab urine protein/creatinine (Up/C) ratio =1.0 on first morning urine **or** serum albumin <3.0 g/dl. If a pt had proteinuria at home but central lab studies did not confirm relapse, the pt continued MMF. One pt was excluded following a protocol violation after 2 days of therapy. The other 32 pts had the following features at the time of study entry: Age: = 6.8 ± 2.7 years; Range = 2-15 years; 56% Male; 44% Female: Race/ethnicity = 50% White; 25% African American; 25% Other. Entry Classification: 81% FR; 19% SD. Number of Pre-Entry Relapses: 4.3 ± 2.3 per year. Estimated GFR at entry was 138 ± 42 ml/min/1.73m². All pts had a normal serum albumin at entry. Although adverse events were uncommon, one pt stopped MMF because of an absolute neutrophil count <1000/m³. 24 of 32 pts (75%) stayed in remission throughout the 6 months of MMF therapy. 10 of these pts stayed in remission during the entire 6 months post MMF period, whereas 12 relapsed after stopping MMF; 2 are still in the study. 8 of 32 pts (25%) relapsed while on MMF (5 relapsed while on both P and MMF during the first 3 months of study, the other 3 relapsed while on MMF alone, during the second 3 months of study.) We conclude from this study that MMF is an effective agent for maintaining remission in NS patients who receive treatment for at least 6 months and can effectively decrease the AE that occur with P in such patients. Long-term studies of MMF in pts with SDNS are warranted.

(ACCEPTED FOR BOTH FREE COMMUNICATION AND POSTER PRESENTATION ON 6/12/03.)

Latest News Regarding the NIH-Sponsored FSGS Study

Steady progress has been made with the protocol for the NIH study of therapeutic options for the treatment of FSGS in children and young adults (defined by the Steering Committee as patients less than 36 years of age). The Steering Committee has settled on two arms for the study: cyclosporine in combination with alternate day steroid, compared to mycophenolate mofetil (Cellcept) in combination with oral Decadron pulses and alternate day steroid. The treatment period will last a year, with an initial assessment of response at six months, although follow-up will extend beyond that. It is anticipated that all patients will also receive either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB).

The Steering Committee is well aware that there are several questions of interest that cannot be addressed through the primary grant funding. However, there will be other funding mechanisms to support ancillary studies, including a soon-to-be published NIH program announcement, specifically inviting applications for ancillary studies in clinical trials.

The protocol will be presented to the NIH-appointed External Advisory Committee for this study in May. We are all looking forward to the prospect of getting started on patient enrollment into this very important study later this year.

If you have not already "signed up" with one of the 5 core centers that are involved in the FSGS Study, please consider doing so. More information about how you can participate in this study is available by contacting Dr. Marva Moxey-Mims at NIDDK. Her email address is: Moxey-MimsM@extra.niddk.nih.gov