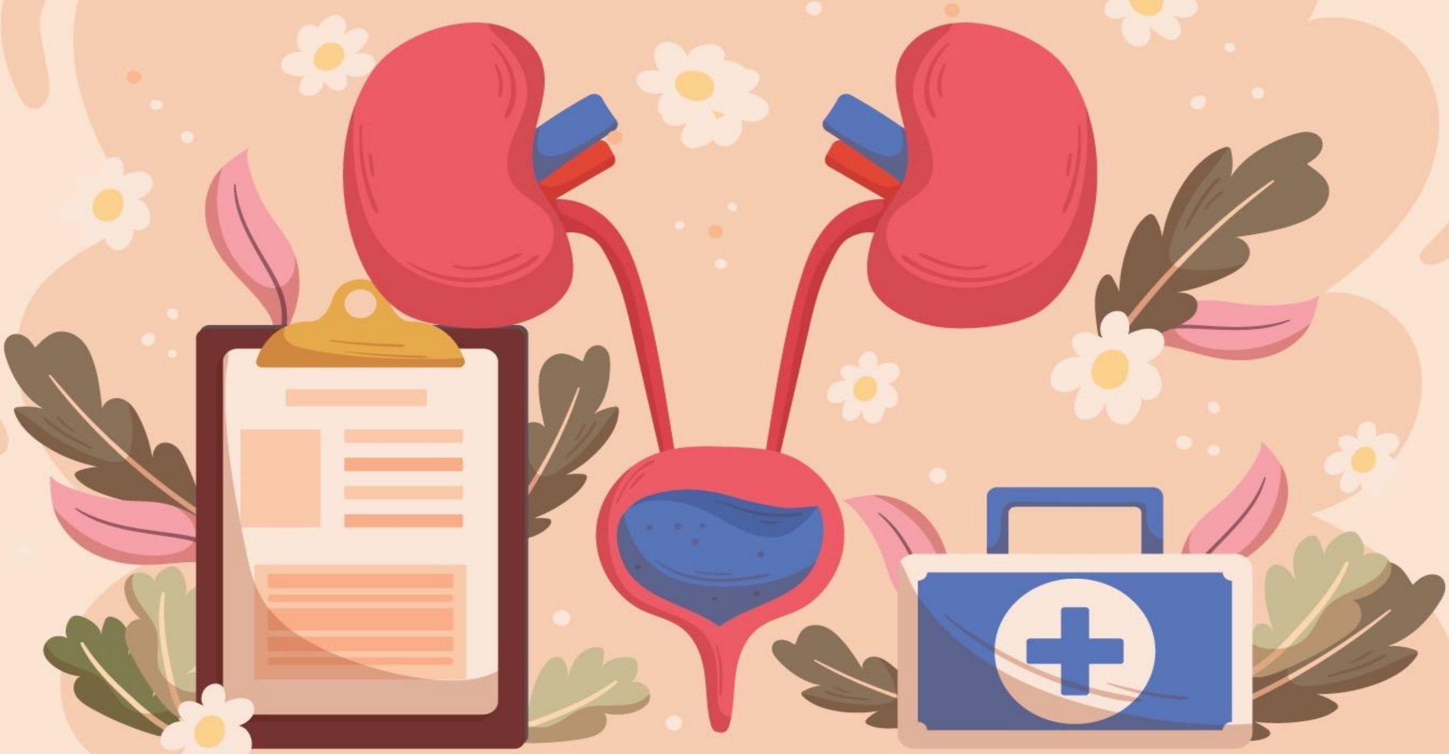
IPNA

International Pediatric Nephrology Association

X SEPNWG MEETING AND TEACHING COURSE 2023



Macedonian Society for Rare Diseases

LIFE with CHALLENGES

Life is a puzzle, collect it.

РЕТКО Е ДА СИ РЕДОК

RRALLË ËSHTË TË JESH I RRALLË

RARE IS TO BE RARE

PEDIATRIC ASSOCIATION OF MACEDONIA

OUR CHILDREN'S SAFETY COMES FIRST

Hotel Aleksandar Palace

Skopje, Republic of North Macedonia

1st to 3rd June 2023

IPNA
International Pediatric Nephrology Association

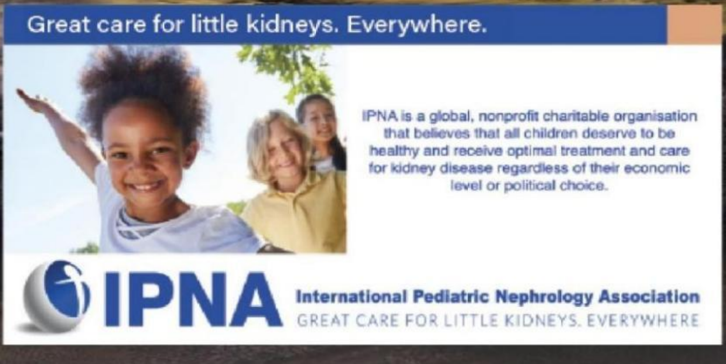
X SEPNWG MEETING AND TEACHING COURSE 2023

Course Director: Velibor Tasic (Skopje)

Scientific Committee: Constantinios J. Stefanidis (Athens), Danko Milosevic (Zagreb), Velibor Tasic (Skopje), Rezan Topaloglu (Ankara), Dimitar Roussinov (Sofia), Tanja Kerstnik Levart (Ljubljana), Brankica Spasojevic (Belgrade), Danka Pokrajac (Sarajevo), Diamant Schtiza (Tirana), Adrian Lungu (Bucharest), Valbona Nushi Stavilleci (Prishtina)

Organizing Committee: Velibor Tasic, Nora Abazi Emini, Aleksandra Jancevska, Ardiana Beqiri Jashari, Julija Gjorgjievska, Ivan Akimovski

1st to 3rd June, Skopje



SUPPORTED BY:

Macedonian Society for Rare Diseases

LIFE with CHALLENGES
Life is a puzzle, collect it.

РЕТКО Е ДА СИ РЕДОК
RARE IS TO BE RARE

PEDIATRIC ASSOCIATION OF MACEDONIA
OUR CHILDREN'S SAFETY COMES FIRST

International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

X SEPNWG MEETING AND TEACHING COURSE 2023
(IPNA Sponsored Teaching Course)

(Supported by the Macedonian Pediatric Association,
Macedonian Society for Rare Diseases, Life with Challenges, Rare is to be Rare)

Hotel Aleksandar Palace, Skopje, Republic of North Macedonia 1st to 3rd June 2023

Course Director

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Editor of Abstract Book

Ivan Akimovski

WELCOME MESSAGE

Dear colleagues, friends and young participants of the teaching course

SEPNWG (South Eastern European Pediatric Nephrology Working Group), which was founded at the end of the last millennium, has a strong commitment to teaching and training young staff in the field of pediatric nephrology.

This year, the teaching course is being held in Skopje, the city of solidarity that was hit byt he catastrophic earthquake in 1963. We deeply sympathize with our Turkish colleagues regarding the recent catastrophic earthquake in Turkey. That is why a colleague from Turkey will dedicate a lecture to this occasion under the title Disaster and Children.

This teaching course is designed to include lectures on the latest achievements in the diagnosis and treatment in nephrourological diseases in children, but there will also be a lot of practical presentations, such as images in nephrourology, clinical quizzes, creation of surveys, round tables, genetic counseling, etc. I hope that in a pleasant and relaxed working atmosphere you will complete and refresh your knowledge and, of course, establish new contacts and friendships.

Hereby, I would like to express gratitude to the International Pediatric Nephrology Association (IPNA), which provided us with strong financial support to make this course possible.

Sincerely yours,
Prof. Velibor Tasic
Course Director

PROGRAM

THURSDAY, JUNE 1, 2023

20.00	**Welcome and opening, Hotel Aleksandar Palace, Skopje**

FRIDAY, JUNE 2, 2023

SESSION I (HALL A)
Meet the expert
Moderators: Adamos Hadjipanayis, Velibor Tasic

08.30 - 09.00	**Goran Roic, Zagreb, Croatia** Images in nephro-urology

SESSION II (HALL A)
Moderators: Constantinos Stefanidis, Yaacov Frishberg, Danko Milosevic

09.00 - 09.30	**Constantinos Stefanidis, Athens, Greece** Neprholithiasis in children: a practical approach
09.30 - 10.00	**Yaacov Frishberg, Jerusalem, Israel** Mitochondrial cytopathies
10.00 - 10.30	**Andrea Cvitkovic Roic, Zagreb, Croatia** Contemporary approach to neurogenic bladder in children
10.30 - 11.00	**Danko Milosevic, Zagreb, Croatia** Distal renal tubular acidosis - an update
11.00 - 11.30	**Adamos Hadjipanayis, Cyprus** Antenatal hydronephrosis. What is the current management by the PCP?
11.30 - 12.00	**Discussion** **Coffee break**
12.00 - 13.00	**Symposium (Hall A)** aHUS - challenges and oppurtunities

SESSION III (HALL B)
Moderators: Jovana Putnik, Constantinos Stefanidis, Yaacov Frishberg

13.00 - 14.00	**Young nephrologists** Oral poster presentations
14.00 - 14.45	**Lunch**

SESSION IV (HALL B)

Moderators: Adrian Lungu, Danka Pokrajac, Tanja Kerstnik-Levart

14.45 - 15.10	**Adrian Lungu, Bucharest, Romania** Breaking Down Lupus Nephritis: The Power of Kidney Biopsy in the era of genetics
15.10 - 15.35	**Rezan Topaloglu, Ankara, Turkey** Treatment and new immunosuppressive agents in Lupus nephritis
15.35 - 16.00	**Dimitar Roussinov, Sofia, Bulgaria** New insights into treatment of lupus nephritis (monoclonal antibodies)
16.00 - 16.25	**Tanja Kerstnik-Levart, Ljubljana, Slovenia** C3 glomerulopathy - novelities, dilemmas, challenges
16.25 - 16.45	**Discussion** **Coffee break**

SESSION V (HALL B)

Moderators: Dimitar Roussinov, Valbona Nushi Stavilleci, Brankica Spasojevic

16.45 - 17.10	**Jovana Putnik, Belgrade, Serbia** Pediatric nephrologist and inherited metabolic diseases
17.10 - 17.35	**Stella Stabouli, Thessaloniki, Greece** Hypertension in CKD
17.35 - 18.00	**Brankica Spasojevic, Belgrade, Serbia** BK polyomavirus-associated nephropathy, prevention and treatment. How much different protocols we have?
18.00 - 18.25	**Maria Gaydarova, Sofia, Bulgaria** Membranous glomerulonephritis in Bulgarian children
20.00 - 24.00	**Dinner for the Speakers**

SATURDAY, JUNE 3, 2023

SESSION VI (HALL A)

09.00 - 09.30	**Lale Sever, Istanbul, Turkey** Disasters and Children

SESSION VII (HALL B)

Moderators: Vesna Stojanovic, Danka Pokrajac, Velibor Tasic

09.30 - 10.00	**Vesna Stojanovic, Novi Sad, Serbia** Novel biomarkers in acute kidney injury
10.00 - 10.30	**Danka Pokrajac, Sarajevo, Bosnia and Herzegovina** Mechanisms of obesity-related renal disease
10.30 - 11.15	**All participants** Images in nephro-urology
11.10 - 11.35	**Discussion** **Coffee break**
11.35 - 12.35	**Symposium (Hall A)** A new path forward in the management of PH1

SESSION VIII (HALL B)

12.35 - 13.05	**All participants** Round table: Antibody-mediated rejection - prevention and management
13.05 - 13.20	**Young nephrologists** Clinical Quizz 1
13.20 - 14.00	**Velibor Tasic, Adrian Lungu, Valbona Stavilleci,** **Nora Abazi Emini, Danka Pokrajac, Nedima Atic** Images in Nephrology
14.00 - 15.00	**Lunch**

SESSION IX (HALL B)	
15.00 - 15.30	**Todor Arsov, Skopje, North Macedonia** Genetic Counselling in Pediatric Nephrology: a practical approach
15.30 - 16.15	**All participants** Creation of a survey Images in nephrology
16.15 - 17.30	**All participants** Clinical Quizz 2 Clinical Quizz 3 Clinical Quizz 4 Closing remarks
20.00 - 24.00	**Dinner for the Speakers and Participants**

Venue

Hotel Aleksandar Palace, Skopje
Republic of North Macedonia

Language of Meeting: English

Certificates of Attendance will be provided by Prof. V. Tasic

SPEAKERS

ADAMOS HADJIPANAYIS

Dr. Adamos Hadjipanayis is an Associate Professor of Paediatrics. His primarily teaching areas include paediatrics, communication skills and information technology.

His research has mainly been focused on environmental hazards, human biomonitoring, use and abuse of antibiotics and vaccines. Dr. Hadjipanayis has published more than hundred peer reviewed articles in paediatric journals. He is an author and co-editor of the book "European Mastercourse in Paediatrics" and he has also published numerous books for parents.

He has been the President of the European Academy of Pediatrics since 2018. He is the director of the paediatric department of Larnaca General Hospital and the medical director of the hospital.

ANTENATAL HYDRONEPHROSIS. WHAT IS THE CURRENT MANAGEMENT BY THE PCP?

Adamos Hadjipanayis

Larnaca General Hospital, Larnaca, Cyprus

Antenatal hydronephrosis is the most common abnormality revealed by prenatal ultrasound. Therefore, the primary paediatrician should be well trained in managing such cases. Most identified cases spontaneously resolve within the first twenty-four months of life. Moreover, there is no study that can accurately differentiate a child with clinically significant disease from one with a benign or transient finding. Thus, the primary care paediatrician should not abuse the child with unnecessary imaging tests, but at the same time should be careful not to miss any significant disease. The aim of this presentation is to present to the audience the current practice in approaching an infant with antenatal hydronephrosis.

Key words: Antenatal hydronephrosis, management, imaging.

ADRIAN LUNGU

Dr. Adrian Catalin Lungu is a consultant Pediatric Nephrologist in Fundeni Clinical Institute, Bucharest, Romania, one of the largest University hospitals in his country. Besides his daily clinical work of taking care of the small patients, he is also involved in teaching activity and research projects.

He had the opportunity to organize the first IPNA teaching course in Romania in November 2017, which was a real success with more than 200 participants and 20 international speakers.
His interests in research cover areas like Immunology and genetics of renal diseases, SLE, aHUS, C3 nephropathy, Complement, FSGS, ADPKD, tubular disorders and they involve collaborations with colleagues from Hungary, Germany, Italy, USA, Australia, Turkey, Macedonia, Croatia, Slovakia, and Slovenia.

Starting with 2022, he is leading the Bucharest, Fundeni Clinical Institute, ERKNet Reference Center, part of the European Reference Network for Rare Kidney Diseases. From 2019 he is part of IPNA council, representing ESPN and having active roles in Juniors and Specific priorities in Low Resourced Countries Committees.

He is involved in registries work and in reviewing activities for International Journals and in the scientific selection of abstracts for national and European medical meetings.

He represented Romania for Young Nephrologists Platform (YNP) at the ERA-EDTA, being involved in the webinars project. He is responsible for the Romanian events linked to World Kidney Day, and is also involved in advocacy and awareness with local patient associations. He is the secretary of the National Committee for Pediatric Nephrology from the Romanian Ministry of Health.

He is curious by nature and has always enjoyed embarking on new challenges.

BREAKING DOWN LUPUS NEPHRITIS: THE POWER OF KIDNEY BIOPSY IN THE ERA OF GENETICS

Adrian Catalin Lungu

Pediatric Nephrology, Bucharest, Romania, ERKNet Bucharest Reference Center

Kidney involvement is a major complication of systemic lupus erythematosus (SLE). Although patients with SLE may have no obvious urinary symptoms, up to 60% of them may develop silent lupus nephritis, which can lead to chronic kidney disease and end-stage renal disease if left untreated. Therefore, it is essential to detect kidney involvement early in the disease course to prevent irreversible damage.
Even in the absence of obvious urinary abnormalities, kidney biopsy can reveal early histologic changes that may indicate kidney damage.
The traditional histologic classification of lupus nephritis based on the International Society of Nephrology/Renal Pathology Society (ISN/RPS) system is widely used in clinical practice to guide treatment decisions. However, recent studies have shown that the ISN/RPS classification may not always reflect the underlying pathogenic mechanisms of lupus nephritis. To address this issue, new approaches to kidney biopsy interpretation are being developed, which incorporate information about the immune cell infiltrate, the activation of complement and coagulation pathways, and the expression of cytokines and chemokines in the kidney tissue. Moreover, recent advances in genetics have shed new light on the pathogenesis of lupus nephritis and may help refine the histologic classification. Kidney biopsy is crucial tool for detecting and monitoring kidney involvement in patients with SLE, even in the absence of obvious urinary symptoms. Incorporating information about the immune cell infiltrate, complement, activation, cytokine expression, and genetic markers into the histologic classification of lupus nephritis may help tailor treatments and improve outcomes for patients with this complex disease.

Key words: Lupus nephritis, biopsy, genetics.

ANDREA CVITKOVIC ROIC

Dr. Andrea Cvitković Roić is professor of pediatrics and pediatric nephrologist with more than 20 years of experience in the field of pediatric nephrology with special interest in neurogenic and non-neurogenic bladder dysfunctions, anomalies of the urinary tract, urodynamics, videourodynamics, contrast-enchanced voiding urosonography and prenatal nephrology.

She graduated from School of Medicine, University of Zagreb and completed pediatric residency training at Children's Hospital Zagreb. She was the Head of Nephrology, Toxicology and Clinical Pharmacology Department in Children's hospital Zagreb before she joined Helena Clinic for pediatric medicine in 2005. She was trained at the world's top pediatric hospitals in Seattle, Boston, London, Ghent, Vienna, Goteborg, Utrecht, Aarhus etc. and learned from leading experts in the field of pediatric nephrology, ultrasound and pediatric urodynamics.

She established the first Urodynamic Unit in Children's Hospital Zagreb, was the first to introduce the biofeedback and neuromodulation therapy for voiding disorders in Croatia and is a head of Regional center for bladder and bowel dysfunction where children from the whole region are treated.
She is the author of many scientific articles which are cited in the international indexes. Along with her team at Clinic for pediatric medicine Helena she organizes international courses in the field of pediatric ultrasound, contrast-enhanced ultrasound voiding cystography and urodynamics.

She is the vice-president of Croatian Society for Pediatric Nephrology and a member of several medical associations and societies. She has been invited as a lecturer to numerous scientific congresses and courses, both in Croatia and abroad and received numerous awards for her publications.

CONTEMPORARY APPROACH TO NEUROGENIC URINARY BLADDER IN CHILDREN

Andrea Cvitković Roić

Helena Clinic for Pediatric medicine, Branimirova 71, Zagreb, Croatia
Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Josipa Huttlera 4, Osijek, Croatia
Faculty of Medicine, University of Rijeka, Braće Branchetta 20/1, Rijeka, Croatia

Neurogenic urinary bladder is caused by impaired innervation of the lower urinary tract and is a risk factor for recurrent urinary tract infections, vesicoureteral reflux, hydronephrosis, urolithiasis and impaired renal function. It is a heterogeneous entity that may result from a different congenital or aquiredconditions affecting the central or peripheral nervous systems. Urodynamic studies have allowed us better understandingof the pathophysiology of these disorders and early detection of risk factors for renal parenchymal damage. Immediately after the suspicion on a neurogenic dysfunction, complete diagnostic workup is necessary, which includes ultrasound methods, 4-hour voiding observation, contrast-enchanced voiding urosonography, urodynamics and videourodynamics. Treatment includes clean intemittentcatheterization and the addition of medications in an individualized manner. If the desired goal is not achieved with anticholinergics or alfa blockers, another combination of medications, Botulin toxin A, endoscopic management or neuromodulation may be tried prior to surgical reconstructive procedures.
The main goals of treatment and follow-up are the preservation of renal function, and after school age, socially acceptable continence and independence. We present up-to-date medical management of the neurogenic bladder and highlight the need for further research to improve evidence-based medical and surgical decision-making strategies for children with different types of neurogenic bladder.

Key words: Neurogenic urinary bladder, spina bifida, urodynamics, contrast-enchanced voiding urosonography, videourodynamics, children

BRANKICA SPASOJEVIC

Dr. Brankica Spasojevic-Dimitrijeva is an assistant professor of pediatrics and a specialist in pediatrics with more than 20 years of experience with special intrest in hemodialysis and transplantation as a chairman.

She graduated from Faculty of Medicine, University of Banjaluka, Bosnia and Herzegovina and completed pediatric residency at University Children's Hospital in Belgrade, Serbia. She finished her Master Program in nephrology after which she got her training in pediatric nephrology. She has a PhD in nephrology.

She is the author and co-author of 55 articles and 4 book chapters which are cited in international indexes.

She is member of the Pediatric School of Serbia, part of the Ethical board of University Children's Hospital in Belgrade. She is on the Rare diseases board in the Ministry of Health in Serbia. She also takes part as an active member in the Serbian Medical Society/Section of Nephrology.

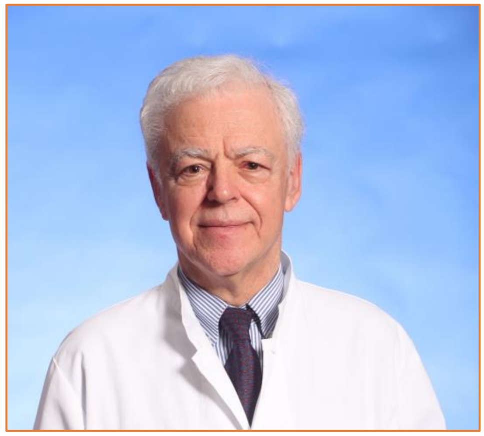
BK POLYOMAVIRUS - ASSOCIATED NEPHROPATHY, PREVENTION AND TREATMENT. HOW MANY DIFFERENT PROTOCOLS DO WE HAVE?

Brankica Spasojević
University of Belgrade, Faculty of Medicine, Serbia
University Children's Hospital, Nephrology Department, Belgrade, Serbia

After solid organ transplantation, immunosuppressive therapy attenuates cellular immunity and increases risk of opportunistic viral infections caused by cytomegalovirus, Epstein-Barr virus, or BK polyomavirus (BKPyV). After primary asimptomatic infection, typically during early childhood, BKPyV persists in the kidney and uroepitehlial cells resulting in lifelong latent/persistent infection. Since cellular immunity is most suppressed in the first post-transplant year as a result of induction therapy, viral replication can frequently ensue during this period. The infection occurs in the following chronologcal stages – viruria, viremia, and allograft nephropathy. Viruria and viremia are detected in approximately 30% and 12% of kidney transplant recipients, respectively . BKPyV associated nephropathy (BKPyVAN) occurs in 1-10% of kidney transplant recipients and represents an important cause of graft loss. Identifying the histologic features of polyoma virus infection on renal biopsy is currently the gold standard for the diagnosis of "definitive" BKPyVAN. There is currently no specific antiviral drug available, and the mainstay of therapy for significant BKV replication is timely reducing immunosuppressive drugs, which leads to the resolution of BKPy viremia in up to 80-100% of the cases. The various immunosuppressive regimens on BKPyV infections are currently under discussion. The stepwise approach for the reduction in immunosuppression in the setting of BK viremia and BKPyVAN is based on trials in adult and pediatric kidney transplant recipients. Other therapies utilized to treat BK virus infection include quinolones, cidofovir, leflunomide, and intravenous immunoglobulin (IVIG). IVIG is probably the only viable adjunctive therapy as other therapies failed to show any benefit in prophilactic or therapeutic regimen. On the other hand, following immunosuppression reduction, T-cell mediated and/or antibody mediated rejection occurs in 4 to 15% of the cases, and can also increase the risk of graft loss. There is growing evidence that BKPyV-specific T cells monitoring may identify patients at risk of BKPyVAN and avoid unnecessary pre-emptive reduction of immunosuppression.

Keywords: BK polyomavirus-associated nephropathy, immunosuppression, pediatric kidney transplantation.

CONSTANTINOS STEFANIDIS



Dr. Constantinos J. Stefanidis is *Head of Pediatric Nephrology, "Mitera" Children's Hospital. Athens, Greece.* His main research interests are: Pediatric dialysis, nutritional and bone disorders management of children with Chronic Kidney Disease, Acute Kidney Injury in children.

Interesting facts: in 1973 he got his Medical Degree (Magna Cum Laude), valedictorian of the class in the University of Athens, Greece. In 1978 - Certified Pediatrician (Greece) also Certified by the College of Physicians and Surgeons of Ontario Canada. In 1982 - part of the American board of pediatrics eligibility. In 1984 he got his PhD (Magna Cum Laude), University of Athens, Greece. In 2021 - Fellow of the European Society of Pediatric Nephrology.

From1974-78 - Resident in Pediatrics, University of Athens, Greece. From 1978-82 - Resident in Pediatrics and Fellow Western University and University of Toronto. From 1982-04 - Consultant Pediatric Nephrologist, "A. and P. Kyriakou" Children's Hospital, Athens, Greece. From 2004-18 - Head of Pediatric Nephrologist, "A. and P. Kyriakou" Children's Hospital, Athens, Greece. Since 2018- Head of Pediatric Nephrology, "Mitera" Children's Hospital. Athens, Greece.

In 1997 - President of the 31st Meeting of European Society of Pediatric Nephrology(ESPN). From 1999-02 - Councilor of ESPN. From 2007-11 - Chair of the Tertiary Group of European Academy of Pediatrics. Since 2009- Editor of the journal "Pediatric Nephrology" of the International Pediatric Nephrology Association(IPNA). In 2010 - Chair of the Organizing Committee of the 3rd Congress of the European Academy of Pediatric Societies, Copenhagen 2010. From 2012-19 - ESPN-ERA Registry representative. From 2013-21 - Board member of the Dialysis Working Group of ESPN. Since 2020- Associate Editor of the journal Frontiers in Pediatrics -Pediatric Nephrology.

104 publications in peer-reviewed medical journals

3056 Citations (August 2022), h-index: 31, i10-index: 68

NEPHROLITHIASIS IN CHILDREN: A PRACTICAL APPROACH

Constantinos J. Stefanidis, MD, PhD, FESPN.

“Mitera” Children’s Hospital, Athens, Greece.

Nephrolithiasis is frequently diagnosed in adults, in contrast it is rare in children and adolescents.Recent population-based studies have demonstrated that the prevalence of pediatric nephrolithiasis has been increasing for the past decades. Nephrolithiasis is not a disease, but a symptom of different diseases. Therefore, a prompt diagnostic evaluation has to be performed to identify its cause. Most pediatric patients with nephrolithiasis have a combination of low urinary volume, hypercalciuria, hyperoxaluria, and hypocitraturia. These predisposing factors lead to elevated supersaturation of calcium phosphate and/or calcium oxalate. Primary idiopathic hypercalciuria is the leading cause of nephrolithiasis. This is a multifactorial disease in which complex interaction of environmental and individual genetic factors lead to hypercalciuria /hypercalcemia and often to nephrolithiasis. Up to 50% of these patients have a positive family history. The association with congenital anomalies of the kidney and urinary tract (CAKUT) andabnormalities of metabolismor raremonogenic kidney stone diseases should be diagnosed on time. Recently, a number of patients with hypercalcuria /hypercalcemia and elevated 1.25-dihydroxy-vitamin D3were diagnosed with mutations of SLC34A1, SLC34A3 and CYP24A1. Primary hyperoxaluria might be another rare diagnostic consideration. Preventive management is primarily based on the reduction of the concentration of lithogenic or increased excretion of antilithogenicfactors in urine. A high fluid intake (>1.5 - 2L/1.73m^2) is recommended regardless of the underlying disease. A low Na and high K diet is recommended in children with hypercalciuria. A reduced calcium intake should be avoided in these patients, because it leads to an even riskier increase in oxalate excretion.Crystallization inhibitors, mostly potassium citrate increase the solubility product of urine.The management of pediatric nephrolithiasis is challenging, because of its variable clinical presentation and its high recurrence rate. In addition, these patients have a lower rate of spontaneous passage of the stone(s) and may more often require surgical intervention.

Key words: Nephrolithiasis, children, hypercalciuria.

DANKA POKRAJAC

Assistant Professor Danka Pokrajac was born on the 6th August 1961. The Faculty of Medicine in Sarajevo she finished on February 1986. Since June 1991 she has been working at the Pediatric Clinic of the Clinical Center University of Sarajevo (CCUS) first as a resident, than pediatrician, a sub-specialist of children's nephrology, head of Nephrology Department (2003 – 2016) and from August 2016 until now as head of Pediatric Clinic 1, Discipline for the Child's Health CCUS.

During that period, she together with her colleagues introduced kidney biopsy under ultrasound, all types of dialysis techniques (peritoneal dialysis, hemodialysis and plasmapheresis) for children, the first in Bosnia and Herzegovina. She has completed her professional education in the field of health management for operational management - the basic level of SHCE 1.

Master's thesis entitled "Etiology and Sociodemographic Characteristic of the Night Enuresis in Children" was defended in 2004 at the Faculty of Medicine University of Sarajevo. On the same Faculty in 2013 she defended her doctoral thesis "Renal Parenchymal Damage in First Febrile Urinary Tract Infection in Infants". She got the academic title Assistant Professor at the Faculty of Medicine University of Sarajevo on 2013. She is a member of seven associations in the Bosnia and Herzegovina and abroad.

Danka Pokrajac was on medical training in Belgium, Slovenia and the USA. She has participated in numerous national and international scientific conferences with articles and presentations. She was a coauthor of 7 university textbooks, 2 monographs, author of one personal book ("Urinary tract infection in children", 2018) and a reviewer of 2 books and 6 original articles in international and domestic medical journals. In addition, she published 37 scientific articles and 58 abstracts of conference announcements.

So far, she has been a mentor for graduate students, a sub-specialist of pediatric nephrology and a member of the commissions for master's and doctoral thesis at the Medical Faculty in Sarajevo.

MECHANISMS OF OBESITY-RELATED RENAL DISEASE

Danka Pokrajac

Pediatric Clinic II, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina.

The increase in overweight children in the world is a fact that is very worrying for the health system and the entire social community. While obesity is known to increase a variety of cardiovascular and metabolic diseases, excess weight and obesity are important risk factors for chronic kidney disease (CKD), because it predisposes to diabetic nephropathy, hypertensive nephrosclerosis, focal and segmental glomerulosclerosis, nephrolithiasis, and for malignancies including kidney cancer. Excess weight and obesity are associated with complex mechanisms which include hemodynamic, structural, inflammation, oxidative stress, metabolic and biochemical alterations, activation of the renin-angiotensin-aldosterone system (RAAS) and histological renal changes, which lead to kidney disease. Adipose tissue is very dynamic and it is involved in the production of "adipokines", such as leptin, adiponectin, tumor necrosis factor-α, monocyte chemoattractant protein-1, transforming growth factor-β and angiotensin-II. A series of pathophysiological mechanisms are triggered by obesity, including renal hemodynamic changes, neurohumoral pathways that activate the sympathetic and renin- angiotensin-aldosterone systems, proinflammatory and profibrotic effects of various adipokines, what together with insulin resistance may explain the excessive risk of CKD development and progression in obese patients. It is very important to start immediately with a preventive strategy to stop this scourge of the 21st century. However, there is no targeted treatment for obesity-related kidney disease. Maybe RAAS inhibitors and melatonin have some therapeutic potential. So, that is one of the reasons to create new therapeutic options for slowing or stopping disease progression. Further studies are required for the improvement of kidney outcomes in obese patients with chronic kidney disease.

Keywords: Kidney diseases, obesity, prevention.

DIMITAR ROUSSINOV

Dr. Dimitar Roussinov is Pediatric Nephrologist, Hospital “The Health”, Sofia. He is also a Member of the Paediatric Committee of European Medicines Agency and a Member of the Editorial Board of “Pediatria”, Sofia. He is also a Representative of Bulgaria in ESPN / ERA-EDTA Registry.

In 1985 – M.D., Medical University, Sofia. From 1985-1987 – District pediatrician, Pazardjic City. From 1987-2004 – Assistant Professor, Dialysis Unit, Department of Pediatric Nephrology, University Pediatric Hospital, Sofia. From 2004-2005 – Head Department of Pediatric Nephrology, University Pediatric Hospital, Sofia. From 2005-2019 – Assistant Professor, Dialysis Unit, Department of Pediatric Nephrology, University Pediatric Hospital, Sofia. From 2019-2021 – CEO, University Pediatric Hospital, Sofia. In 2021 – Associated Professor, Department of Pediatric Nephrology, University Pediatric Hospital, Sofia. In 1991 – B.C. in Pediatrics. In 2006 – B.C. in Pediatric Nephrology. In 2016 – Ph.D. From 2015 – 2021 – Member of the Management Board of Bulgarian Nephrology Society.

NEW INSIHGTS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATHOPHYSIOLOGY AND EMERGING TREATMENTS

Dimitar Roussinov

Hospital "The Health", Sofia, Bulgaria

Although the pathophysiology of the Systemic Lupus Erythematosus (SLE) is generally well known, treatment options and guidelines exist, there is an unmet medical need still due to the complexity of the disease. Increased knowledge in details of different pathophysiological mechanisms opens the door for new treatments. Monoclonal antibodies (MA) are a promising products. Blocking single cytokine pathway may enhance treatment efficacy in autoimmunity without increasing systemic immunosuppression. Interferones are involved in SLE pathophysiology. Anifrolumab binds to subunit 1 of the type I interferon receptor and blocks the biologic activity of type I IFNs. Authorized for use in SLE in adults.BIIB059 (litifilimab) is a MA against BDCA2, a plasmacytoid dendritic cell specific antigenunder investigation for SLE and cutaneous lupus erythematosus (CLE). Obinutuzumab, a next generation anti-CD20 MAlicensed for haematological malignancies might be effective in renal and nonrenal SLE patients. Interleukin-23 and IL-17A play important role in lupus nephritis. MAs targeting them – ustekinumab and secukinumab are authorized in other indications and under investigation in SLE. Anti-IL21 MA avizakimab is also under development.Dapirolizumab pegol binds to CD40L and inhibits interaction with its receptor CD40. It is used in clinical trials for treatment in SLE patients. Daxdilimab is a MA directed against human immunoglobulin-like transcript 7on the surface of plasmacytoid dendritic cells and is under investigation. Development of some other MA as epratuzumaband tabalumab in SLE have been discontinued.

Key words: Systemic Lupus Erythematosus, monoclonal antibodies, treatment.

GORAN ROIC

Prof.dr.sc. Goran Roić, dr. med. Was born in Zagreb on 29 December 1961.

In 1987 he Graduated from the Faculty of Medicine of the University of Zagreb. In 1989 - Specialization in radiology /*KB* "*Sestre milosrdnice*", Zagreb /. From 1989-90 - Postgraduate study "*Radiology*". From 1990-91 - Postgraduate study "*Ultrasound in Clinical Medicine*". In 1992 - Specialist examination of radiology. From 1992-93 - Specialist radiologist at the Polyclinic for Med. Diagnostics, Zagreb.- 1993 - Specialist radiologist at the Children's Hosp., Zagreb. In 1994 - Head of the Center for Ultrasound and got his Defense of Master's Thesis. In 1996 - Permanent Judicial Medical Practitioner / Radiology / County Court Zagreb. In 1997 - Study visit to the LKH Graz Radiology Department, Austria. In 1998 - Accepted topic of doctoral dissertation. In 1999 - Two-month study stay at LKH Salzburg, Austria. From 1999-2002 - President of the Professional Council of the Children's Hosp.

In 2000 - Head of Radiology Dpt. From 2000-05 - Secretary of the Croatian Society of Radiologists. In 2001 - Doctoral dissertation defense also a Regular member of the European Society of Pediatric Radiologists / ESPR /. From 2001-04 - Member of the Croatian Institute for Radiation Protection. From 2001-02 - Completed Health Management Management Study / LMHS /. In 2003 - Assistant professor at the Faculty of Medicine of the University of Rijeka. He also got his Affiliate title *"Primarius"*. In 2005 - Scientific Research Associate, a Member of Ministry of Health /MZ/ Radiology Committee, Subspecialist – Ultrasound Diagnostics and First vice-president of HLZ */Croatian Medical Ass./*. In 2008 - Senior Research Associate. In 2009 - Science and teaching associate professor Med. faculty of the University of Rijeka. From 2009 -12 – Secretary of Croatian Society of Radiologists /HDR/ of HLZ. From 2007-10 - Director of Children's Hosp. Zagreb. From 2010-12 - Deputy Director of KBC "*Sestre milosrdnice*" and Head of Clinical Dpt. of Radiology KBC "*Sestre milosrdnice*".

In 2012 - Head of Department of Pediatric Radiology of the Zagreb Children's Hospital and First Vice President of HDR. In 2013 - Member of the HLZ Supervisory Board */Croatian Medical Ass./*. In 2014 - Full Professor at the Faculty of Medicine of the University of Rijeka and a Scientific Research Adviser. In 2015 - Member of the HLZ Senate */Croatian Medical Ass./*. In 2016 - Head of the Study of Radiological Technologies of the Zagreb Polytechnic. In 2017 - Member of Board of the Croat. Society for Ultrasound in Medicine and Biology (HDUMB) and a Secretary of the Senate of the HLZ */Croatian Medical Ass./*. In 2018 - Director of the Zagreb Children's Hosp. and a Member of the Presidency of the Employers' Association (UPUZ). In 2019 - Assistant Professor at the Faculty of Medicine of the University of Zagreb. In 2021 - Governing Council member KB "*Merkur*", Scientific advisor in permanent position, Professor in permanent position, Medical Faculty, Rijeka University, President of Croatian Society of Radiologists /HDR/, member of the Zagreb City Health Council. In 2022 - President of Association of Employers in Health Care /UPUZ/.

IMAGING IN PEDIATRIC NEPHRO – UROLOGY

Goran Roić

Children, Hospital Zagreb

Department of Pediatric Radiology

Imaging modalities in pediatric nephrology and urology are evolving rapidly over the last decade largely because of advancement of modern technology. Newer diagnostic techniques for imaging the urinary system in childhood, given the potential to characterize the anatomy and physiology of the kidney and urinary system without the use of ionizing radiation, have attracted increasing attention as innovative and noninvasive diagnostic tools for pediatric nephrologists and urologists. Advances in ultrasound diagnostics, which are characterized by a high safety profile, low cost, wide application and availability by the bed, are especially promising. Ultrasonographic evaluation of the kidneys includes detailed depiction of the renal parenchyma, pelvicaliceal system and vasculature, and it is well established as reliable the first-line imaging method in pediatric nephro-urology. The development of ultrasound contrast medium and contrast specific software has enabled the routine use of contrast enhanced urinary urosonography (ceVUS) in the diagnosis of vesicoureteral reflux (VUR) instead of Voiding urethrocystography (VCUG), and contrast enhanced urosonography (CEUS) in the diagnosis of focal and cystic kidney lesions. MR urography (MRU) including functional MR urography (*f*MRU) are essential and inevitable diagnostic tools in modern clinical pediatric nephro-urology. MR urography gives us insight into the morphology of the urinary tract, and is of particular value in the evaluation of complex congenital anomalies of the urinary tract as well as rare or unusual varieties of development. In such situations it is necessary to estimate a separate one and the overall function of the renal parenchyma to reliable and timely diagnose and differentiate obstructive from non-obstructiveuropathy.The absence of ionizing radiation and the possibility of integrated analysis of the morphology and function of the urinary tract provides these diagnostic methods an important comparative advantages compared to other diagnostic imaging methods.

Key words: Pediatric radiology, contrast enhanced urinary urosonography (ceVUS), contrast enhanced urosonography (CEUS).

JOVANA PUTNIK

Dr. Jovana Putnik graduated from the Medical Faculty in Belgrade 1995. She was employed at the Institute for Mother and Child in Belgrade where she completed training in pediatrics in 2000 year and subspecialization in pediatric nephrology in 2008.

Her current position is Clinical Assistant Professor and Consultant Pediatric Nephrologist. Her focus of interest is acute dialysis in infants and children, management of inborn errors of metabolism, and rare kidney diseases. She participated in international projects and studies on acute kidney injury, primary hyperoxaluria, Alport syndrome and CAKUT.

She promoted cross border collaboration for children with AKI needing urgent renal replacement therapy with colleagues from Bosnia and Herzegovina, Montenegro, Kosovo and North Macedonia.

PEDIATRIC NEPHROLOGIST AND INHERITED METABOLIC DISEASES

Dr Jovana Putnik, Assistant-professor in pediatrics

Nephrology department, Institute of Mother and Child Health Care of Serbia "Dr Vukan Čupić", Belgrade, Serbia

Faculty of Medicine, University of Belgrade

Inborn Errors of Metabolism (IEM) include a group of genetically transmitted disorders in which a single gene defect causes a clinically significant block in a metabolic pathway resulting either in accumulation of substrate behind the block or deficiency of the gene product.Clinical manifestations can appear at any age group, but the most of these disorders are recognized in pediatric age.This heterogeneousgroup of diseases usually involve multiple organ systems. In some metabolic disorders, kidney disease can be the first orthe only symptom leading to the diagnosis of an underlyingmetabolic defect.Increased survival of some inherited metabolic diseases has led to the development of renal dysfunction even in those disease in which it is not a part of the phenotype. Kidney manifestations of metabolic disorders are various. The most frequent are Fanconisyndrome, nephrolithiasis, nephrocalcinosis, renal tubular acidosis, renal cysts and acute kidney injury. The progression of the metabolic disorder usually leads to the end stage kidney disease.
Pediatricians should be aware of these rare, mostly severe and progressive diseases. Nephrologist should consider a possibility ofa metabolic disorder in every child with kidney disease and additional extrarenal symptoms. Early recognition and adequate treatment of inborn metabolic disorder could delay progression of the disease or even preserve the function of affected organs.

Keywords: Inborn errors of metabolism, kidney manifestations, Fanconi syndrome, nephrolithiasis.

LALE SEVER

Dr. Lale Sever is Emeritus Professor, Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Dept. of Pediatrics, Division of Nephrology.

1972 - 1978: Cerrahpasa School of Medicine. From 1978 - 1982: Residency in Pediatrics. From 1986 - 1989: Fellowship in Pediatric Nephrology. From 1987 - 1989: Founding of Pediatric Nephrology Dept. In 1990 - Observer in Cleveland Clinic Foundation. From 1991 - 1996: Ass. Prof. of Pediatrics. From 1993 - 1996: Initiated pediatric dialysis and transplantation programs in Cerrahpasa. In 1996 - Prof. of Pediatrics. From 1997 – 2009: Member, Continuous Medical Education Commission, Cerrahpasa School of Medicine. From 1998 – 2003: Editor of Turkish Archives of Pediatrics. In 2000 - : Member, Teacher of Teachers Group, Cerrahpasa School of Medicine. From 2004 – 2020 : Chief, Dept. of Pediatric Nephrology, Cerrahpasa School of Medicine. Since 2019- : Member - Turkish Board of Pediatrics. From 2020 - 2021 : Senator of Istanbul University-Cerrahpasa.

She served as chief and board member of many national and international scientific working groups and contributed to many projects in various fields of pediatric nephrology, including disaster medicine. More than 100 publications on PubMed with more than 4000 citations.

DISASTERS AND CHILDREN

F. Lale Sever

Emeritus Professor, Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine,

Dept. of Pediatrics, Division of Nephrology

The frequency and intensityof natural and man-made disasters are increasing and expanding their harmful effects.Although the whole population is at risk of being affected by disasters, children are physically, psychologically and socially more vulnerable than adults due to their limited self-protection skills and dependence on their parents/caregivers. Because of the need for extensive infrastructure, equipment, medications and well-trained medical personnel, chronically ill children, especially those with end-stage kidney disease constitute an extremely sensitive group. Earthquakes are among the most devastating and large-scale disasters. Crush injury and subsequent crush syndrome related acute kidney injury (AKI) occurs very frequentlyin disaster victims who are trapped under collapsing material. Early and sufficient fluid administration is essential to prevent AKI or improve the outcome in crush syndrome. Dialysis treatments are challenging for acute and/or chronic patients under disaster circumstances. Hemodialysis may be impossible because of structural damage to the hospitals and shortage of dialysis machines, material and healthcare professionals as well as infrastructural damage which results in disruption of clean water, electricity and transportation. Lack of peritoneal dialysis (PD) solutions and supplies, and also increased risk of infectious/non-infectious complications make PD applications problematic. Non-availability of immunosuppressants and increased risk of infections may cause graft losses and mortality among kidney transplant patients. To mitigate the risks, it is vital to be prepared for renal disasters. Predisaster preparedness and scenarios for disaster response should include not only healthcare providers, but also training of the patients and their caregivers. If problems cannot be coped locally, calling for national and/or international help is mandatory.

Key words: Crush syndrome, children, disaster preparedness.

MARIA GAYDAROVA

Current position: Head of Paediatric Nephrology and Dialysis Clinic, at the University Paediatric Hospital “Ivan Mitov”, Sofia, Bulgaria.

Research interests: Assoc. Prof. Dr. Maria Gaydarova has a specialty in Paediatric and subspecialty in Paediatric Nephrology. She has a special interest and focus on Intensive care of children on hemo- and peritoneal dialysis, Management of infectious renal diseases in children, Screening for renal anomalies, Management of end-stage renal failure, preparing children for renal transplantation. She has published a total of over 60 scientific papers and publications in national and international journals.

Memberships: Assoc. Prof. Dr. Maria Gaydarova, MD is a member of the Rare Disease commission in University Paediatric Hospital “Ivan Mitov”, Sofia, Bulgaria. She is also a member of the Bulgarian Society of Nephrology, Bulgarian PaediatricSociety. She obtains educational course at European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and is a member at European Society for Paediatric Nephrology.

MEMBRANOUS GLOMERULONEPHRITIS IN BULGARIAN CHILDREN

M.Gaydarova, G.Zlatanova, S.Yankova,G.Mihneva
University Pediatric hospital-Sofia, Bulgaria

Introduction: Membranous nephropathy (MN) is immune-mediated disease, which can occur in every age – from infancy to adults. In childhood the secondary form as a result of systemic diseases, is more frequent while the primary is thought to be an adult disease. We have difficulties of diagnosing these children, because of the unspecific clinical presentation, lack of enough clinical trials and therapeutic protocols. The aim of this study is to discuss the clinical features, treatment, and outcome of Bulgarian children with membranous glomerulonephritis.
Materials and methods: For a period of 12 years(2010-2022) in the Paediatric nephrology and dialysis clinic in University Paediatric Hospital in Sofia, Bulgariawere performed over200 kidney biopsies, from which11 are with histological signs of membranous glomerulonephritis. The children are compared based on clinical presentation, presence of proteinuria and/or haematuria, kidney function and treatment.
Results: In this retrospective study of 11 children with histologically proven membranous glomerulonephritis, in 5 patients we found secondary form (CVID, HBV,Immune thrombocytopenia,LAD 1 immune deficiency, vasculitis). All of them were with clinical presentation of nephrotic syndrome and treatment with corticosteroids was started. In 4of them the therapy was switched to CyA and in 1 was added therapy with MMF. In three children the immunosuppressive therapy discontinued because of suspension of nephrotic syndrome.
Conclusions: Because of the relatively rareness of membranous glomerulonephritis compared with the other causes of nephrotic syndrome, the data is insufficient. It is very important to distinguish the primary from the secondary one, because most of the secondary causes as SLE, hepatitis B and C and malignancy, are treated successfully. We need more clinical trials in this area to compare the aetiology, treatment options and outcome of children with membranous glomerulonephritis.

Key words: Membranous glomerulonephritis, children, outcome.

NORA ABAZI EMINI

Nora Abazi Emini was born in 1976 in Gostivar, North Macedonia. Graduated from Medical Faculty Skopje in 2002. Completing training in pediatrics in 2011. Since 2013 she is working in the nephrology department, at University Children's Hospital. Also, she is a Ph.D. candidate in pediatric nephrology, her research field is familial hematuria. She has a special interest on congenital anomalies of the urinary tract, rare inherited renal diseases, glomerular and tubular diseases.

During her career, she participated in several national and international projects, large number of scientific meeting and congresses. She is the author and co-author of several publications in professional journals. Also, participant in ESPN/ERA-EDTA registry and European National/Regional registries for children on renal replacement therapy.

She enjoys spending her time with her daughters, travelling and reading.

IMAGES IN NEPHROLOGY

Nora Abazi Emini

University Children's Hospital, Skopje, North Macedonia

Images in nephrology give a special approach to the presentation of cases in nephrology so the case is experienced closer through the images that are shown and the listeners have the feeling that they are taking part in the diagnosis and management of the patient. Presentation of the case through images can be combined with a clinical quiz, which is even more intriguing.

For example, a patient with the appearance of red urine comes to the clinic due to suspicion of hematuria. It carries several portions of urine and a different color of each urine is noticed, from yellow to black. The dipstick gives a negative result for blood in the urine, but the test with sodium hydroxide is positive. Suspicion was raised for alkaptonuria, which was proven by genetic testing.

Showing the patient's phenotype is only possible by showing the patient's picture normally with the patient's prior permission. A 13-year-old girl with severe short stature, facial dysmorphia, sparse eyebrows, slow growing hair and nails, brachydactyly and bilateral renal hypo dysplasia suggesting trichorhinophalangeal syndrome.

Renal ultrasound can give us wide spectrum of differential diagnoses, so additional testing should be done, like the example with an 8-year-old boy with nocturnal enuresis, polydipsia and hyperechogenic dots on both kidneys, surprisingly genetically confirmed mutation in PKHD1 gene.

Keywords: Images in nephrology, clinical quiz, diagnosis.

REZAN TOPALOGLU

Prof. Dr. Rezan Topaloglu is a Professor of Pediatrics, Pediatric Nephrologist & Rheumatologist in Ankara, TURKE. She is an Immediate Past president of ESPN and a Chair IPNA Junior Master Classes.

She has Degrees in Medicine, Pediatrics, Pediatric Nephrology and Pediatric Rheumatology at Hacettepe University Faculty of Medicine Ankara, Turkey. Her further Training in Pediatric Nephrology: Guy's and Hammersmith Hospitals London, UK and NIDDK, NIHUSA. Academic Degrees: Associated Professor of Pediatrics and Professor of Pediatrics in 1991 and 1999 respectively. Head of the department of since 2015.

She is an Author and co-author of 243publication recorded in Pub Med, H factor 42,7500citations.
Her main Interests and Research Area: Renal transplantation, Hereditary Renal Diseases, Glomerulonephritis, Nephrotic syndrome and Familial Mediterranean Fever.
She is a Coordinator of Turkish Cystinosis Registry, Turkish Coordinator of ESPN d-RTA Registry. A Member of Certain Registry, Coordinator of ERKNet -ESPN Lupus nephritis registry. A Scientific Journal Editorial Board: Journal of Pediatric Nephrology section editor of Renal Hereditary Diseases, 2002-2005, Journal of Nephrology section editor of Immunology and Glomerular Diseases 2005-2011, Journal of Pediatric Nephrology Section editor of Transplantation 2018-. Invited Speaker at International Congresses of Nephrology: ESPN, IPNA, WCN, ERA-EDTA, AsPNA Congress, IPNA-ESPN Junior Classes, and others.

Other duties: Member of Medical Faculty Executive and Faculty Administration committees 2003-2012. Faculty Coordinator of Socrates Erasmus Exchange Program 2003-2012. General Secretary of Turkish Society for Pediatric Nephrology 2003-2006.

Vice President of Turkish Society for Pediatric Nephrology 2014-2016. Councilor of ESPN 2009-2011. IPNA Councilor 2013-2019. IPNA executive Committee Member 2019-2022. Chair IPNA Junior Master Classes Committee 2013-. Assistant President of ESPN 2015-2019. ESPN President 2019-2022.

TREATMENT AND NEW IMMUNOSUPRESSIVE AGENTS IN LUPUS NEPHRITIS

Rezan Topaloglu

Childhood-onset SLE is characterized by a more activedisease course and more frequent renal involvement comparedwith adult-onset SLE. Lupus nephritis (LN) is a majorcause of mortality and morbidity both in adult and pediatricpatients . Renal involvement has been reported to occur in25–80% of pediatric SLE patients, either as an initial presentationor later in the disease course.
In recent years there have been significant improvements inthe diagnosis and treatment protocols for LN.However, the rate of renalremission is still suboptimal and the progress of LN is more aggressive in childhood, it is necessary to treat it properly.

Glucocorticoids are still the most common drugs used to treat cSLE, and hydroxychloroquine is recommended for nearly all cSLE patients. In LN strict control of proteinuria and blood pressure is required with angiotensin-converting enzyme inhibitor and angiotensin receptor blockers.

Mycophenolate mofetil or intravenous cyclophosphamide is suggested as induction therapy for LN classes III and IV. Calcineurin inhibitors appear to be another good option for cSLE patients with LN. Regarding B-cell-targeting biologic agents, rituximab may be used for refractory LN patients in combination with another immune suppressive drug.Furthermore belimumab was recently approved by the FDA for cSLE treatment, in children aged > 5 years. Anti-interferon therapies could be alternative treatments for pediatric patients with severe interferon-mediated inflammatory disease in the future.

In contrast to adult LN, the data regarding long-term prognosis of pediatric LN are still very limited. Since the progress of LN is more aggressive in childhood, it is necessary to treat it properly.

Key words: Lupus, lupus nephritis, treatment.

STELA STABOULI

Stella Stabouli is Associate Professor of Pediatrics-Pediatric Nephrology at Aristotle University of Thessaloniki, Greece. She received her Medical and Doctoral Degree at the National and KapodestrialUniversity of Athens, and continued her training in Hypertension and Nephrology at the University of Mississippi Medical Centre and the Nephrology Department of Boston Children's Hospital in USA. She currently serves as President of the the European Society Hypertension working group on Blood Pressure in Children and AdolescentsandCouncilor of the European Society of Pediatric Nephrology.

She is a member of the Editorial Board of scientific journals in the field of pediatric nephrology and hypertension and she has authored more than 100 scientific publications with more than 3,500 citations.

HYPERTENSION IN CHILDREN WITH CKD

Stella Stabouli, Aristotle University Thessaloniki, Greece

Hypertension is common in children and adolescents with chronic kidney disease (CKD). It is associated with CKD progression and may be uncontrolled or undiagnosed. KDIGO suggests that in children with CKD, 24-hour mean arterial pressure (MAP) by ambulatory BP monitoring (ABPM) should be lowered to $\leq 50^{th}$ percentile for age, sex and height. This is, however, based on a single randomized controlled trial (RCT), and evidence is lacking for the clinical benefits of lowering BP in different populations. There are no head-to-head RCTs comparing antihypertensive drug classes in children with or without CKD. In both children and adults, renin-angiotensin-aldosterone inhibitors (RAASI) are first-line therapy to control BP and proteinuria, and to attenuate CKD progression to end stage kidney disease and initiation of dialysis. RAASi-associated hyperkalemia can often be managed by measures to reduce serum potassium level, instead of reducing the dose or stopping treatment. According to KDIGO guidelines continue therapy unless serum creatinine rises by >30% within 4 weeks following initiation of treatment or increase in dose. Reduce or discontinue the dose in either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms when eGFR is <15 ml/min/1.73^2.Effective management of BP also involves non-pharmacological measures, including individualized support for physical activity, adequate sleep, a healthy diet and weight control.

Key words: Hypertension, chronic kidney disease, ambulatory blood pressure, children.

VALBONA NUSHI STAVILECI

Valbona Nushi Stavileci, Specialist of Paediatric Nephrology.

Specialized on Pediatrics on 2007, and worked at University Clinical Centre of Prishtina -Kosovowith children with renal problems. During 2010, fellowship at Great Ormond Street Hospital for Children, London UK. Training on managing kidney diseases , dialyses and transplant. Attended subspecialized course on Dialyses at Royal free Hospital, London 2010. And Kidney biopsy hand on course on 2013, Laipzig Germany. During 9 years was part of a joint work project and teamtraining by Swedish Urodinamic team of Linkping University. Completed Pediatric Nephrology, IPNA ESPN Master Classes 2014-2016. And during 2022 at Wilhelmina Childrens Hospital, Nederland, trained for VideoUrodinamike and Urotherapy course.

During2014 and further four years was Coordinator of National team on Assessment of Childrens Hospital services in Republic of Kosova, joint project of Kosovo MofH and WHO. Contributed as a lecturer at University of Medical Sciences in Gjakova. Giving profesional experience contribution, participated in several Nephrology Meetings and Other Pediatric meetings.

Workes at private practice as Consutant Nephrologis in Prishtina at Elita Plus Center, and in Gjakova at European Clinic Hospital. Aplicating modern diagnostic techniques as Voiding contrast enchanced Ultrasound.

VELIBOR TASIC

Graduated: Medical School, Skopje, 1980, Employment: Clinic for Children's Diseases, Skopje 1980, Specialization in pediatrics: 1986. Stipends: The British Council 1991- London; International Society for Peritoneal Dialysis 2001 Hannover. Training in pediatric nephrology: Belgrade 1986, London 1991, Birmingham 1991, London 1998, Hannover 2001. PhD: "Clinical, biological and prognostic aspects of acute poststreptococcal glomerulonephritis in children, University Sv. Kiril i Metodij-Skopje, 1997. Academic degree: Full Professor of Pediatrics and Pediatric Nephrology, Medical School, Skopje

Membership: International Pediatric Nephrology Association, European Society for Pediatric Nephrology, EDTA-ERA, European Academy of Pediatrics, Macedonian Pediatric Association
Working Groups: South Eastern European Pediatric Nephrology Working Group, Inherited Renal Disorders (ESPN), CAKUT/UTI/Bladder dysfunction (ESPN), WGIKD (ERA-EDTA), Tertiary Working Group for Rare Disease (European Academy of Pediatrcis). Secretary General, Macedonian Pediatric Association 2004-2006. Council Member of the European Society of Pediatric Nephrology 2009-2012. Director, SEPNWG Teaching Course Ohrid 2012. Skopje 2016. Scientific Chair, BALKAN Alport Meetings, Ohrid 2018,2022. Invited Lecturer at ESPN/IPNA/EDTA teaching courses in Pediatric Nephrology; Moderator and Lecturer in Nephrology Session at Serbian, Croatian, Kosovo and Macedonian Pediatric School. Scientific Chair of Rare Disease Conferences Skopje 2012, 2013. Publications: >200 Pubmed Papers. Conference papers/abstracts ≈400

PROJECTS AND STUDIES:

- Hereditary and tubular disorders-inherited disorders of magnesium metabolism with M Konrad and S. Weber (Germany)
- Cystic kidney diseases with Carsten Bergmann (Germany), Peter Harris (Mayo, USA)
- Alport syndrome with J Hoefele (Germany)
- Dent1/Dent2 disease with M Ludwig (Germany),
- Congenital anomalies of the kidney and urinary tract – S. Weber, F. (Germany), F. Hildebrandt (Harvard, US), S Sanna-Cherchi (Columbia, US) J Hoefele (Germany), R. Weber (Germany).
- Primary distal renal acidosis with F. Karet (UK), HI Cheong (Korea)
- Study on genetic basis of cystinuria in SouthEastern Europe, Macedonian Academy of Sciences and Arts
- Rare and inherited kidney diseases in Macedonian Children and adolescents (national project)

The result of abovementioned collaboration and projects are papers published in the following journals: New England Journal of Medicine, American Journal of Human Genetics, Journal of the American Society of Nephrology, Kidney International, American Journal of Kidney Diseases, Pediatric Nephrology, Journal of Medical Genetics, Nephrology Dialysis Transplantation etc.

CLINICAL QUIZZES IN PEDIATRIC NEPHROLOGY

Velibor Tasic

University Children's Hospital, Medical School, Skopje, North Macedonia

Clinical quizzes are very suitable educational tools for educating young staff at the beginning of their careers. The purpose of the quizzes is to improve the ability of young doctors to think critically and connect facts. The goal of the clinical quiz is not to guess the final diagnosis, but to create a wide differential diagnostic array from which the most probable diagnostic option will emerge. When analyzing the clinical quiz, it is important to analyze the facts and confront them with each other. Such is the example of a child who is severely dehydrated, and you perform an ultrasound examination of the abdomen and find that his/her bladder is full of urine. This is contradictory because in a dehydrated child, the organism, ie the kidney, conserves every milliliter of urine and you would expect a half-full or empty bladder. So, you state that the problem is in the kidney. You are on the right path and you are developing a differential diagnostic array, starting with chronic renal insufficiency, diabetes mellitus or insipidous diabetes. At the SEPNWG Teaching Course 2023, young doctors will present several clinical quizzes. They arise from everyday practice. Through discussion and cross-arguments, they will practice clinical/critical thinking, which is very important in the career of every young doctor.

Key words: Cinical quizz, young doctors, clinical thinking.

VESNA STOJANOVIC

Dr. Vesna Stojanovic is a pediatrician-nephrologist. My current position is the Head of Pediatric Intensive Care Unit at the Institute of Child and Youth Healthcare of Vojvodina, Novi Sad, Serbia. I am a full professor of Pediatrics at the Medical Faculty in Novi Sad.

She is a Member of MENSA (2000–Present). She was President of Pediatric Association of Vojvodina(2012–2018), Deputy chair of CRRT section of ESPNIC(2013–2020), Vice President of Pediatric Intensive Care Active of Serbian Medical Association(2016–2020), President of Pediatric Nephrology Active of Serbian Medical Association (2018 – 2022).

She has been working at the PICU/NICU for the last 15 years. In addition to her engagement at PICU/NICU she works with patients with all kinds of kidney diseases. She has worked for 10 years at the Department for nephrology prior to her transfer to PICU/NICU.

Her PhD thesis was in the field of experimental nephrology. In experimental work my fields of interest are biomarkers of acute renal failure - KIM-1, NGAL, IL-18 etc., ischemia-reperfusion and damages occurring upon it. She also worked in an animal model of intrauterine growth restriction and examine renal glomeruli of these rats.

She was engagedas one of authors on the book focused on pediatric AKI and RRT for Springer titled *"Critical Care Nephrology and Renal Replacement Therapy in Children"* endorsed by the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) under the supervision of Stuart Goldstein and Akash Deep (2018). She has founded a new subject on the Medical Faculty of Novi Sad: Pediatric Intensive Care, which she also lectures to the students.

She is the author and co-author of several chapters in textbooks on pediatrics, more than 50 articles in journals on the SCI list. She is the editor of the textbook "Hitna stanja kod dece I novorođenčadi" (Emergencies in children and newborns) published in 2022. She is a lecturer in the field of pediatric intensive care and neonatal nephrology in the country and abroad.

NOVEL BIOMARKES IN ACUTE KIDNEY INJURY

Acute kidney inury (AKI) is a common clinical condition associated with a number of adverse outcomes. More timely diagnosis would allow for earlier intervention and could improve patient outcomes. The goal of early identification of AKI has been the primary impetus for AKI biomarker research, and has led to the discovery of numerous novel biomarkers. Furthermore, AKI biomarkers could also function as molecular phenotyping tools that could be used to direct clinical intervention. The most investigated biomarkers are neutrophil gelatinase–associated lipocalin, kidney injury molecule 1, IL-18, liver-type fatty acid–binding protein, angiotensinogen, tissue inhibitor of metalloproteinase-2, and IGF-binding protein 7. There are four broad areas, as follows: (1) AKI risk assessment; (2) AKI prediction and prevention; (3) AKI diagnosis, etiology, and management; and (4) AKI progression and kidney recovery.Most of these biomarkers have a potential role in clinical practice for diagnosing AKI, to determine the severity of AKI, but only few biomarkers are investigated and can be used for AKI risk assessment, prediction of AKI and for predicting kidney recovery after AKI.Further studies and investigations are required to come to the final conclusions.

Key words: Biomarkers, acute kidney injury, diagnosis, prediction, prognosis.

YAACOV FRISHBERG

Yaacov Frishberg, born in Israel, obtained his MD degree from the Hebrew University of Jerusalem in 1984 and completed a residency in Pediatrics at the Beilinson Medical Center (Petah Tikvah, Israel) followed by a fellowship in Pediatric Nephrology at the Children's Hospital of Philadelphia, PA, USA. During his fellowship, he conducted research in renal immunology at the University of Pennsylvania and the UCSD.

He served for 25 years as the Director of the Division of Pediatric Nephrology at the Shaare Zedek Medical Center in Jerusalem, Israel and a Professor of Pediatrics at the Faculty of medicine, The Hebrew University of Jerusalem. He remains the Primary Investigator for the Pediatric Nephrology Research Lab in the same institution.

His research has focused on hereditary kidney diseases in childhood including kidney stone disease, nephrotic syndrome, hyperphosphatemia and mitochondrial cytopathies. In 2010, his group described a new form of primary hyperoxaluria, namely primary hyperoxaluria type 3 (PH3), delineating the clinical characteristics of the disease and the gene HOGA1, which in its mutated form, is responsible for this clinical entity. Also, they have shown that loss-of-function mutations in the gene HAO, encoding glycolate oxidase, cause isolated asymptomatic glycolic aciduria. This served as a proof of principle that GO inhibition may serve as a therapeutic for patients with PH1 and was the impetus for the development of Lumasiran. Further research conducted by his team identified derangements in glyoxylate metabolism which have shed light on the pathophysiological mechanisms underlying PH3.

In 2011, his group described a new form of multi-system mitochondrial cytopathy, designated

MITOCHONDRIAL CYTOPATHIES

Yaacov Frisberg

Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel

Mitochondria are intracellular organelles involved in a number of key biologic processes in the cell, including energy production, redox signaling, calcium homeostasis, inflammation and immune response.
Mitochondrial cytopathies include a heterogeneous group of diseases that are characterized by impaired oxidative phosphorylation. Mitochondrial cytopathies can result from mitochondrial or nuclear DNA mutations. The latter is inherited according to classic Mendelian rules. Kidney involvement may be underestimated if it is asymptomatic or rather shadowed by the severity of other organ systems involved. The age of onset of symptoms may vary from infancy to well into adulthood. The prevalent kidney phenotypes include tubulopathies, ranging from mild urinary wasting of electrolytes to complete Fanconi syndrome, tubulo-interstitial and cystic diseases and various forms of proteinuria associated with histological findings consistent with focal segmental glomerulosclerosis. HUPRA syndrome (HyperUricemia, Pulmonary hypertension, Renal disease, Alkalosis) and its underlying genetic basis serve as a disease model for multi-system mitochondrial cytopathies. Mitochondrial disorders, such as perturbations in the biosynthesis of coenzyme Q10, which are amenable to treatment will be discussed as well.

Key words: Mitochondrial cytopathy, FSGS, mitochondrial DNA, coenzyme Q10, HUPRA syndrome.

YOUNG NEPHROLOGISTS

IgA NEPHROPATHY WITH BILATERAL HYDROCALYCOSIS

Boris Adašević[1], Daniel Turudić[2], Ivana Sosa Filjak[1], Goran Roić[3,4], Danko Milošević[1,5]

[1]Department of Pediatrics, General Hospital Zabok and Hospital of Croatian Veterans, Bracak 8, 49210, Bracak, Croatia
[2]Department of Pediatrics, University Hospital Centre Zagreb, Kispaticeva 12, 10000, Zagreb, Croatia
[3] Department of Radiology, Children's Hospital Zagreb, Ul. Vjekoslava Klaića 16, 10000, Zagreb, Croatia
[4] Faculty of Medicine, University of Rijeka, Braće Branchetta 20/1, 10000, Zagreb, Croatia
[5]Croatian Academy of Medical Sciences, Kaptol 15, Zagreb, Croatia

Objective: Presentation of a child with IgA nephropathy and bilateral hydrocalycosis, with consideration of treatment options.
Case report: In a previously healthy six-year-old child, the appearance of macrohematuria and proteinuria suddenly occurs without worsening the overall renal function. The initial diagnosis showed IgA nephropathy, histologically consistent with focal segmental necrotizing glomerulonephritis and cellular crescents in 17.5% of glomeruli. She was treated with corticosteroid and supportive therapy, after which proteinuria normalized, but microhematuria remained. Already at that time, bilateral cystic changes of all calyces of both kidneys were noticed, which proved to be permanent on ultrasound examination of the kidney imaging. Kidney scintigraphy with Tc-99m DMSA after one year showed multiple "cold" zones of both kidneys, more on the left kidney. Functional magnetic resonance urography (fMRU) at the age of 14 revealed bilateral hydrocalycosis. Global renal function remained stable within normal GFR for now.
Conclusion: Even today, there is still no approved and effective therapy for IgA nephropathy. The possible treatment with dapagliflozin or sparsentan is considered with IgA nephropathy progression (1). Regarding the treatment of hydrocalycosis, many questions remain open. Potential endoscopic treatment is not an option. We are open to suggestions.

UNUSUAL PRESENTATION OF BECKWITH-WIEDEMANN SYNDROME IN AN INFANT

Jovanovska J[2], Islami Limani M[1], Zdraveska N[1], Kacarska M[1], Memedi R[1]
[1]Neonatology department, University Children's Hospital, Skopje, Republic of North Macedonia
[2]Neonatology department, Clinical Hospital Adzibadem Sistina, Skopje, Republic of North Macedonia

Background: Beckwith -Wiedemann syndrome affects 1 in approximately 14000 newborns. The disorder also known as overgrowth syndrome, can have multiple features, but the characteristic findings are macroglossia, macrosomia, and abdominal wall defects. Affected newborns are large for gestational age, with proportional length and weight, with risk for severe hypoglycaemia in the newborn period and early infancy. These children can have hemihypertrophy due to asymmetric growth, visceromegaly, as well as greater risk for embryonal tumors.

Case presentation: Here we present an atypical case of an infant with mild facial dysmorphia, macroglossia and respiratory and feeding difficulties. A twenty eight day old newborn was admitted at the neonatal department because of respiratory difficulties and cyanosis. The child was born prematurely in 33+3 gestational age, as appropriate for gestational age, there was significant polyhydramnios as a risk factor. Mild facial dysmorphia was present with macroglossia, prominent eyes and large fontanel. Well adopted bottle feeding with adequate weight gain was noted as well as symmetric growth.The baby had frequent apneas, with cyanosis, with the need for treatment on mechanical ventilation, with negative laboratory findings for inflammation, normal blood glucose, and normal auscultatory lung finding.After initial stabilisation of the vital signs, prolonged need for oxygen treatment was noted, with abundant secretion in the respiratory tract and feeding difficulties. The child condition worsened again with impaired consciousness, apnoea and bradycardia, with hight inflammatory parameters and positive blood culture for bacterial infection which was successfully treated. After prolonged hospital treatment, the general condition was greatly improved, but bottle feeding was unsuccessful. Genetic testing confirmed the diagnosis of Beckwith -Wiedemann syndrome with loss of methylation on IC2 on 11p15 chromosome.

Conclusion: Beckwith -Wiedemann syndrome should be suspected in all babies with macroglossia and obstructive airway symptoms which is more commonly present in the later infancy, leading to respiratory distress, apnoea and hypoxia, as in our baby. The large tongue also contributed to feeding difficulties, which can be overcome with growth. Hypomethylation on IC2 on 11p15 chromosome increases the risk of embryonal tumors, therefore pediatric nephrologists should be actively involved in monitoring these patients.

PLEUROPERITONEAL LEAK IN PERITONEAL DIALYSIS -A REPORT ON TWO CASES

Ardiana Beqiri- Jashari [1], Julia Gjorgievska[1], FelinaSapundjija Karadzoska[1], Albina Bektashi Qerimi[1], Simona Antonievska[1],Elena Churkoska Trajkovska[1], Velibor Tasic[1], Nora Abazi-Emini [1]

[1]University Children's Hospital, Medical Faculty Skopje, North Macedonia

Background: Peritoneal dialysis (PD) is a modality of renal replacement therapy that is commonly used in children with end-stage kidney failure. It involves the use of the peritoneal membrane, as a natural filter to remove waste products and excess fluid from the body. PD can have some risks and complications, the most common are ecit site infections, peritonitis, abdominal and inguinal hernias, and less common pleuroperitoneal leak of dialysis solution. The mechanism for the leak is thought to be due to increased intra-abdominal pressure in the presence of underlying congenital or acquired diaphragmatic defect. In most cases pleural effusion is on the right side.

Case presentation: Here, we report two cases of children admitted in the period of one week apart, a 13-year-old girl and a 7-year-old boy, who were both on automated peritoneal dialysis with manifestation of pleuroperitoneal leak. The girl presented to our unit with dyspnea, swelling and hypertension. Chest X-ray and ultrasound revealed large right sided pleural effusion. PD was suspended, and hemodialysis (HD) was initiated. Pleural effusion resolved conservatively.

The boy was admitted with inguinal hernia and dyspnea. X-ray showed massive pleural effusion in the right lung. A pediatric surgeon was consulted who recommended stopping PD and draining the fluid. HD was initiated, and in a short time a living donor kidney transplantation was done.

Conclusion: If pleural effusion does occur, immediate interruption of PD is required, switching to hemodialysis (HD) and also kidney transplantation in the future. Pleuroperitoneal leak should be considered in the differential diagnosis of a pleural effusion, particularly a right-sided effusion, in a patient on peritoneal dialysis.

Keywords: End-stage kidney disease, peritoneal dialysi, pleural effusion.

BK VIRUS-ASSOCIATED NEPHROPATHY (BKVAN) IN A CHILD WITH KIDNEY TRANSPLANT

Julija Gjorgievska[1], Ardiana Beqiri Jashari[1], Jasmina Volcevska[1], Jovana Trpkovska[1], Nikola Gjorgievski[2], Nora Abazi Emini[1],
[1]University Children's Hospital, Skopje,N. Macedonia
[2]University Clinic of Nephrology, Skopje, N. Macedonia

Introduction: BK virus-associated nephropathy (BKVAN) is one of the causes of graft loss in kidney transplant patients. Bk virus nephropathy occurs early after transplant when immunosuppression is more intensive. Early diagnosis and strategy for immediate therapy could reduce the risk factors for graft rejection. The biochemical analysis (BKV - Virus - DNA PCR) and the graft biopsy are gold standards for diagnosis.

Case presentation: We present a 15-year-old girl who underwent a living donor kidney transplant from her mother one year ago. She had ESRD due to a congenital anomaly of the kidney and urinary tract (CAKUT). At the age of 12-year-old she started peritoneal dialysis (PD). Refractory bacterial peritonitis prompted referral for living donor kidney transplantation, in Istanbul, Turkey. She received anti-thymocyte globulin induction therapy and continued on a regimen of tacrolimus, mycophenolate acid, and prednisone. She had an unremarkable post-transplant course (serum creatinine 80-90 micromol/l) until two months ago when she presented with gastroenterocolitis, anaemia, metabolic acidosis and severe decline of the graft function (serum creatinine 190 micromol/l). PCR for Polyoma BK Virus in blood were positive (11.000 copies/ml) and immediately graft biopsy was done with finding of abundant lymphocytic infiltration, atrophic changes in the tubules with pseudo inclusions in distal tubules. SV-40 staining was not done due to technical issues. Immunosuppression therapy was reduced gradually to 50% and we started monthly treatment with intravenous immunoglobulins (500 mg/kg) and other supportive therapy. If there is no improvement in graft function, the next step in the treatment strategy will be the administration of cidofovir, considering the severe findings from the graft biopsy.

Conclusion: BKVAN, although uncommon, represents a threat to allograft survival. Our understanding of the risk factors has improved, and prospective screening strategies exist, but we have not eradicated this disease. Lack of effective viral therapy remains a key limitation. Judicious immunosuppression reduction with awareness of the accompanying risks remains the best therapeutic option.

Keywords: BKVAN, chronic kidney disease kidney transplantation, immunoglobulin

ACUTE KIDNEY INJURY IN SUICIDE ATTEMPT DUE TO OVERDOSE OF BISMUTH SUBCITRATE

Jovana Putnik, Aleksandra Paripović, Nataša Stajić
Mother and Child Health Care Institute of Serbia „Dr Vukan Čupić“

Bismuth salts, especially colloidal bismuth subcitrate, are widely used to treat peptic ulcers and chronic gastritis. The reported toxic effects caused by overdose of bismuth salts include nephropathy, encephalopathy, osteoarthropathy, gingivostomatitis and colitis. The concentration of bismuth in the kidney, and its retention time is higher than in other organs and nephrotoxicity is the most frequent serious manifestation.

Case presentation: We report a female adolescent with acute kidney injury after bismuth subcitrate intoxication due to suicide attempt. She was first admitted to the National Toxicology Center at the military hospital and next day transferred in the psychiatric hospital. Third day after ingestion of 3,2 g of bismuth subcitrate, she started to vomit and became oliguric and admitted in our hospital. Renal replacement therapy was started 56 hours after overdose ingestion of bismuth subcitrate.Two days later, the stool became blue-black colored. Continuous hemodiafiltration and five single pass albumin dialysis were performed during two weeks. Urine output progressively increased and renal function improved. Clinical outcome was favorable and after 21 days, the patient was discharged from the hospital. Bismuth in urine remained detectable even one year after ingestion of bismuth citrate.

Conclusion: Bismuth intoxication is a rare cause of acute renal failure and is usually reversible if early diagnosed and properly treated. Clinicians should be aware that acute renal failure could occur after bismuth intoxication.

Key words: Bismuth subcitrate, acute kidney injury, renal replacement therapy

ACUTE KIDNEY INJURY IN CHILDREN: SINGLE CENTER EXPERIENCE FROM SERBIA

Maja Samardžić Lukić[1,2], Nataša Kovač[1,2], Vesna Stojanović[1,2], Dušan Božić[1,3]

University of Novi Sad, Faculty of Medicine Novi Sad[1]
Institute for Child and Youth Health Care of Vojvodina Novi Sad, Pediatric Clinic[2]
Clinical Center of Vojvodina, Clinic for Internal medicine[3]

Purpose: There is an increasing interest about AKI in pediatric population considering the possibility of long-term consequences of renal function and quality of patients' life. These studies are mostly coming from developed countries. Still, data on AKI characteristics in developing countries remain scarce. The aim of our study was to assess the incidence rate of AKI, identify risk factors and evaluate clinical outcome in a hospitalized children in our region.
Methods: This retrospective research included all cases of pediatric AKI admitted to our hospital from January 2016 to December 2020, excluding neonates. AKI was defined according to Kidney Disease: Improving Global Outcome criteria.
Results: In total of 13.213 hospitalized children, 65 developed AKI (stage I 12.7%, stage II 23.9%, stage III 63.4%), yielding incidence of 5.38/1.000 admissions per year. The largest number of children had pre-renal kidney injury (66.2%), while we did not registered post-renal AKI. There was no statistically significant correlation between average age of patients with different forms of AKI. Community acquired AKI was registered in 41 patient (63.1%) while 24 (36.9%) had hospitalized acquired AKI. Acute gastroenteritis and glomerulonephritis were the most common causes for community acquired AKI. Sepsis and multi organ dysfunction syndrome were the most common causes for hospital acquired AKI. Presence of comorbidities such as hemato-oncological diseases (15.39%) and cardiac and urinary congenital defects (13.85%) were the top risk factor of AKI. Also, exposure to nephrotoxic medication, mostly non-steroidal anti-inflammatory drugs, was associated with higher risk of AKI. One quarter of patients were treated with one of the procedures for renal replacement therapy. Death occurred in 18 (29.2%) children and 4 (6.2%) developed chronic kidney disease.
Conclusions: Pediatric AKI is substantially underdiagnosed in our region. It is necessary to raise awareness about the frequency of AKI in children and it is association with poor outcome, including high mortality.
Key words: Acute kidney injury, children, epidemiology, risk factors, low income country

ASYMPTOMATIC MICROSCOPIC HEMATURIA IN CHILDREN

Nataša Kovač[1,2], Vesna Stojanović[1,2], Maja Samardžić Lukić[1,2]

[1]Institute for Health Care of Children and Youth of Vojvodina, Novi Sad, Serbia

[2]University in Novi Sad, Faculty of Medicine, Serbia

Background/aims: Asymptomatic microscopic hematuriais indicative of a wide range of etiologies of varying pathogenic significance which significantly influence the increase in the morbidity and mortality rates in children. The aim of this research is to determine the demographic and clinical characteristics of patients with asymptomatic microscopic hematuria in order to detect etiologic factors most likely to cause asymptomatic microscopic hematuria.

Methods: This retrospective study includeddata on patients who were first time hospitalized for asymptomatic microscopic hematuria in a period from 2018 to 2022. Demographic, clinical, laboratory and radiological findings were analyzed in order to establish definite diagnosis.

Results: The study included a total of 77 patients, out of whom 39 (50,56%) patients were male while 38 (49,35%) patients were female. Most of the patients belonged to the 6-12 age category. Average age of the patients was 8 years. The largest number of examined patients had isolated and recurrent microscopic hematuria. Microscopic hematuria of glomerular origin is more often found when compared to nonglomerular microscopic hematuria. The most common cause of microscopic hematuria was hypercalciuria. The most frequenlty diagnosed anomaly by ultrasound was hydronephrosis. A positive family history with microscopic hematuria was present in 20 patients (25,97%). Alport syndrome was confirmed in one patient.

Conclusion: Regarding the fact that urine screening for urine abnormalities in our country is not carried out routinely and that microscopic hematuria can be an isolated sign of a large variety of different conditions, out of which some are progressive and can lead to the development of chronic renal insufficiency, timely diagnosis, regular monitoring of these patients in order to early detect any signs of exacerbation and initiation of treatment are necessary.

Key words: Hematuria, pediatrics, nephrology

PROVIDING VASCULAR ACCESS FOR URGENT HEMODIALYSIS IN CHILDREN: SINGLE CENTER EXPERIENCE

Nikola Gjorgjievski[1], Nora Abazi[2], Ana Stojanoska Severova[1], Vladimir Pushevski1, Zoran Janevski[1], Vlatko Karanfilovski[1], Julija Gjorgievska[2], Pavlina Dzekova-Vidimliski[1], Irena Rambabova Bushljetik[1], Adriana Vasilova Spasovska[1], Zaklina Sterjova[1], Petar Dejanov[1], Velibor Tasic[2].

[1]University Clinic of Nephrology Skopje, N. Macedonia
[2]University Children's Hospital Skopje, N. Macedonia

Introduction: Providing pediatric vascular access (VA) for urgent hemodialysis (HD) is a demanding and onerous field. Procedures are infrequent, technically challenging, and associated with high complications and exorbitant failure rates. Achieving and maintaining pediatric VA is arduous and it requires a multidisciplinary approach.
Clinical presentation: We presented four children, aged 3 to 12 years, in the period from January 2022 to March 2023 year, which required VA for urgent HD. On two of the children, we performed urgent HD and plasmapheresis (PF) due to diagnosed hemolytic uremic syndrome (HUS), and the other two were treated only with urgent HD due to worsening of the established chronic kidney disease. To provide a successful VA, we needed a multidisciplinary team of interventional nephrologists, pediatric nephrologists, pediatric intensivist, and hemodialysis nurses. The type of VA was determined by the size of the individual, age, and medical condition.
We placed a central venous catheter in the femoral vein in all cases. The procedures were performed in the aseptic room under local anesthesia (2 ml Lidocaine 2%) and short sedation with Midazolam (0.1-0.3mg/kg BW). We used Seldinger's technique, in three children with weights between 10 and 20 kg were placed 8 French size (F) dual lumen catheters from 11 cm length (Arrow®), but in one child we placed 11F x 15 cm (Medcomp®) dual lumen catheter due to its weight above 40 kg. During the HD session, we used a Polyflux dialyzer depending on the surface area of each individual, and the extracorporeal volume was calculated as 8-10% of the child's total blood volume. Maximum blood flow was calculated as 8ml/kg body weight.
Ultrafiltration was available and did not generally exceed 5% of the child's total body weight for each dialysis session, based on a rate of 13ml/kg/hr. We used Heparin as a standard anticoagulant in a dose of 30 units/kg.
The improvement of renal function was achieved in the children with HUS and they were discharged from the hospital in better condition with recommendations for regular medical controls. In one of the other two children, kidney transplantation was done, and the other one was transformed by the peritoneal disease.
Conclusion: Although PD is widely used in children, there are cases where only urgent HD is possible, and furthermore, even more helpful. Pediatric VA decisions are largely based on incomplete, low-level adult and pediatric data. The type of VA is often the most important part of future therapy and should be selected according to the child's age, size, and medical condition.

BEST POSTER PRESENTATIONS

PRES IN PEDIATRIC NEPHROLOGY PATIENTS

E. Zaharieva[1], T. Tsonkova[2], G. Mihneva[1], M. Gaydarova[1]

[1]Nephrology and Hemodialysis department, University Pediatric Hospital Sofia, Bulgaria
[2]University hospital "Proff. Ivan Kirkovich", Stara Zagora

Introduction: Posterior Reversible Encephalopathy Syndrome (PRES) is characterized by headache, seizures, mental and visual disturbances. It is caused by vasogenic edema and primarily affects the posterior and parietal regions of the brain, and the diagnosisis based on typical pattern on MRI.The prevalence of PRES in the general pediatric population is 0.04%, with the highest percentage attributed to cases with underlying kidney diseases ranging from 4% to 9%. With proper treatment, the clinical manifestations of PRES usually resolve gradually within a few days, but they can persist for weeks. PRES should be considered in the differential diagnosis of patients with encephalopathy and underlying kidney disease. Timely diagnosis and appropriate therapy significantly reduces the risk of permanent neurological damage and fatal outcomes.

Case presentations: We present three cases from the Nephrology and Hemodialysis department at the University Pediatric Hospital in Sofia, Bulgaria. All three children have pre-existing kidney damage and accompanying arterial hypertension as part of PRES. Their primary diagnoses are atypical hemolytic uremic syndrome (aHUS), corticosteroid-resistant nephrotic syndrome, and typical HUS. In all three cases, headache and seizures were observed as the first symptom of PRES on the background of acutely increased blood pressure. One of the patients fell into a coma and required mechanical ventilation for two days. All three cases were managed in the Intensive Care Unit and showed improvement after treatment with intravenous antihypertensive drugs, antiepileptics, and anti-edema therapy. The condition was recognized by the physicians, confirmed through MRI imagingand treated early, resulting in the resolution of the clinical syndrome within a week for all patients. Currently, they do not have any residual neurological symptoms.

Conclusions: These cases demonstrate that PRES is not uncommon in children with underlying kidney disease. These patients have high risk factorsforsevere hypertension, poorly answering to anti-hypertensive treatment. Familiarity with PRES among pediatricians and nephrologists enables recognition of the condition and timely intervention.

Key words: PRES, kidney disease, hypertension

ATYPICAL HEMOLYTIC UREMIC SYNDROME: A CASE REPORT

Felina Sapundjija Karadjoska[1], Ardiana Beqiri Jashari[1], Sebehat Sejdiji Saiti[1], Julija Gjorgievska[1], Velibor Tasic[1], Nora Abazi Emini[1]

[1] University Clinic for Children's Diseases, Medical Faculty, Skopje, North Macedonia

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy, caused by dysregulation of the complement alternative pathway. The purpose of this case report is to emphasize the need for precise national strategies regarding the availability of complement blockade therapy, since early treatment initiation is associated with long term preservation of renal function in patients with aHUS.

Case presentation: We report here on a case of a 13-year-old boy with a fourth relapse of aHUS. The measurement of complement factors showed increased activity of the terminal complex, and from the genetic analysis the patient was found to carry a heterozygous mutation in CFHR5 and two a-HUS risk SNPs in CFH and one risk haplotype in MCP. These variations were not considered as causative genetic predisposing factors in this patient. Plasma exchanges were initiated, but significant proteinuria and mild to moderate hemolytic anemia still persisted after the tenth cycle. Exit site infection of the femoral venous catheter occurred, leading to a septic state and the need for two week course of double parenteral antibiotic treatment. We started therapy with ravulizumab six weeks after disease onset, due to limitations in its availability, giving a maintenance dose two weeks after the initial dose, after which hematological remission occurred, as well as normal kidney function with normal range proteinuria. The patient will continue to receive ravulizumab maintenance dose every eight weeks. Now three months after therapy onset our patient is still in remission. Close follow-up as well as patient and family education on meningococcal infections were applied, to ensure early recognition and treatment of such, as well as relapse of the disease.

Conclusion: Terminal complement blockade is the first line therapy in aHUS that can rescue native kidney function, since plasma therapy is associated with considerable morbidity among children, in most cases catheter-related complications.

Keywords: Atypical hemolytic uremic syndrome, complement, plasma exchange, ravulizumab

A Rare Case Of 'Idiopathic Infantile Hypercalcemia' Changes The Whole Concept Of The Disease. Are We Mistaken?

Ivan Akimovski[1], Natalija Chaneva[1], Nora Abazi-Emini[1], Nikola Gjorgjievski[2], Velibor Tasic[1]

[1]*University Children's Hospital, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia*
[2]*University Clinic of Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia*

Background: Inherited metabolic disorders such as 'Idiopathic Infantile Hypercalcemia' (IIH) are rare conditions. It is a mineral metabolism disorder caused by gene mutations in *CYP24A1* and *SLC34A1*. Due to high levels of calicum in the blood (hypercalcemia), in infants typical signs and symptoms of IIH are vomiting, polyuria, dehydration, constipation, weight loss and an inability to grow and gain weight as expected (failure to thrive). Some progress to have delayed development of mental and movement abilities and some are presented with hypercalciuria and nephrocalcinosis. However, recent papers show that this disorder is not only found in infants. As they suggest, some patient can go years before symptoms are present and they usually show in nephrocalcinosis and end-stage renal disease (ESRD).

Objective: The objective of this case report is to determine if this disorder is only present in infants or it can also be present with different clinical presentation in adults as well.

Methods: We did a comparative analysis of two patients who underwent a detailed clinical assessment, complete blood work, complete urine panel, ultrasonography of the urinary tract and genetic work-up.

Results: A 2 month old infant presented with failure to thrive, poor appetite, polyuria and severe dehydration. The blood work showed extremely high calcium of 4,12 mmol/l out of which ionized calcium of 2,85 mmol/l. Due to this, the patient had suppressed PTH < 3,0 pg/ml. The urinalysis showed hypercalicuria with a urinary calcium/creatinine ratio of 2,87 mmol/mmol (referent limits: <2,2 mmol/mmol or 0,77 mg/mg). On ultrasonography bilateral nephrocalcinosis was found. Genetic testing confirmed the diagnosis of IIH with a finding of *CYP24A1 (E143del)*. On the other hand we present a 57 year old male with bilateral nephrolithiasis and grade IV chronic kidney disease with a positive finding of *CYP24A1 (E143del)*.

Conclusion: There are reports in the literature that point to IIH not being a disorder limited to the infancy. This comparative analysis of two case reports points to different phenotypic expressions in infants and in adults with mutation in *CYP24A1* gene. The prenatal or early postnatal diagnosis of this disorder has a great practical importance in next pregnancies. Mutation in *CYP24A1* gene is an absolute contraindication for vitamin D prophylaxis. Also, one should take into consideration the possibility of 'IIH' in adults with idiopathic nephrolithiasis and ESRD.

Keywords: Idiopathic Infantile Hypercalcemia, hypercalicuria, nephrocalcinosis, CYP24A1.

ATTACHMENTS

Adrian Lungu - Romania

Prof. Danko Milosevic - Croatia

Dimitar Roussinov - Bulgaria

Constantinos Stefanidis - Greece

Tanja Kerstnik Levart - Slovenia

Yaacov Frishberg - Israel

Jovana Putnik - Serbia - Interview for Media

Velibor Tasic - Course Director

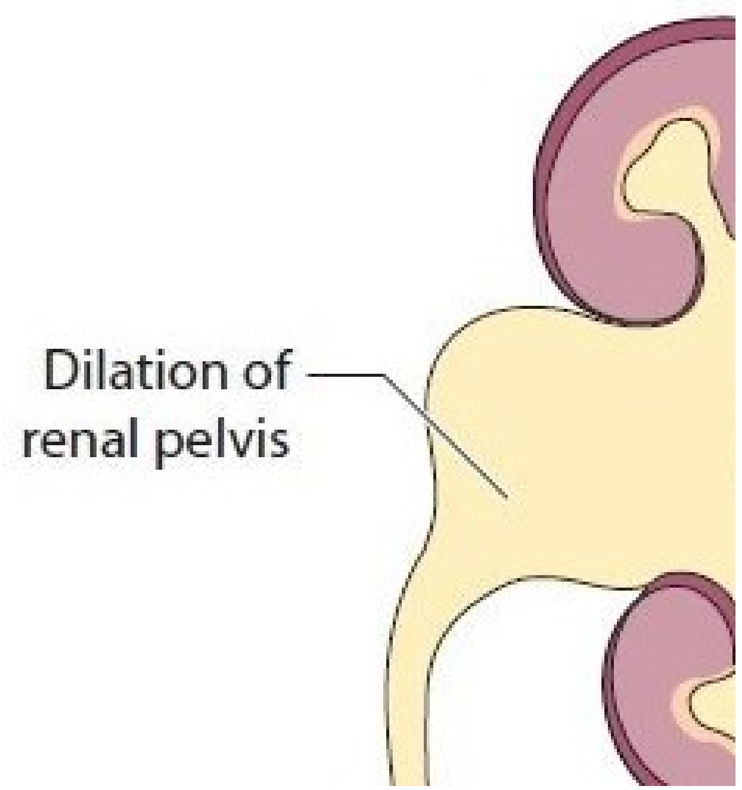
Young attendants

Antenatal hydronephrosis - What is the current practice

Prof. Adamos Hadjipanayis
Pediatrician, Larnaca, CYPRUS
President of the European Academy of Paediatrics

Definition of antenatal hydronephorsis

"dilation of the renal pelvis and/or calyces"



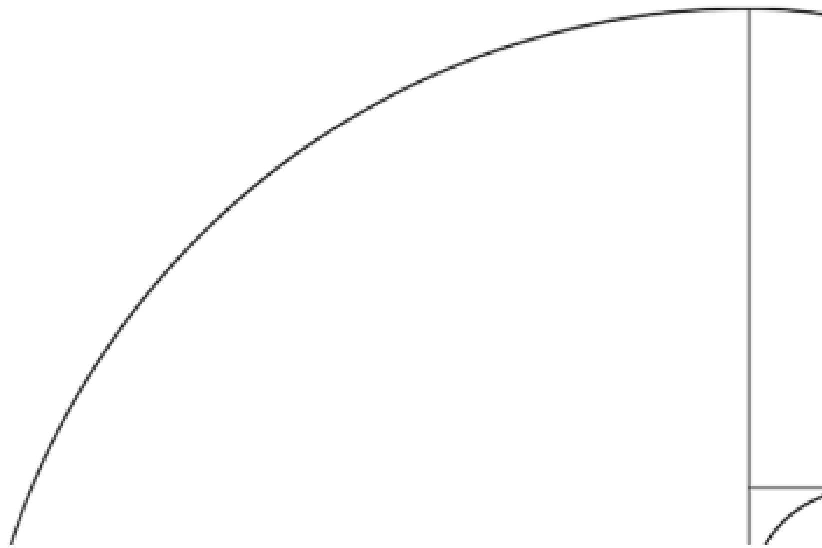
Facts for antenatal hydronephrosis

- The majority of identified cases spontaneously resolve within the first year or two of life.
- There is no finding or study that can accurately differentiate an infant with clinically significant disease from one with a benign/transient finding.

The management of **antenatal hydronephrosis is a challenge**

The “art” of the management of antenatal hydronephorsis

1. Avoid unnecessary testing and excessive anxiety for parents.
2. Not to delay the diagnosis of a clinically significant developmental anomaly of the kidney and/or urinary tract.



Grading Systems for Fetal/Antenatal Hydronephrosis

1. Renal pelvic diameter – RPD
2. Society of Fetal Urology
3. Open Grading System
4. UTD Tract dilation classification - 2014

Renal pelvic diameter grading system

Classifications

- **Mild:** 7 —9 mm
- **Moderate:** 9 —15 mm
- **Severe: >** 15 mm

Recommendations

RPD > 10 mm in 3rd trimester and/or postnatal ultrasound

Start prophylactic antibiotics and obtain VCUG

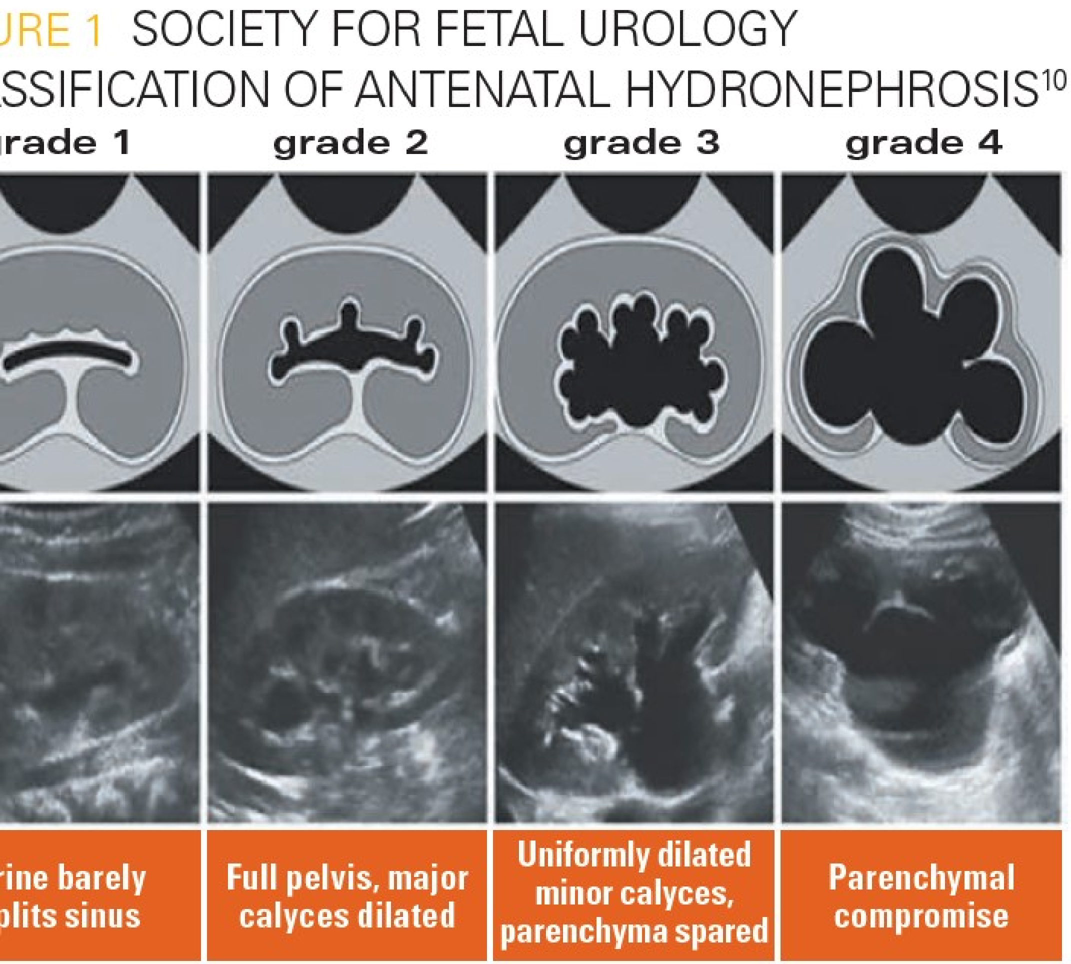
Why RPD alone is not accurate?

Clinically significant disease was identified in:

- 10 - 12% of fetuses with mild antenatal hydronephrosis.
- 24 - 45% of moderate.
- 47 - 88% of severe hydronephrosis.

Thus, while lower cut off points are more sensitive in detecting clinically significant disease, the trade-off is in higher false-positive rates and increases in unnecessary testing and follow-up

ociety of Fetal Urology grading system



Grade 0: Normal; no splitting of renal sinus.

Grade 1: Urine in pelvis barely splits sinus.

Grade 2: Urine fills intrarenal pelvis an major/central calyces may be dilated.

Grade 3: Grade 2 and minor/periphera calyces uniformly dilated.

Grade 4: Grade 3 and parenchyma is thinned.

Urinary tract dilatation (UTD) classification system - 2014

- Radiologists
- Urologists
- Maternal–fetal medicine practitioners
- Nephrologists

It incorporates RPD as well as criteria of calyceal dilation, renal parenchymal thickness/appearance, and bladder/ ureteral abnormalities.

Management of Antenatal Hydronephrosis

or all cases timing ultrasound.

or <u>low risk infants</u> is typically avoided in the first two or thr
ays after birth because worsening hydronephrosis may not
etected until after neonatal **extracellular fluid shifts occur**
nd **urine output increases**.

ceptions: solitary kidney, bilateral hydronephrosis

Management of Antenatal Hydronephrosis

Hydronephrosis has been reported as part of a multiple malformation syndrome in more than 60 genetic and sporadic malformation syndromes.

Management of Antenatal Hydronephrosis

Management of Antenatal Hydronephrosis

RPD is < 10 mm (third trimester) **only** → no further follow up

RPD is > 10 mm (third trimester) →
1. Prophylaxis
2. U/S

Postnatal imaging RPD > 10 mm → VCUG

Postnatal imaging RPD > 15 mm
+
No VUR detected
→ MAG3

Management of Antenatal Hydronephrosis

r fetuses with **<u>bilateral RPD >4 mm</u>**
a <u>solitary affected kidney</u>

rial ultrasounds every two to three
eeks after diagnosis are
commended.

Urinary Tract dilation(UTD
classification

UTD A2-3: Intermediate Risk

Antenatal

PRD> 10 mm;

and

Peripheral calyceal dilation, abnormal parenchymal appearance and/or thickness, abnormal ureters/bladder,

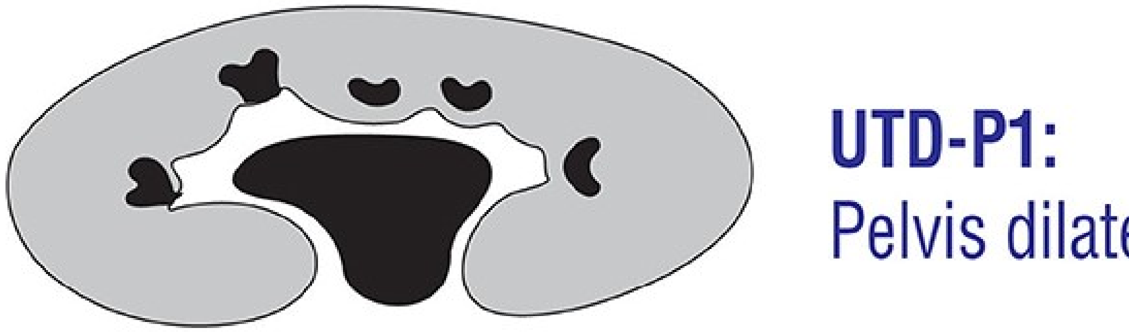
or

unexplained oligohydramnios

- Ultrasound at 48 h.
- Ultrasound 1 month of age.
- Consult specialists.

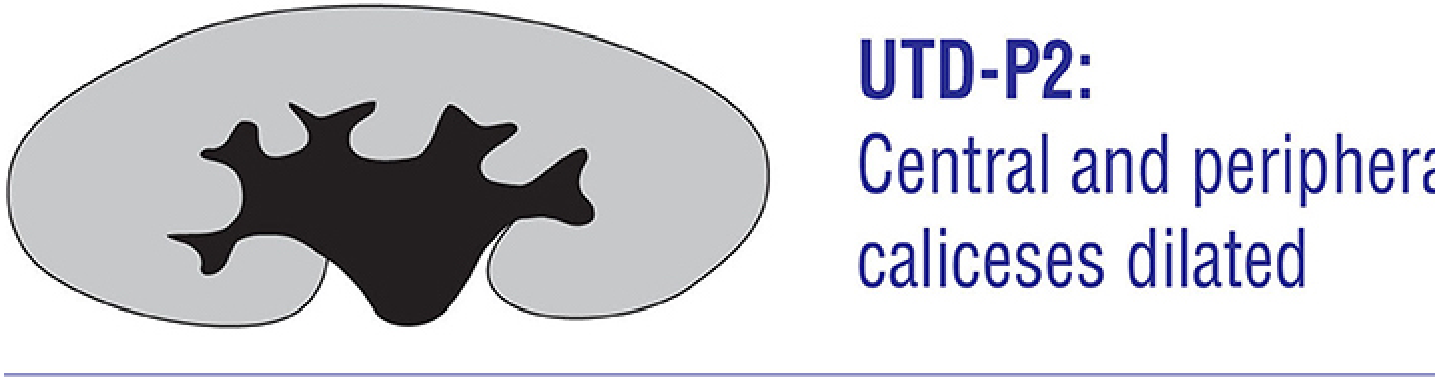
UTD P1: Low Risk
Postnatally

- >48 h old
- RPD 10 —15 mm
- Central or no calyceal dilation.
- Normal parenchymal appearance and thickness, normal bladder and ureters; no unexplained oligohydramnios.



Follow up US in 1–6 months

UTD P2: Intermediate risk Postnatally

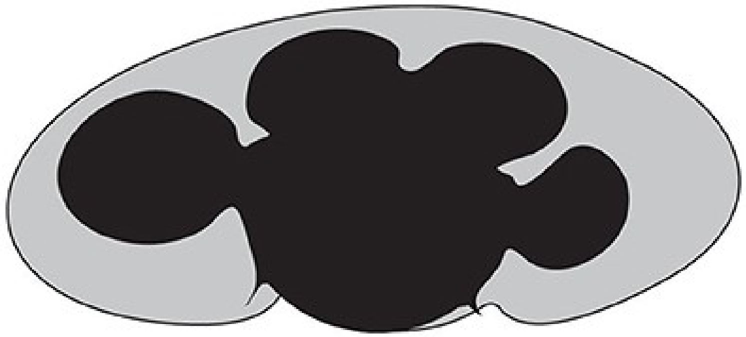


- 48 h old;
- RPD >15 mm; **and**
- Peripheral calyceal dilation **and/or**
- abnormal ureters

- Follow up US in 1–3 months
- Per provider for: VCUG and/or antibiotic prophylaxis

UTD P3: High Risk
Postnatally

- >48 h old;
- RPD > 15 mm, and
- Peripheral calyceal dilation, abnormal parenchymal appearance and/or thickness, abnormal ureters/bladder



- Follow up US in 1 month
- Recommend VCUG and antibiotic prophylaxis

Antibiotic prophylaxis – No consesus

- Infants with hydronephrosis have been shown to have higher rates of UTIs and hospitalizations for pyelonephritis in the first year of life compared to the general population.

- The benefits preventing such complications in infants at increased risk must be balanced with the adverse effects of selecting drug-resistant bacteria in infants exposed to continuous antibiotic prophylaxis.

Underlying causes of antenatal hydronephrosis

- Transient/physiologic renal pelvis dilation 46–87%
- Vesicoureteral reflux 08–38%
- Ureteropelvic Junction obstruction
- Ureterovesical obstruction
- Bladder outlet obstruction

Causes of Transient/physiologic renal pelvis dilation

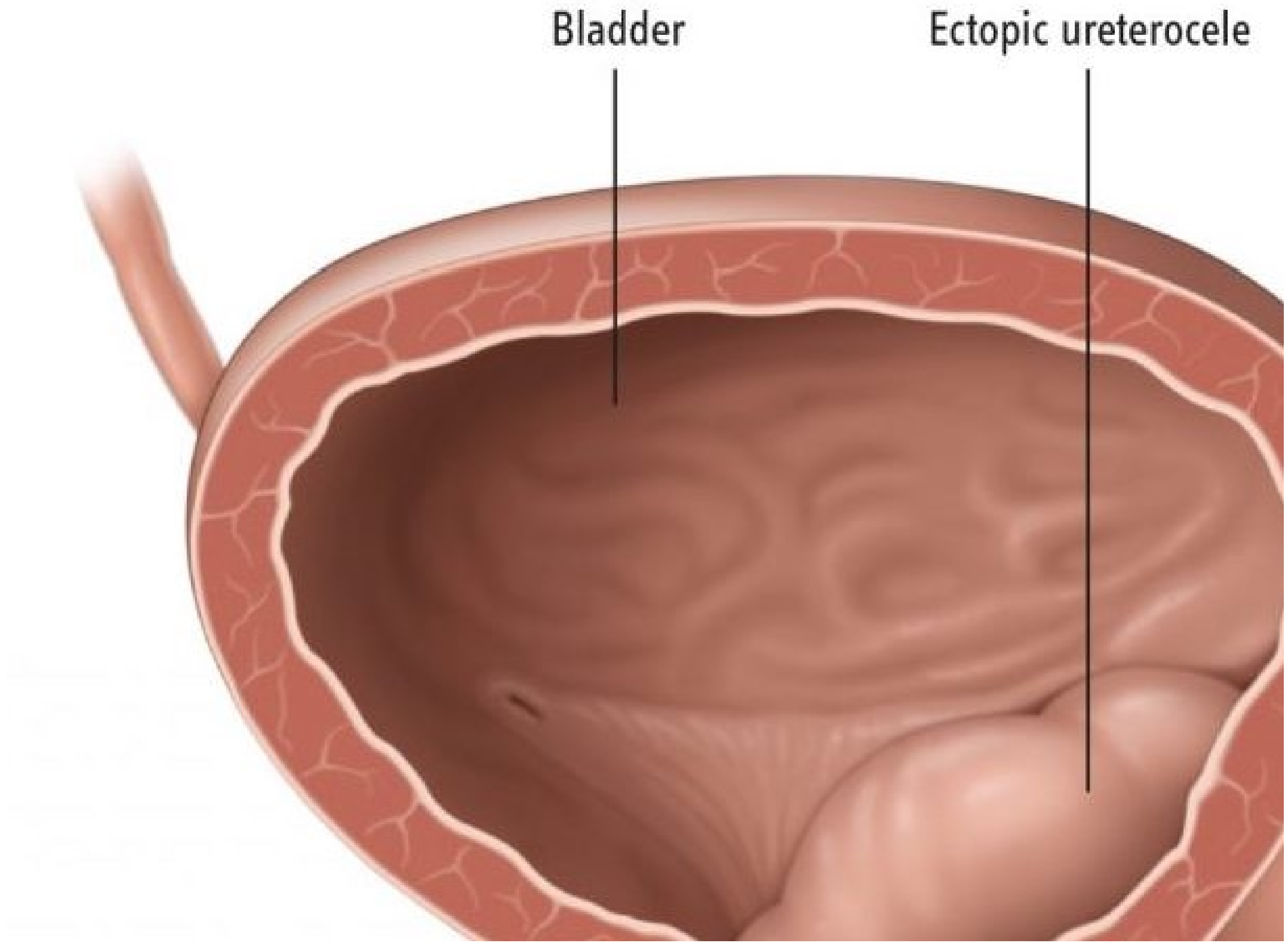
- Maternal hydration.
- Bladder distension/ cycling.
- Transient narrowing of the UPJ.
- Delayed development of peristalsis that resolves with maturation.

Causes Bladder outlet obstruction

- Posterior urethral valves (PUV).
- Urethral atresia.
- Cloacal/urogenital sinus anomalies.
- Ureterocele that obstructs the urethra.
- Myelomeningocele.

Severe cases may lead to oligohydramnios, pulmonary hypoplasia, and abnormal renal development

Thank you for your attention



CONTEMPORARY APPROACH TO NEUROGENIC URINARY BLADDER IN CHILDREN:

CROATIAN EXPERIENCE

Andrea Cvitković Roić

Helena Clinic for pediatric medicine
Zagreb, Croatia

Impaired innervation of the lower urinary tract

Neurogenic bladder dysfunction

- *inability to fully empty the bladder*
- *incontinence of urine*
- *lack of sensation of fullness*
- *high intravesical pressures due to detrusor and/or sphincter hypereflexia*

Over 90% of children at birth have a normal upper urinary tract but if left untreated 50% will suffer upper urinary tract damage due to lower urinary tract dysfunction

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Sturm R et al. Curr Bladder Dysfunt Rep 2016

Congenital causes

- Myelomeningocela
- Lypomeningocela

- Sacral agenesis
- Caudal regression syndrome
- Tethered cord syndrome

Acquired causes

- cerebral palsy
- tumors of the spinal cord
- trauma
- multiple sclerosis
- transversal myelitis

Early diagnosis and treatment

- essential to prevent permanent damage of the kidneys and urinary bladder

  - UTI
  - VUR
  - Hydronephrosis
  - Urolythiasis
  - CKD

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EU PROJECT 2016-2018

Regional Pediatric center of excelence

- Neurogenic bladder and bowel
- Contrast ultrasound
- Neuromodulation & biofeedback

Helena Clinic for pediatric medicine

Diagnosis	Number of patients (%)
MMC	306 (70%)
Anorectal maloformations	43 (9,8%)
Other spinal cord anomalies	30 (7%)
Spinal cord lipoma	13 (3%)
Pelvic surgery	9 (2%)
Cerebral paralysis	8 (1,8%)
Tumors	8 (1,8%)
Neuromuscular diseases	7 (1,6%)
Spinal cord trauma	6 (1,4%)
Other	7 (1,6%)

Spina Bifida

- *Neural tube fails to properly close during the 4th week embyogenesis*
- *One of the most common severely disabling birth defects*
- *1-2 per 1000 live births*

Main symptoms:

- *Paralysis of legs*
- *Abnormalities of hips, knees and feet*
- *Hydrocefalus*
- *Arnold-Chiary type II malformation*
- *Neurogenic bowel*

NEUROGENIC URINARY BLADDER

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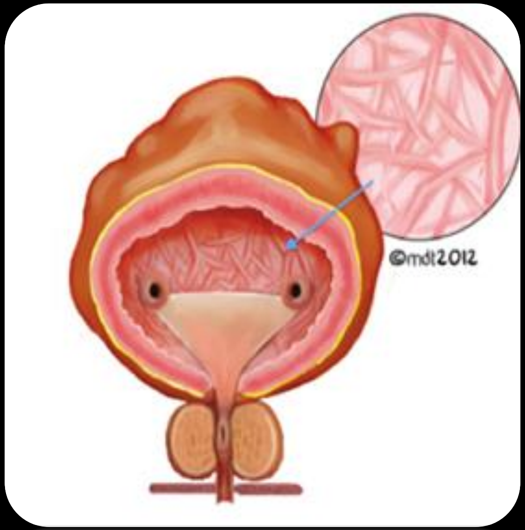
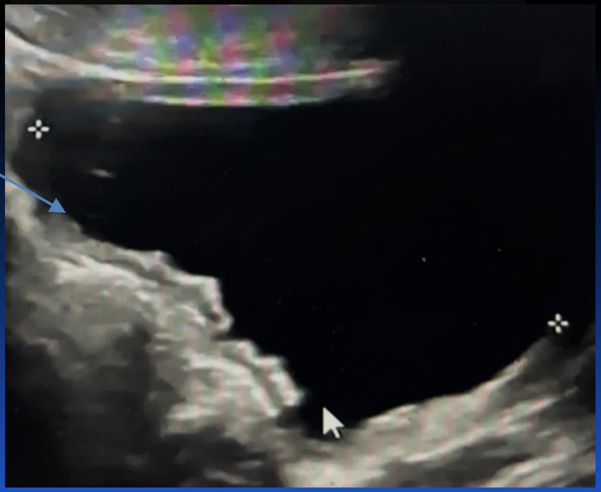
Longlasting neurogenic dysfunction

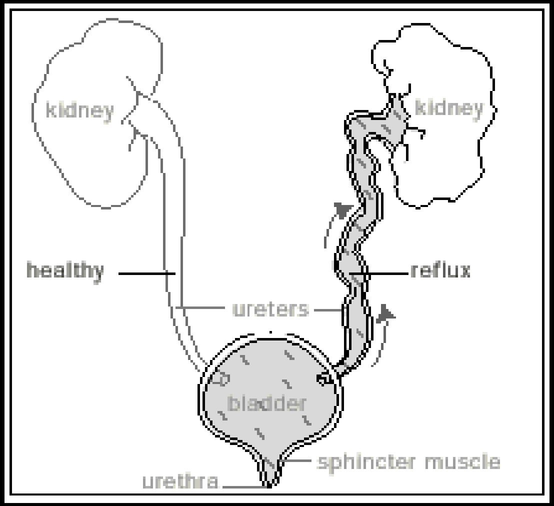
- *smooth muscle hypertrophy*
- *changes in the connective tissue matrix*
- *detrusor hyperactivity, loss of contractility later*



- *trabeculated thickened bladder wall, with low compliance*



- *incompetence vesicoureteric orificium*



Urinary tract infections
Vesicoureteric reflux
Hydroureteronephrosis

Kidney scarring

Cvitković A et al. Paediatr Croat 2002

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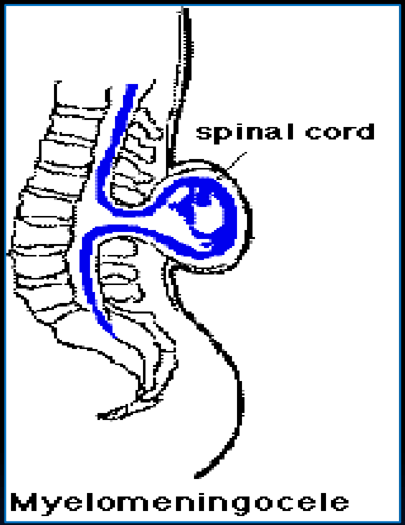
Types of Spina Bifida



- Vertebrae fail to fuse and the protective coverings, spinal nerves and spinal cord protrude
- The spinal cord fails to develop properly and nerves are damaged

➢ Neurogenic bladder in <u>almost all</u> patients

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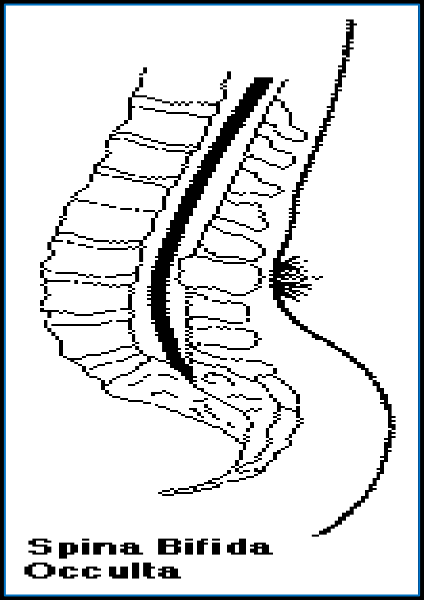
Association for Spina Bifida and Hydrocephalus (www.asbah.org/whatissb.html)

Types of Spina Bifida



- *Abnormal opening of spine- may have dimple on the skin, dark spot, tufts of hair or nothing visible*

- *Sacral agenesis*
- *Tethered cord syndrome*
- *Caudal regresion syndrome*

- Neurogenic bladder ???

CONTEMPORARY DIAGNOSTICS OF NEUROGENIC BLADDER

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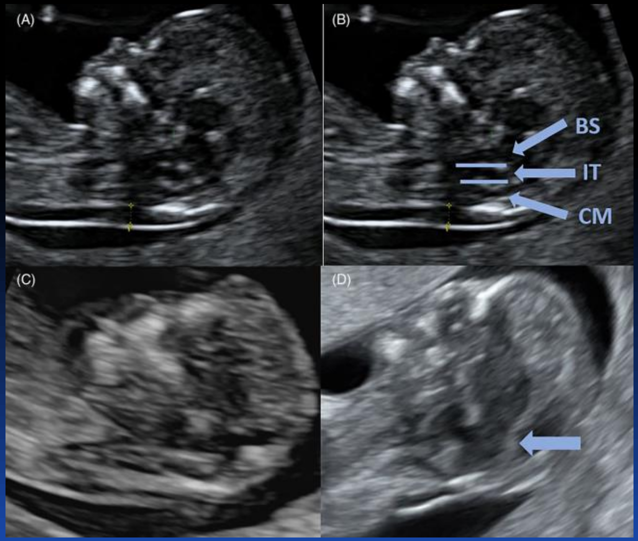
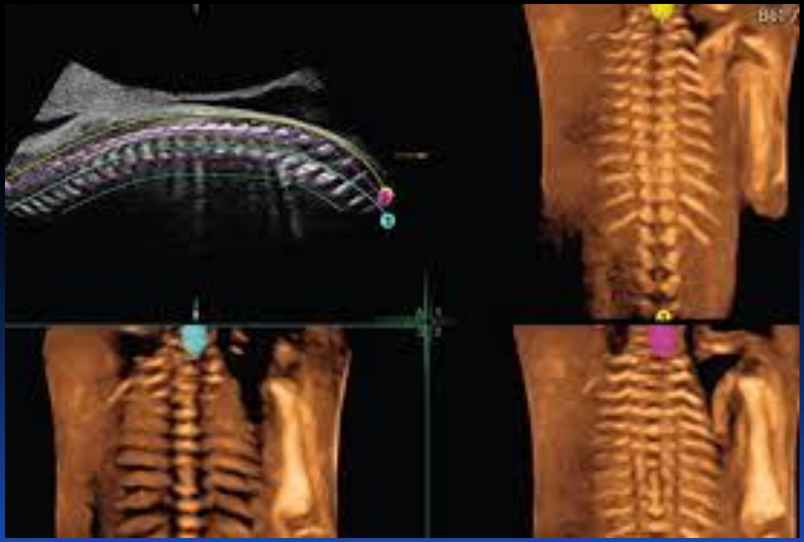
Prenatal diagnosis

Lemon shaped skull, ventriculomegaly; Chiari II malformation; Saccular lesion in fetal spine





Gotha L et al. Prenatal diagnosis 2020

Prenatal approach

- Prenatal surgery- defect closure
- 23. - 26. week of gestation
- Children operatated prenataly less often require v-p shunt due to hydrocephalus and have better motor development at early age

Adzik NS et al. N Engl J Med 2011
Tolcher MC et al. BJOG 2019
Brock JW et al. J Urol 2019

Postnatal diagnostic algoritham

Depeneds on the age

- History and physical examination / neurological exam
  - *Perianal region*
  - *Sphinter tone/ampula*
  - *Evaluation of sensation*

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Postnatal diagnostic algoritham

Depeneds on the age

- US spine / MR spine
- US kidney and uronary bladder
- 4 hours voiding observation
- Contrast-enchanced voiding urosonography (ceVUS)
- Urodinamics
- Videourodinamics
- MRU / fMRU

Urodynamic studies

Gold standard

in

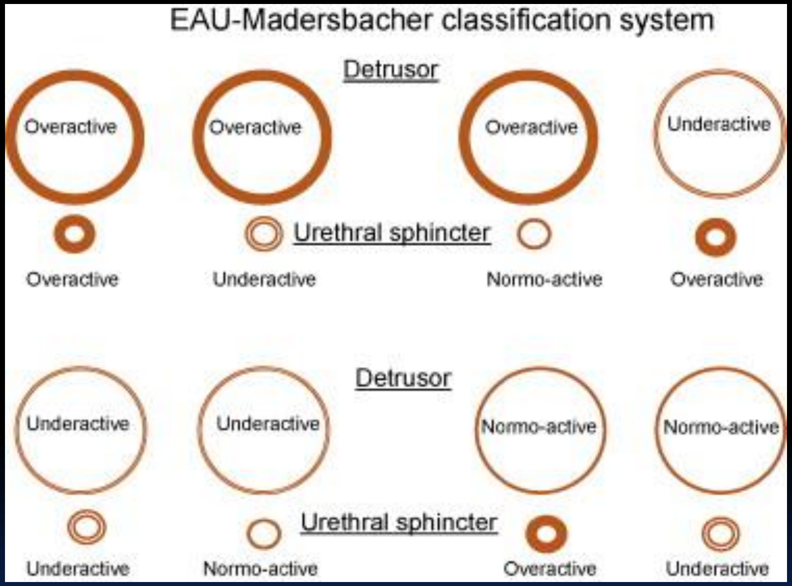
evaluation of the function

of

lower urinary tract

Urodynamic classification

Detrusor and sphincter function:



- *normal*
- *hypo/areflection*
- *hyperreflection*

Van Gool 1995

Bauer et al, Neurourol Urodyn. 2012

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Urodinamic examination

- *Invasive, painfull*
- *Risc of infection*
- *Cost*
- *Long learning curve*
- *Experience of the whole team*

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ICCS International Children's Continence Society

Ultrasound

???

- Can we use ultrasound for screening - neurogenic bladder or not ?

- How to assess the need for invasive urodynamics investigation?

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When to suspect - neurogenic blader ?

US of spine

Sacral dimple

- **Simple:** < 5mm, < 25 mm from anus   Screening **NOT recommended**
- **Atypical:** > 5 mm, > 25 mm from anus   Screening recommended
  - *Multiple dimples or other skin changes*

SB occulta
- Tethered cord
- Dorsal dermal sinus
- Diastematomyelia
- Anterior sacral meningocela
- Spinal lipoma

ICCS: Imaging recommendation in suspected lower urinary tract dysfunction- US of urinary tract

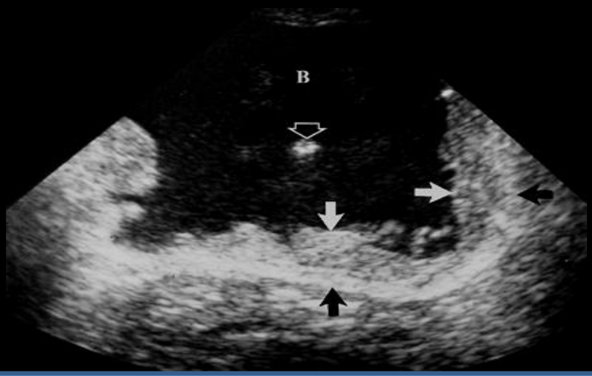
- *Kidney size and growth*
- *Upper tract dilatation*
- *Ureteric dilatation*
- *Bladder wall thickness*
- *Bladder emptying*
- *Rectal diametar*

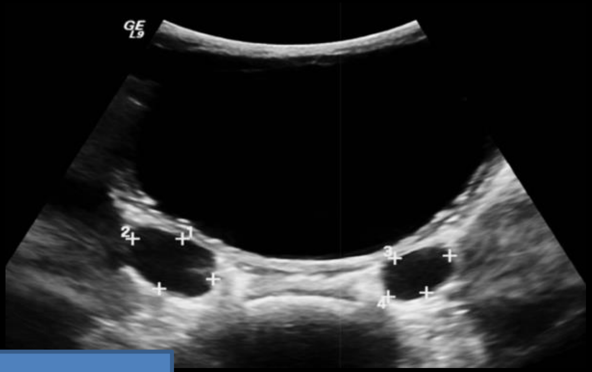
Y F Rawashdeh et al. Neurolurol Urodyn. 2012

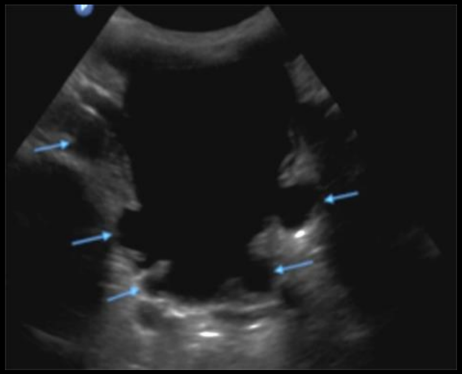
ICCS International Children's Continence Society

US of neurogenic bladder

We look for indirect signs of high bladder pressure







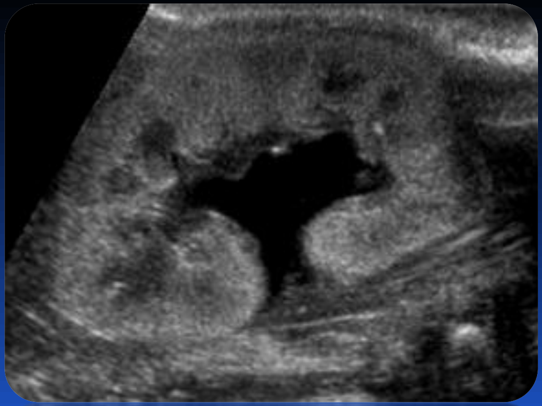
- bladder wall thicknening
- dilatation of ureters/renal collecting system

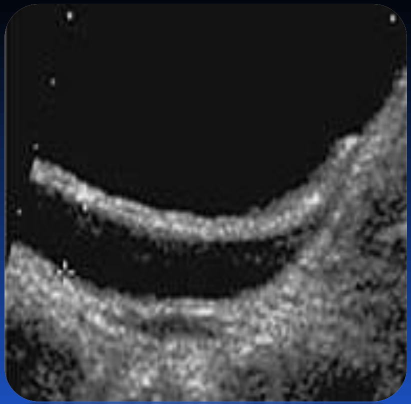
high IV pressure+/- VUR

Cvitković A et al. Eurol Urol 2002

US - dilatation of ureters and collecting system

- *Due to high intravesical pressure during filling and/or voiding*
- *usually in advanced stage*





US - bladder wall thickness (BWT)

BWT is dependent on:

- *Bladder volume/degree of fullness*
- *Quality of US*
- *Standardisation of measurement method*

- *In children it is not age dependent*
- *Medium filling of the bladder*

< 3 mm when bladder is more than **20%** of EBC
< 5 mm when bladder is empty

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J of Urology 2000

US - detrusor thickness (DWT)

- *Detrusor thickening is due to increased workload with hypertrophy and connectve tissue formation*
- *Work load increases due to neurogenic obstruction and raised pressures*

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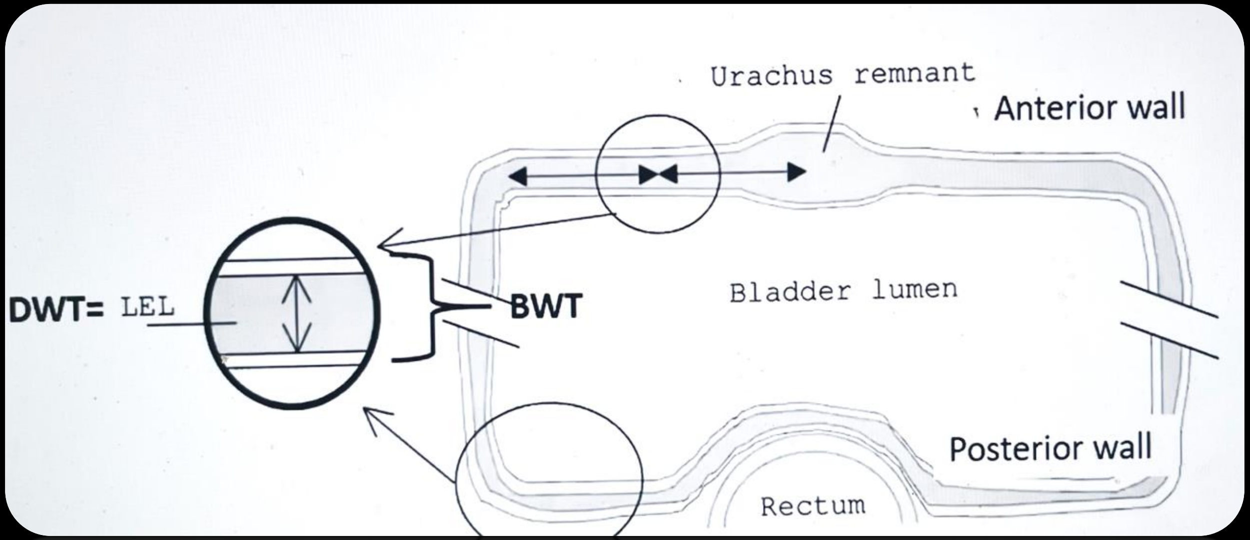
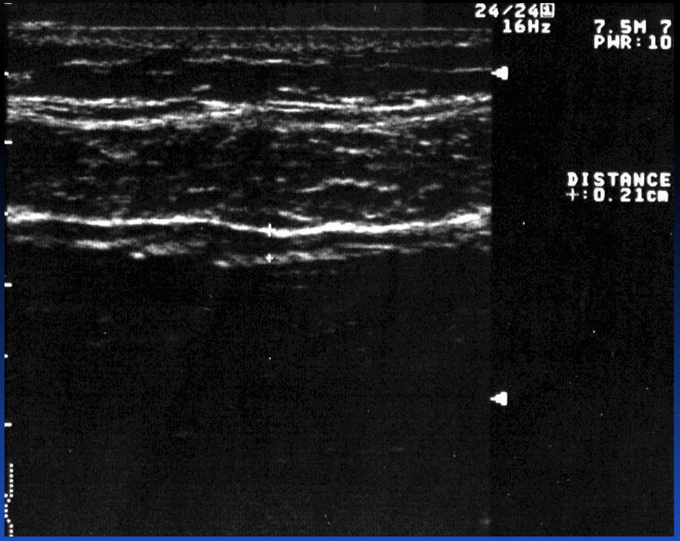
Cvitković A et al. Pediatr Nephrol 2001

US - detrusor thickness



- *At medium filling of the bladder*
- *The best - the anterior wall*
- *Linear probe 7.5-10 MHz*

  - *mucosis, submucosis, detrusor, serosis*
  - *Detrusor = hipoehogenic layer*



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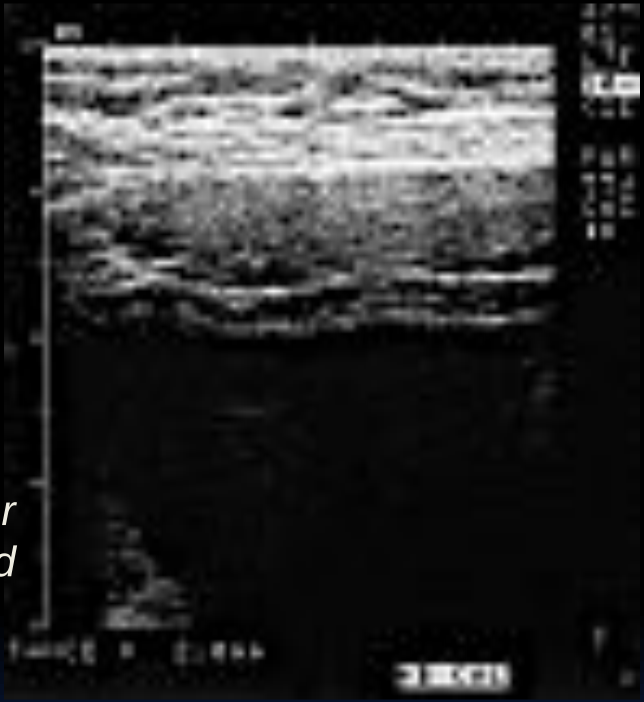
Cvitković A et al. Pediatr Nephrol 2001

US - detrusor thickness

- ➢ with dysfunction mm: **1,9 mm** *(0,8-8 mm)*

- ➢ without dysfunction mm: **1,2 mm** *(0,5-3 mm)*



•There is statistically significant difference in mean detrusor thickness between children with normal urodynamics and children with neurogenic bladder (NB)

• However, due to overlap of measured values, it is not possible to determine the cut-off value that could be used to distinguish children with and without

Cvitković A et al. Eurol Urol 2002

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ICCS International Children's Continence Society - bladder capacity measurement

Normal capacity for age (EBC)

- *(Age yrs + 1) x 30 in ml*
- *Weight (kg) x 7 ml for infants*

Normal: **80-120%** of EBC for age

Y F Rawashdeh et al. Neurolurol Urodyn. 2012

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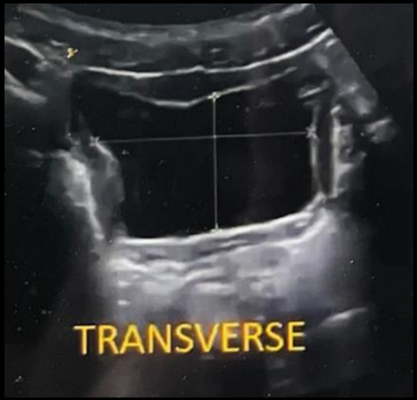
US - bladder capacity measurement

At maximum urge to urinate

- Width x depth x length x K -

- ***K*** *correction factor*
- *"**K**" depends on the shape of bladder*



Cvitković A et al. Pediatr Radiol 2003

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Measurement of bladder capacity

- *Correction coefficient "K"*

- *<u>Round shape</u>*
- *Cuboid shape*
- *Triangular shape*
- *Undefined shape*

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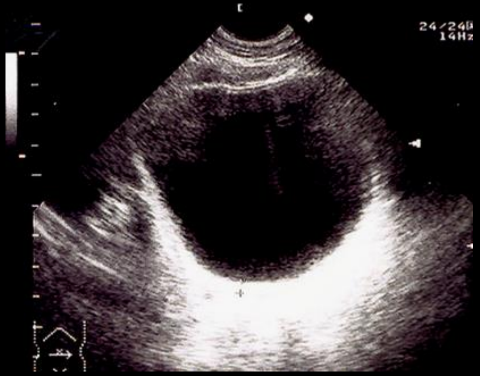
Pediatric correction coefficient **0,66**

146 children referred for urodynamic investigation

Bladder shape	**Frequency (%)**	**K**
Cuboid	*24.7*	*0.923*
Ellipsoid	*21.2*	*0.802*
Triangular	*25.34*	*0.623*
Round	*23.29*	*0.561*

Cvitkovic A. Pediatric Radiology.2003

Cuboid 0,92



Round 0,55

Ellipsoid 0,80

Triangular 0,62

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Post-void residual urine

Measure immediately or document time lapse

A x B x C x k

infants and younger children (< 5 yo): < 5 – 20 ml

4-6 yrs : >20 ml or > 10% BC - repeatedly

7-12 yrs: >10 ml or 6% BC

- *US done within 5 minutes of voiding*
- *Bladder not under or over-filled (50% or 115%)*
- *Subtract 1-2 mls for every minute beyond 5 min*

Chang S et al. Neurourol Urodyn.2013

Ultrasound assessment

- *bladder wall thickening*
- *thickening of detrusor*
- *smaller or larger bladder capacity for age*
- *poor emptying (residual urine)*
- *dilatation of the ureter & renal collecting sy.*

(high pressures IV +/- VUR)

➢ alert us to longstanding problems with bladder storage and emptyng

Cvitkovic A, Palcic I et al. Pediatr Croat 2014

4 hour voding US observation

Used to assess bladder function in children who are not toilet trained

Noninvasive investigation which gives information about:

- Number of micturition
- Bladder capacity
- Residual urine
- Quality of stream

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4 - SATNA OPSERVACIJA MOKRENJA

Ime i prezime: ____________________

Datum rođenja: ____________________

Dijagnoza: ____________________

Terapija: ____________________

Priprema i izvođenje:

- Djetetu nije potrebno ograničiti tjelesnu aktivnost niti unos tekućine
- Prije izvođenja testa izvagati suhu pelenu i staviti ju djetetu
- Vrijeme početka testa i težinu suhe pelene upisati u tablicu pod „0"
- Dijete je pod nadzorom roditelja i uroterapeuta
- Važno je pratiti kada se dijete pomokri
- Odmah po mokrenju izvagati pelenu i UZV metodom odrediti količinu rezidualnog (ostatnog) urina
- U tablicu upisati izmjerene vrijednosti

Datum pregleda: ____________________

	VRIJEME	TEŽINA PELENE (gr)	REZIDUALNI URIN (ml)	VOLUMEN MOKRENJA (ml)
0				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				

Wide P et al. Four-hour voiding observation with provocation test reveals significant abnormalities in children with spinal dysraphism (SD). J Ped Urol 2020

➢ Children with **SB** have smaller or larger capacity, RU, leak on provocation

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US criteria for diagnosis

- *Normal bladder wall thickness **(<3 mm)***
- *Normal detrusor thickness*
- *Normal bladder capacity **(80-120% for age)***
- *No significant residual urine*
- *Without dilatation of ureters and kidney collecting system*
- *Normal 4 hours US voiding observation*

➡ **Further invasive diagnostic investigation is not necessary but always need follow up**

Cvitkovic A, et al. Pediatr Croat 2014

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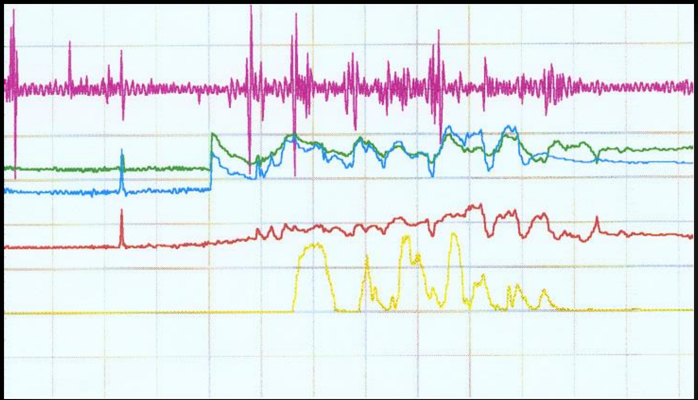
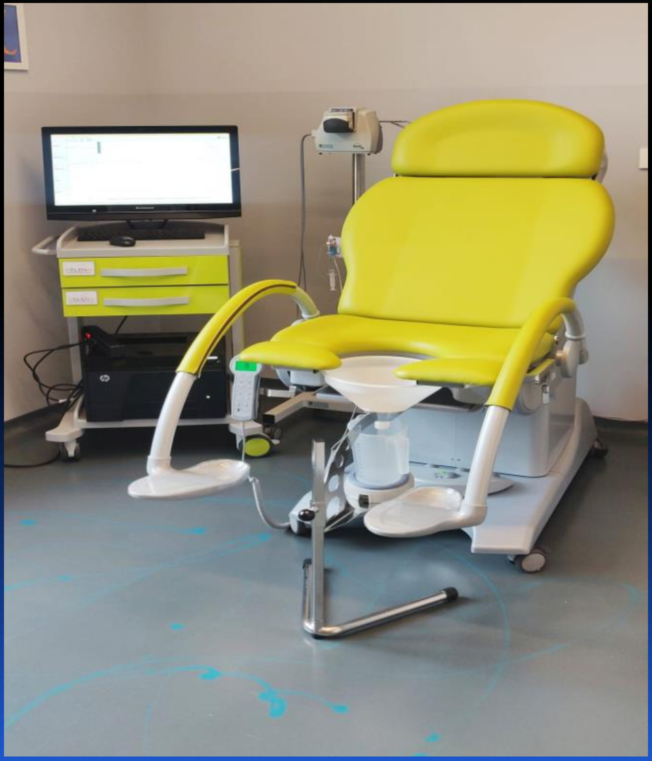
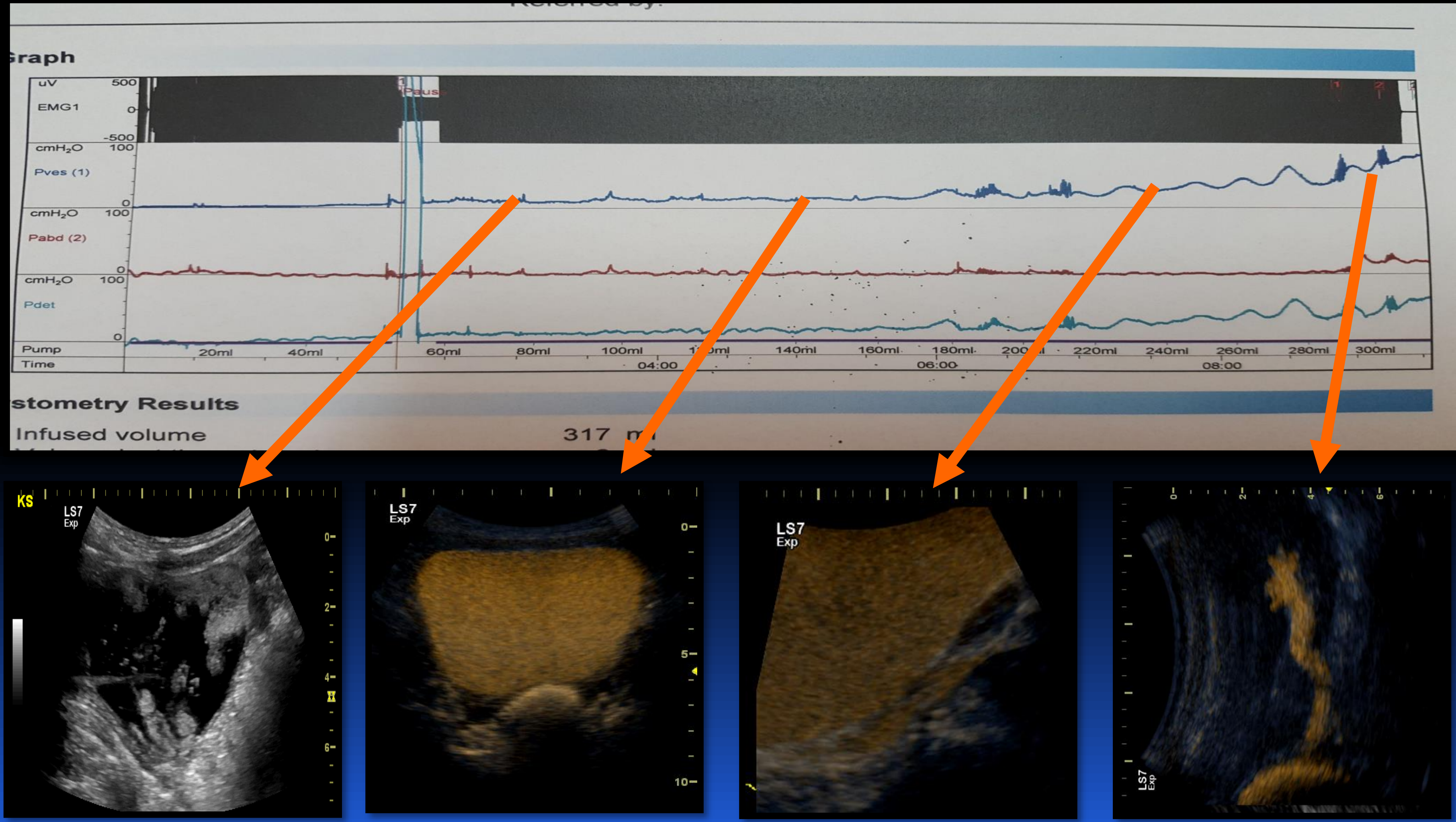
Urodynamic Study: further functional evaluation

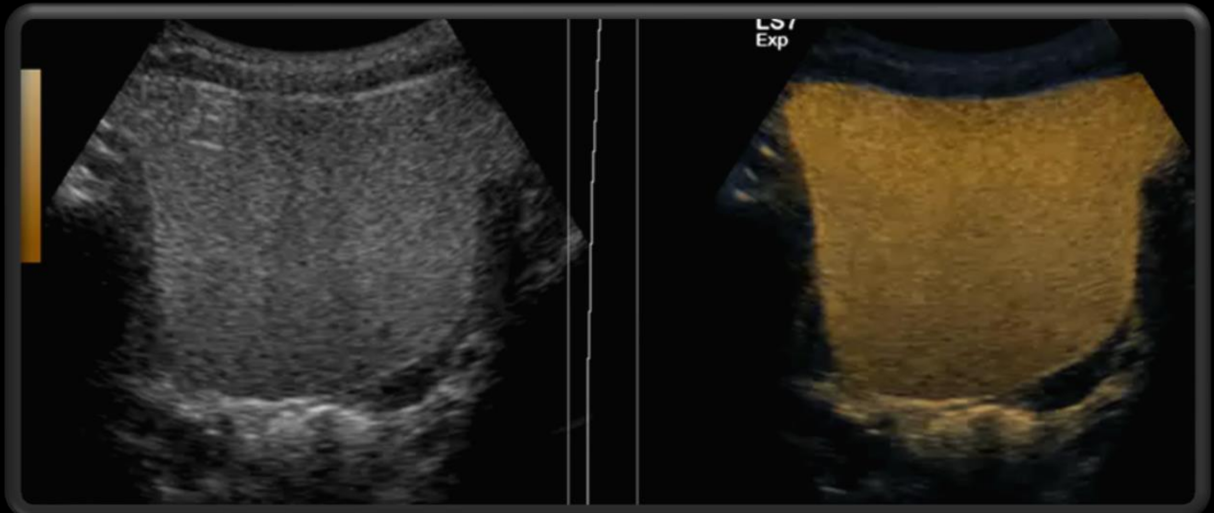


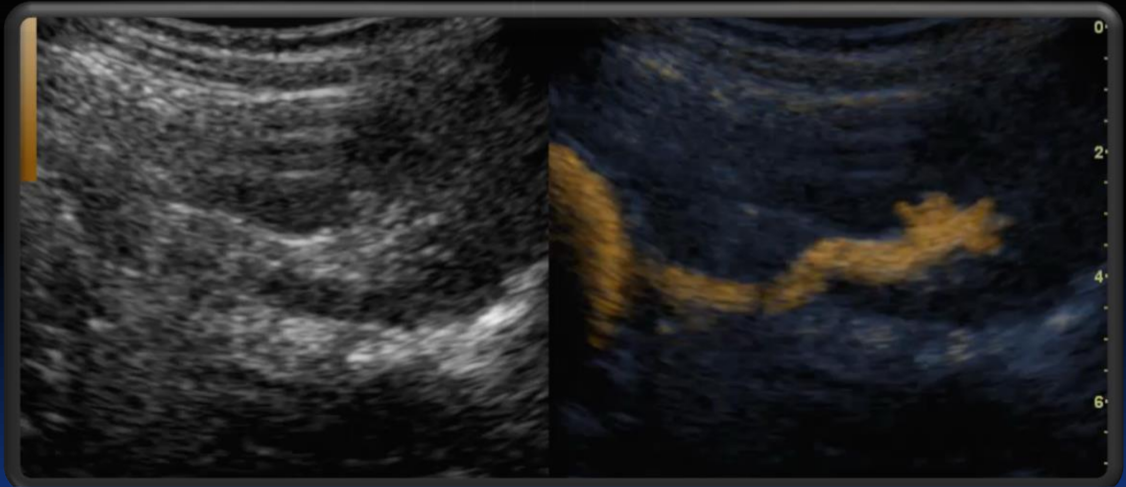


Videourodynamics & ceVUS

Cvitkovic Roic et al An innovative diagnostic procedure in children: videourodynamics with contrast-enhanced voiding urosonography. J Ultrasound. 2022







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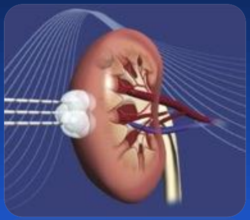
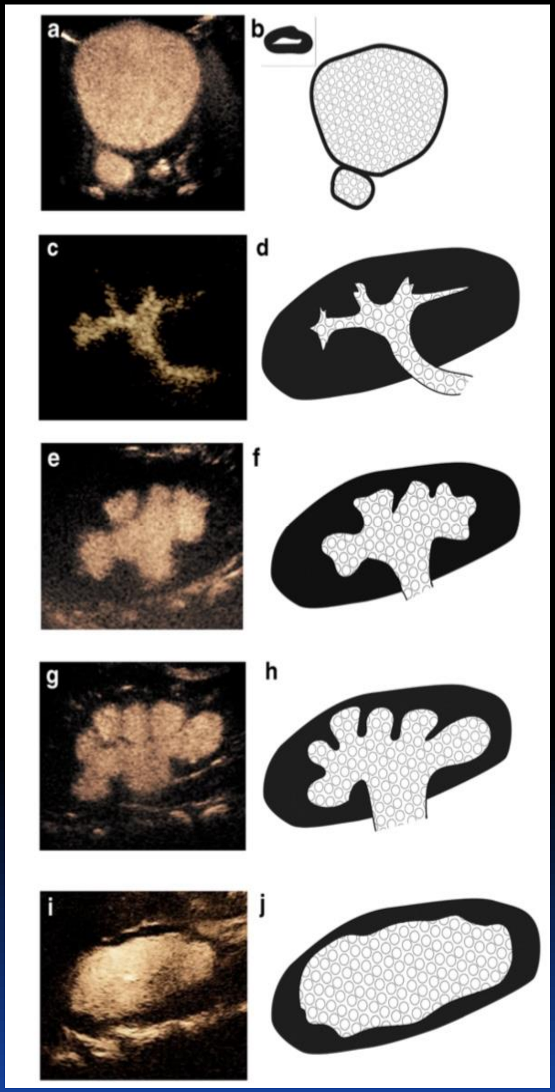
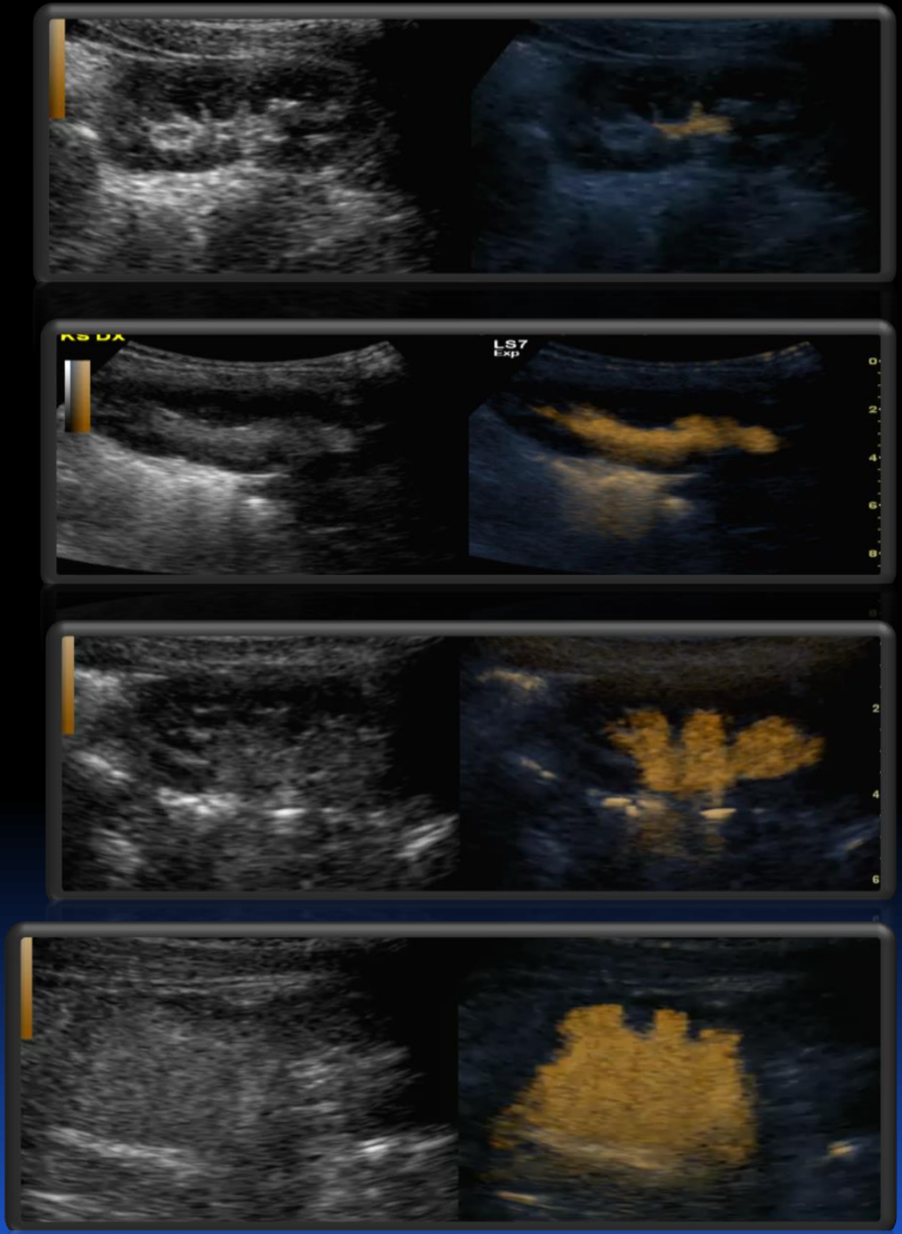


Grading of VUR by ceVUS



Ntoulia A et al. Pediatric Radiology 2020.



ceVUS: our experience since 2006

Advantages

•Pediatric friendly- no radiation; parents presence

•US scan in different positions; voiding in sitting and standing position

• Higher detection rate of VUR compared to VCUG (10-15%)

•Excelent grading of VUR

•Excelent intrarenal reflux display

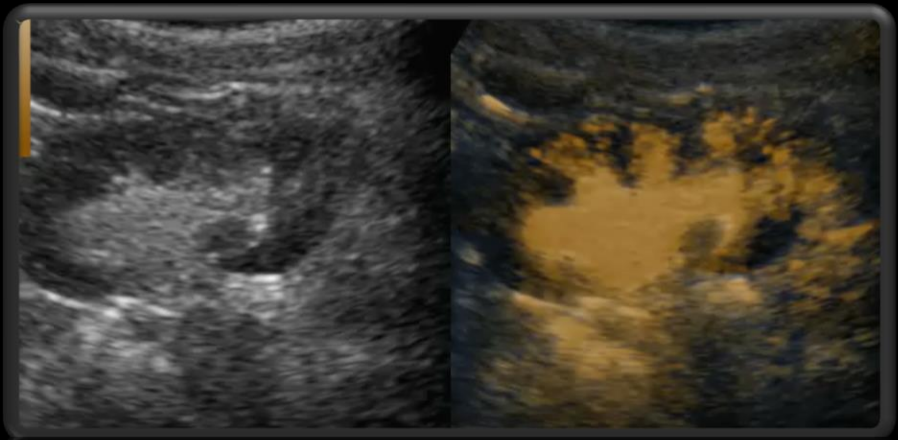
•Possibility to combine with urodynamics- videourodynamics

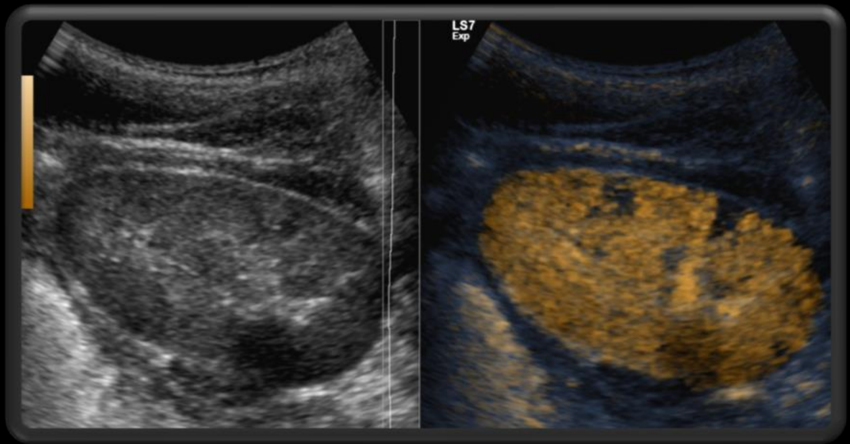
Disadvantages

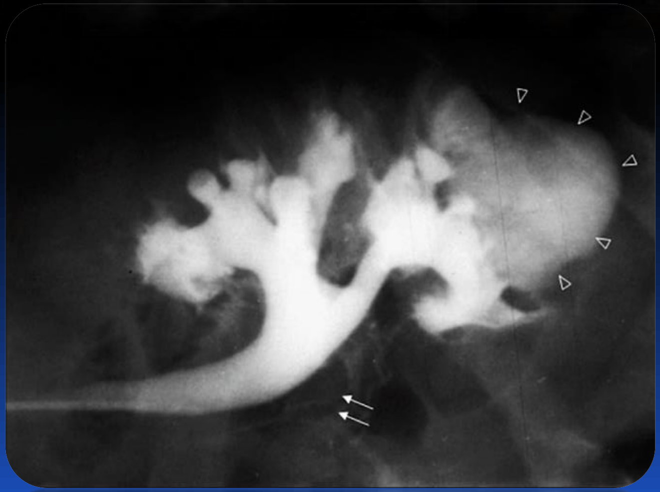
- Price of equipment and contrast
- Longer duration than VCUG (cyclic studies)
- Experienced staff needed
- Anatomical details of lower urinary tract not well shown *(small diverticula or some urethral anomalies)*

Cvitković Roić A, Paediatrics Today. 2016

Intrarenal reflux (IRR)







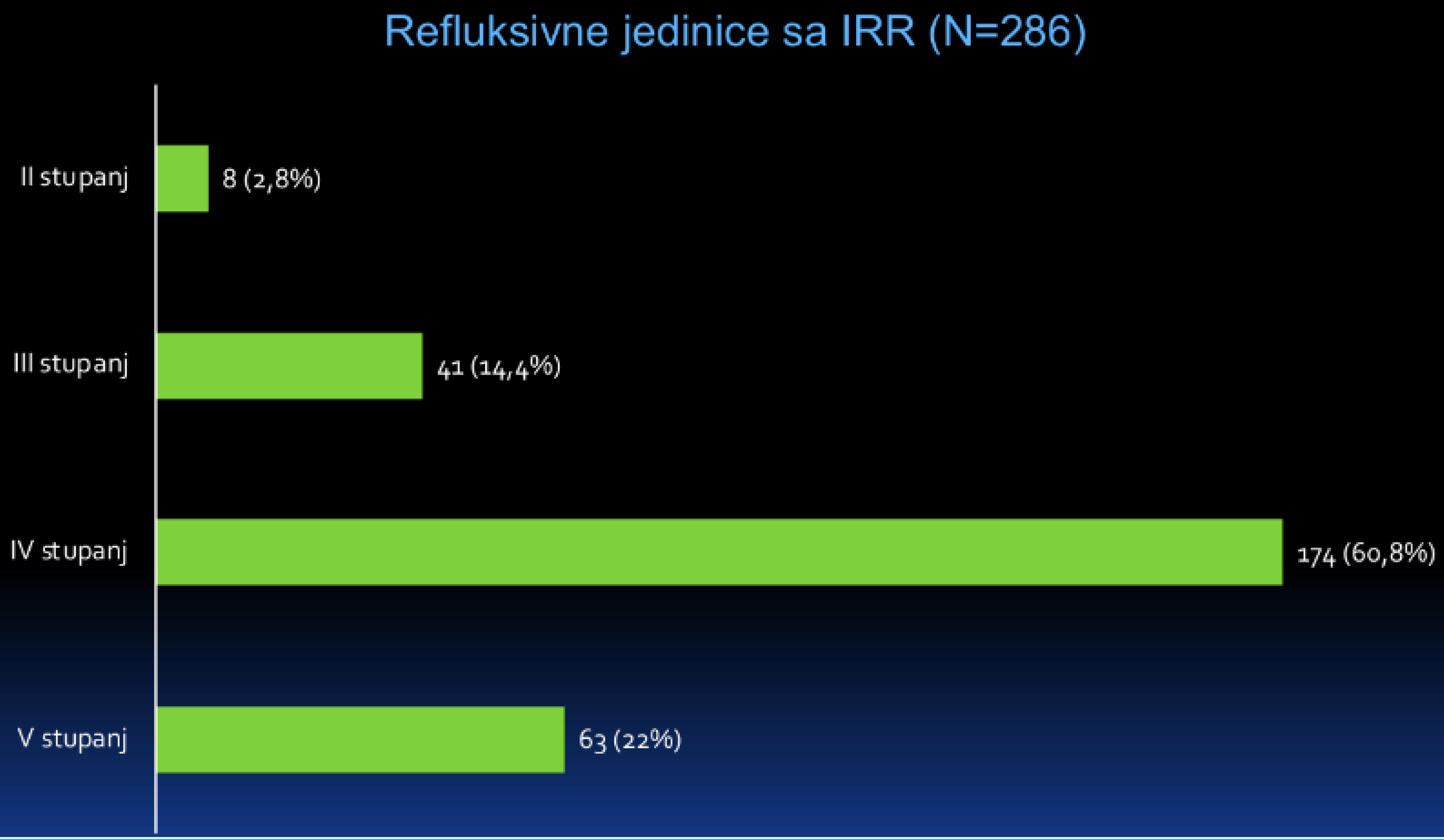
Original Paper | Published: 26 February 2021

Contrast-enhanced voiding urosonography in the diagnosis of intrarenal reflux

Andrea Cvitkovic-Roic, Daniel Turudic ✉, Danko Milosevic, Iva Palcic & Goran Roic – Show fewer authors

Journal of Ultrasound (2021) | Cite this article

Grade of VUR & IRR



Importance of considering IRR in the classification of VUR ?

> J Ultrasound. 2023 Jan 30. doi: 10.1007/s40477-022-00772-2. Online ahead of print.

Intrarenal reflux with low-grade vesicoureteral reflux: an underestimated significance?

Andrea Cvitkovic Roic [1,2,3], Daniel Turudic [4], Danko Milosevic [5,6], Goran Roic [7,3]

- 5 children, 4-42 months
- VUR gr II (3 unilar, 2 bilat) & intrarenal reflux

- Urodynamic investigation:
- 5 children OAB
- 4 low compliance
- 2 high voiding pressure

- Should we introduce/maintain UTI prophylaxis in low-grade VUR with IRR (with/or even without) urodynamic changes?

- Should IRR be recommended as a supplementary aggravating variable to be added in VUR classification guidelines, not only for low-grade VUR but of any VUR degree?
- We recommend further multicenter prospective studies to answer such questions

CONTEMPORARY TREATMENT OF NEUROGENIC BLADDER

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Treatment of neurogenic bladder

Goals:

1. *Prevention of kidney function damage (CKD)*
2. *Continence*

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Kidney parenchimal damage

✓Incomplete bladder emptyng (& high pressure)

✓Recurrent urinary tract infections

✓High intravesical pressures

Cohen RA et al. J Urol 1990
Leonardo CR et al. Pediatr Nephrol 2007
DeLair SM. J Spinal Cord Med 2006

Kidney parenchimal damage

- ✓Incomplete bladder emptyng (&high pressure)
- ✓Ponavljane uroinfekcije
- ✓Povišeni intravezikalni tlakovi

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CLEAN INTERMITTENT CATHETERISATION (CIC)

- empty the bladder at the low pressure
- avoid UTI (*due to the residue urine*)
- protect the urinary tract / kidneys
- improve incontinence

Lapides 1975

- Lapides J,. J Urol. 1972
- Bauer S. Dialog Ped Urol. 2000

Education of parents

- since newborn period
- education of every step
- cooperation with the whole team, consultations and support

Education of selfcatheterization

- starts at 4-6 y
- depending on fine motor skills and mental age
- education with dolls

Kidney parenchimal damage

- ✓High pressure incomplete bladder emptyng
- ✓Recurrent urinary tract infections
- ✓High intravesical pressures

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UTI in neurogenic bladder

- One of most common cause of death in the SCI population (Soden et al (2000). Spinal Cord; De Vivo (1993) Arch Phys Med)
- First cause of rehospitalization (Vaidyanathan S. Spinal cord, 1998)
- 80 % were treated for symptomatic UTI (Scand Urol Nephrol)

First therapeutic message: asymptomatic bacteriuria

- very strong consensus for not treating patients with bacteriuria without symptoms (*EUA guidelines*)

- except for urologic procedures such as urodynamic, cystoscopy (*Esclarin de Ruz 2000 J Urol, Darouiche J Hosp Infec 1994*)

Prophylaxis in neurogenic blader- still debate

*Meta analysis of 15 studies;
Prophylaxis did not significantly reduce symptomatic UTIs in patients with NB

**Prophylaxis performed constantly, without interruption, is associated with a lower risk of developing fUTIs and to develop renal failure in adulthood

***Prophylaxis in children on CIC- causes *increased rates of infection*

****Extensive prophylaxis in children with NB causes *higher intestinal load of resistant bacteria*

*Morton SC, et al. Arch Phys Med Rehabil 2002
**Mariani F et al. Childs Nerv Syst2022
***Clarke SA, et al. J Pediatr Surg 2005
****Mutlu H&Ekinci Z. ISRNPediatr 2012

> Urology. 2022 Jun;164:224-229. doi: 10.1016/j.urology.2021.12.027. Epub 2022 Jan 11.

Risk Factors for Recurrent Urinary Tract Infection in Children With Neurogenic Bladder Following Clean Intermittent Catheterization

Man Jiang [1], Jikui Deng [2], Guanglun Zhou [3], Shoulin Li [3], Gang Liu [4]

- high level of spinal cord lesions
- long duration of NB
- vesicoureteral reflux
- increased bladder wall thickness
- low bladder compliance

→ directly associated with recurrent UTIs in children with NB

- Children with NB might have higher susceptibility to chronic renal insufficiency after recurrent UTIs.

Kidney parenchimal damage

- ✓High pressure incomplete bladder emptyng
- ✓Recurrent urinary tract infections
- ✓High intravesical pressures

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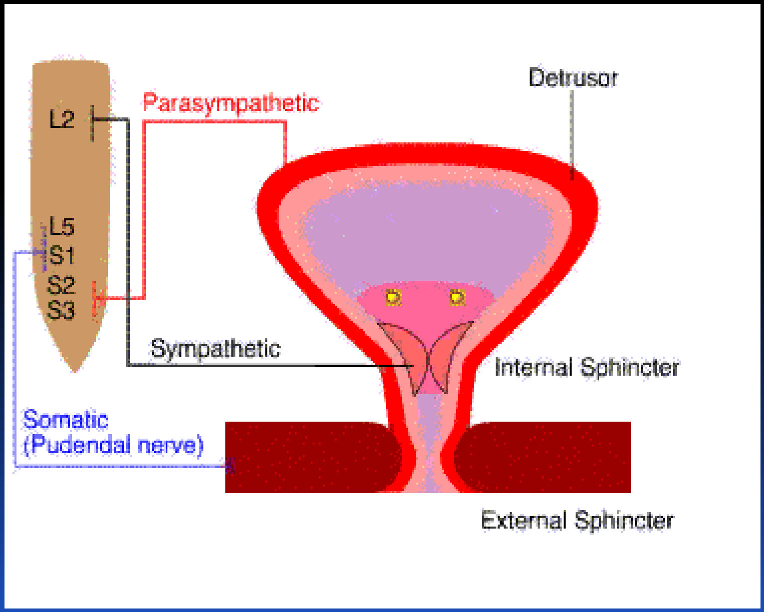
Indications for Proactive Treatment in Myelodysplasia

- Antimuscarinic medication

  intravesical or peroral

  - High detrusor voiding pressure
  - High leak point pressure
  - Poor compliance - high detrusor filling pressure *(> 40 cm H_2O)*
  - High grade reflux on cystography



ANTICHOLINERGIC MEDICATION

DRUG	DOSE	FREQUENCY
Tolterodine	1 – 2 mg	TID[1]
Tolderodine XL	2 - 4 mg	Once-daily
Oxybutynin*	2,5 - 5 mg	BID[2] or TID
Oxybutynin XL	5 - 15 mg	Once-daily
Oxybutinyn transdermal patch	3.9 mg/d	1 patch BIW
Oxybutinyn gel 10%	1 ml	Once-daily
Trospium*	20 mg	BID or TID
Trospium XL	60 mg	Once-daily or BID
Propiverine	15 mg	BID or TID
Propiverine XL	30 mg	
Solifenacin**	5 – 10 mg	Once-daily
Fesoterodine**	4 – 8 mg	Once-daily
Darifenacin**	7.5 – 15 mg	Once-daily

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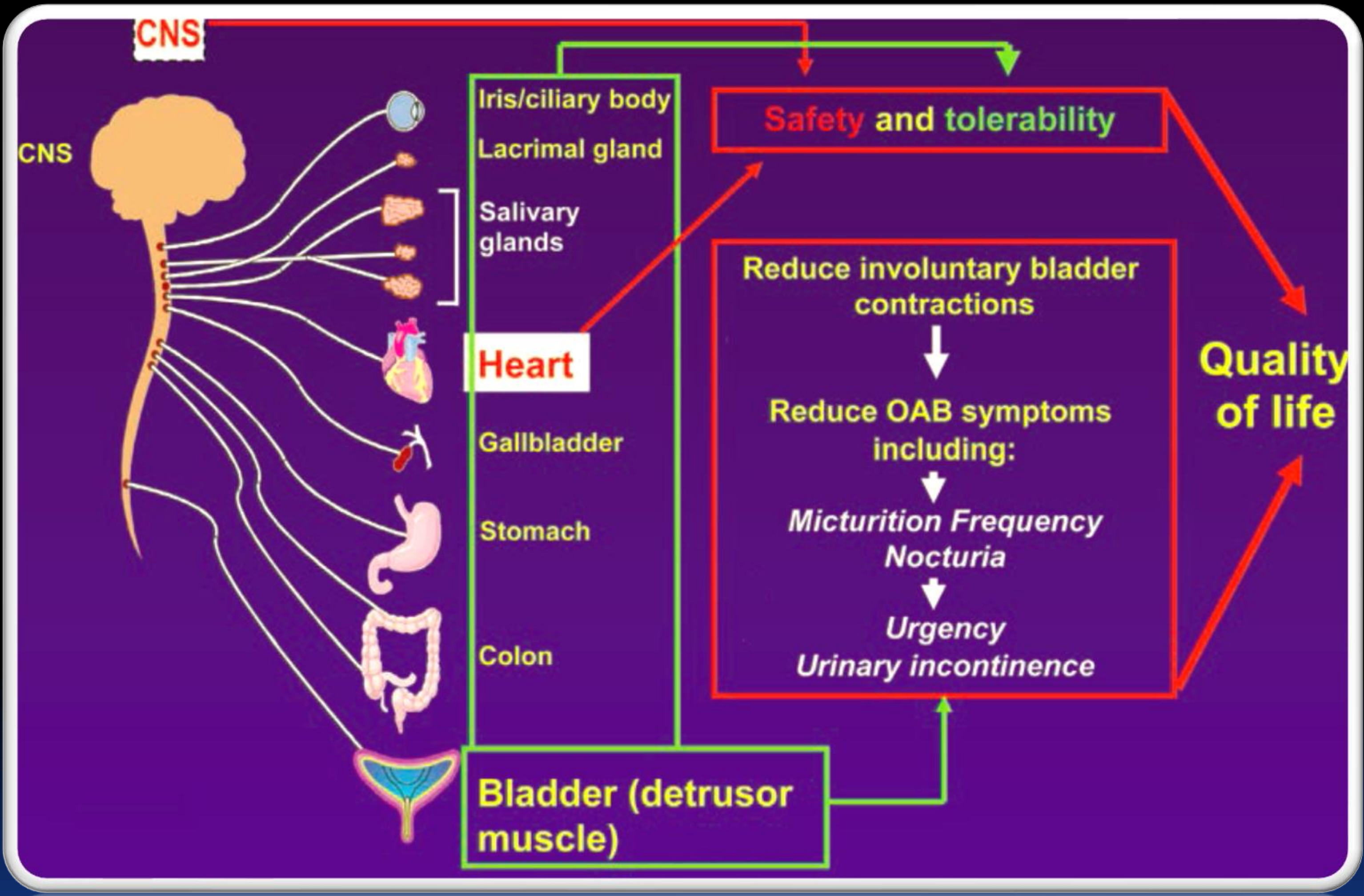
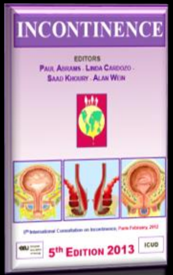
Horstmann M.Neurourol Urodynam 2006

SISTEMIC SIDEFECTS





I *Nardulli R.* nt J Immunopathol Pharmacol. 2012

Mirabegron

- selective beta3 receptor agonist
- ≥ 3 years
- increases bladder capacity, reduces intravesical pressure,

improves continence

- well-tolerated drug, with no significant adverse effects- UTI,

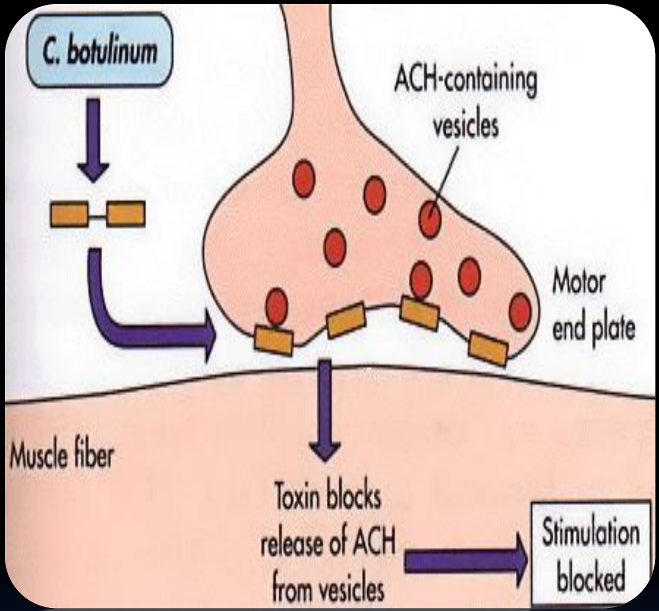
tachycardia

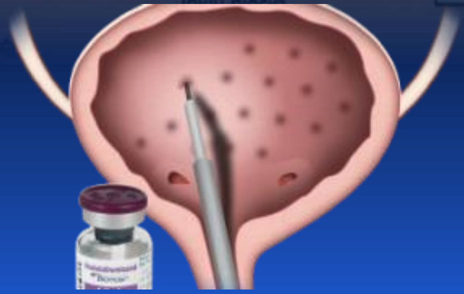
- Dose 1x 25-50 mg

Wollner J et al. Spinal Cord 2016
Park JS. World J Urol 2019
Krhut J. Neurourol Urodyn. 2018

Intravesical Botulin toxin A

- Inhibits release of acetylcholine at the presynaptic cholinergic neuromuscular junction
- also inhibits noradrenaline, dopamine, serotonin, other neuropeptides
- 20-30 injections, 10-20 iu/kg



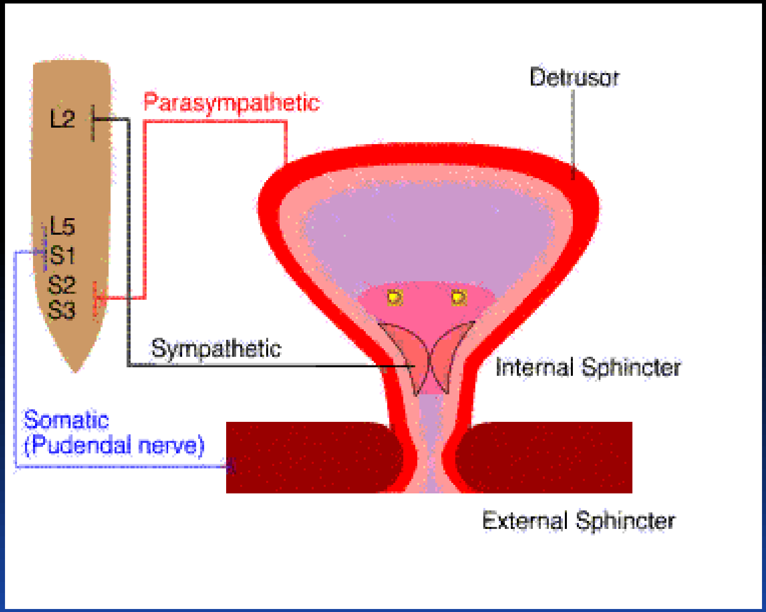


Figueroa V et al. J Pediatr Urol 2014
Pascali MP et al. J Urol 2011
Khan MK. J Pediatr Urol 2015

Botulinum toxin

- Urodynamic effects

  - i mean max detrusor voiding pressure
  - i # DO
  - h volume at 1st detrusor contraction
  - h mean max bladder capacity
  - h bladder compliance



- clinically significant effect
- with minimal systemic side effects
- bladders with fibrosis are least responsive
- Mean duration of effectiveness 4,6 months (0-18 months)

Xavier Game et al. Pediatr Urol 2009

Leon P et al. J Pediatr Surg 2014

Tiryaki S et al. J Pediatr Urol 2015

OUR SECOND GOAL:

URINE CONTINENCE

Continence Management

- CIC + antimuscarinics achieves continence in about 60% with no further treatment

- Augmentation cystoplasty now 'required' in 15%
  - Incontinence,
  - Upper urinary tract deterioration
  - Bladder neck surgery for i outlet resistance

SnowLisy DC et al. U Urol 2015
Schlomer BJ et al. J Pediatr Urol 2014
Grimsby GM et al. J urol 2016

Guideline > Neurourol Urodyn. 2020 Jan;39(1):45-57. doi: 10.1002/nau.24211.
Epub 2019 Nov 13.

EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part I diagnostics and conservative treatment

Raimund Stein [1], Guy Bogaert [2], Hasan S Dogan [3], Lisette Hoen [4], Radim Kocvara [5], Rien J M Nijman [6], Josine S L T Quadackers [6], Yazan F Rawashdeh [7], Mesrur S Silay [8], Serdar Tekgul [3], Christian Radmayr [9]

With conservative treatment:

- the upper urinary tract is preserved in up to 90%,
- urinary tract infections are common, but not severe
- complications of CIC are quite rare
- continence can be achieved at adolescence in up to 80% without further treatment.

Now our goal is:

.... not only that the bladder capacity is sufficient with adequate compliance and sphincter outlet resistances but also that micturition is voluntary and complete

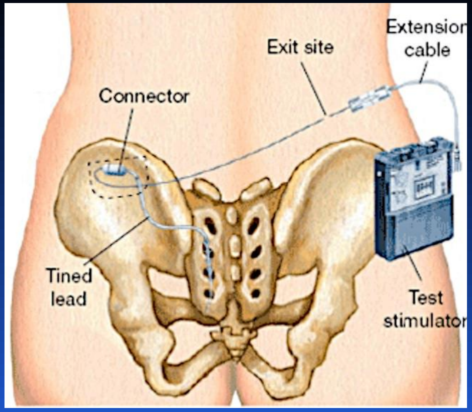
CATHETER FREE NEUROGENIC BLADDERS

Reactivation of some of the afferents or efferents neurologic pathways?

→ **NEUROMODULATION**

- external stimulation (non invasive)

- Internal stimulation



Non Invasive Neuromodulation

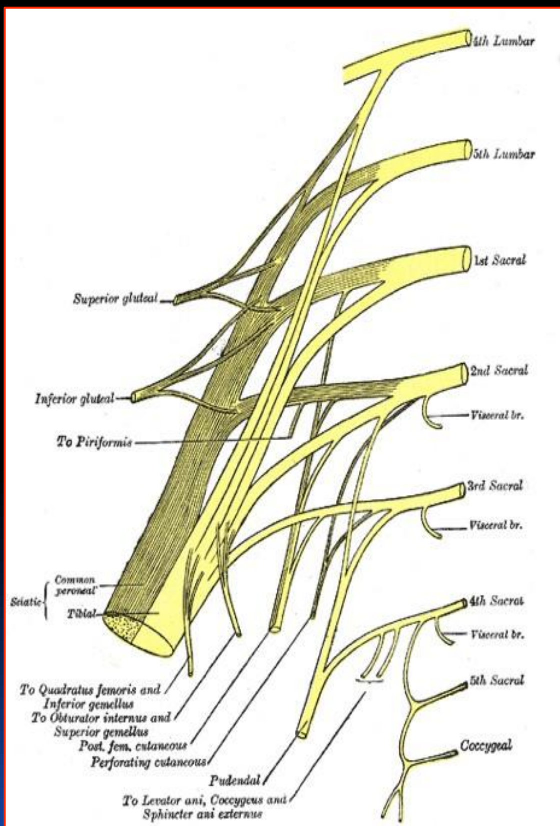
- Increases release of neurotransmitters →
  - ↓cholinergic activity
  - ↑ beta adrenergic activity (-> relax bladder vault)
  - VIP, serotonin

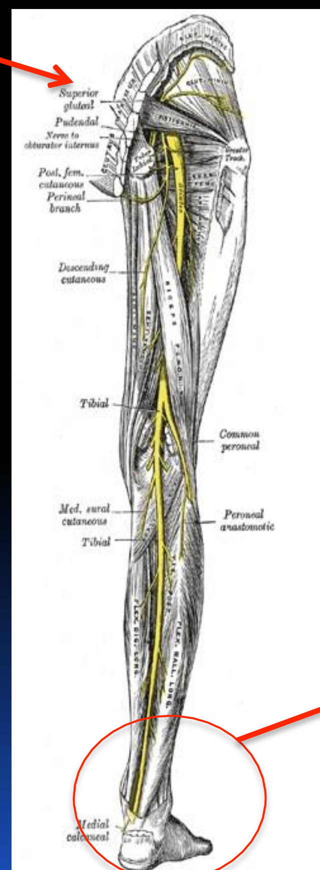
- Inhibition of OAB: 5-10Hz
  - TENS –pudendal afferents, S2,3 foraminae, S3 dermatome
  - SANS/PTNS (20Hz)

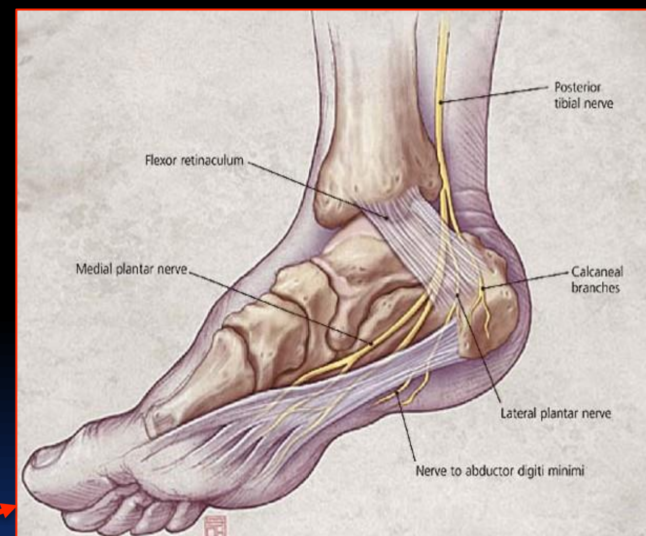
Bartley, J. *et al. Nat. Rev. Urol.* 2013

The Tibial Nerve

- A sensory motor nerve arising from L4 to S3 nerve roots
- Common roots with those serving bladder functions







de Seze M et al. Neurourol Urodyn. 2011

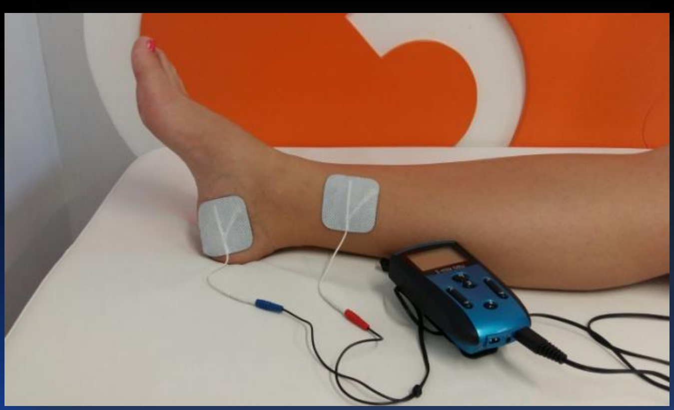
Different techniques of TNS

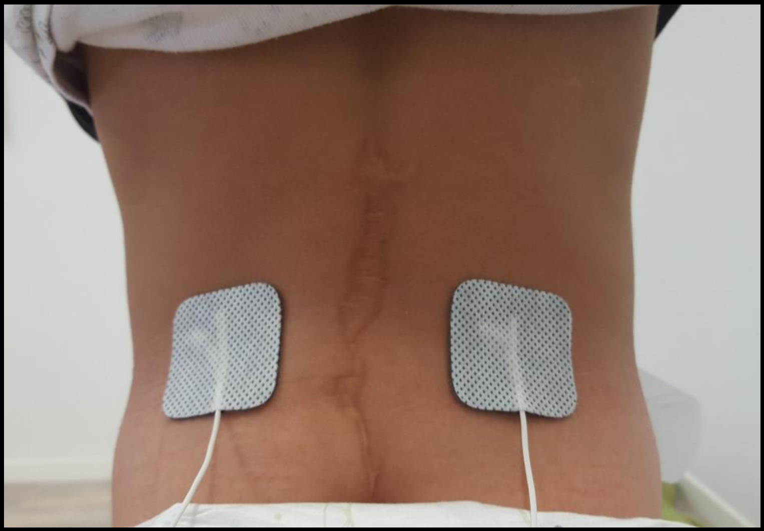
Percutaneous electric stmulation (PTNS)

Invasive, possibly painful Increase cost

Transcutaneous electric stimulation (TTNS)

Painless Non invasive
Low cost




Neuromodulation neurogenic bladder

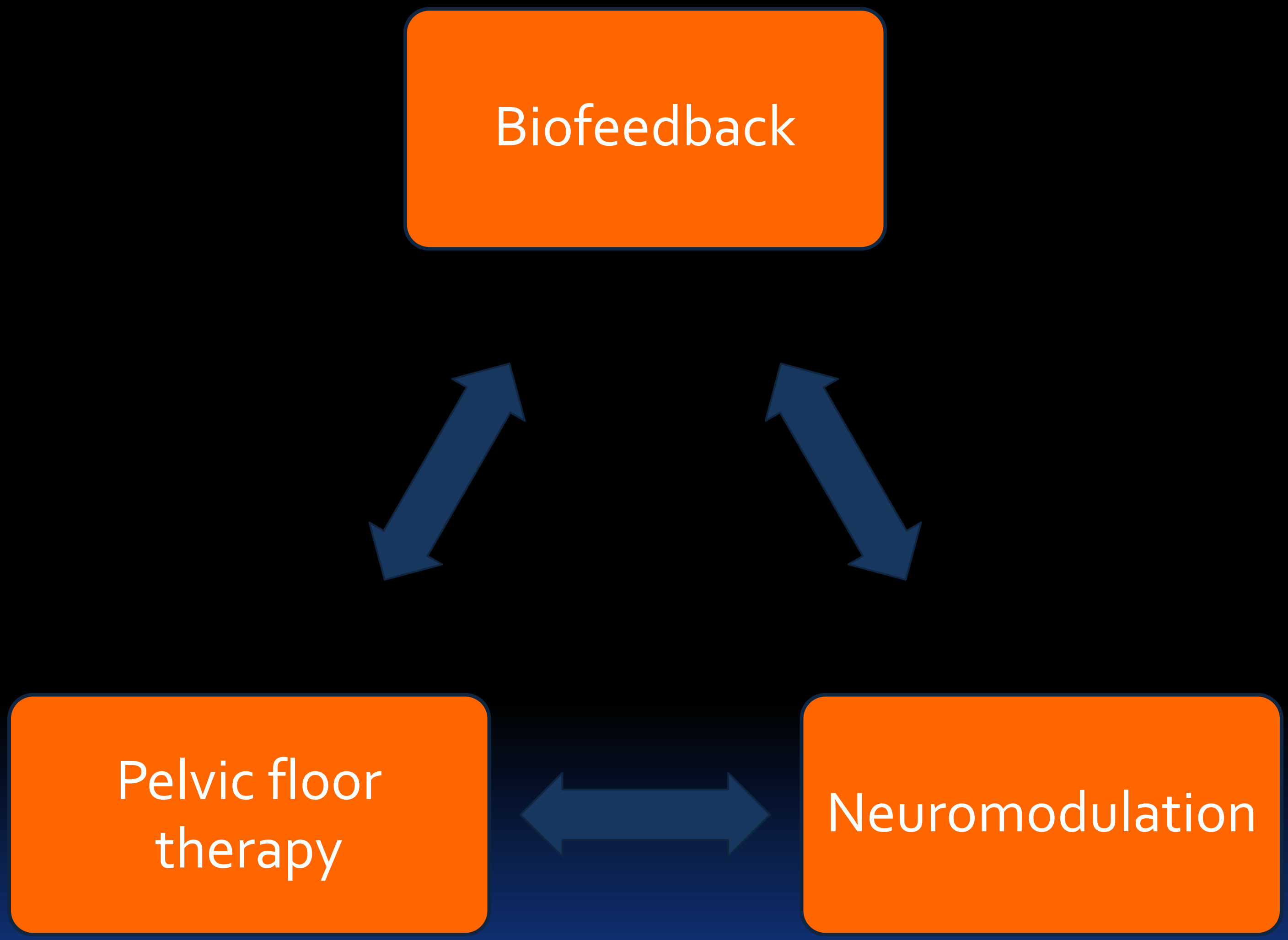
- different outcome measures – difficult to collrelate studies
- better feeling of bladder fullness (30%)
- improvement in continence (15-31%)
- significant improvement in all UDS parameters except for maximum bladder capacity and significant improvement in continence in treatment group
- most of our patients have a positive effect on bowel motility and a better feeling of rectal fullness, which is a prerequisite for achieving continence (51,3%)

- No side effects

Kajbafzadeh et al. *Urology, 2009*
Barroso J, Neurourol Urodyn 2011
Cvitković Roić A, et al. Archives of Disease in Childhood, 2021

Neuromodulation: Summary

- Positive role of neuromodulation in children with LUTD
- Adjunctive to other therapies
- No known predictors of efficacy jet
- Understanding of electrotherapeutics is a prerequisite for clinical use
- Neuromodulation of the bowel shows promise



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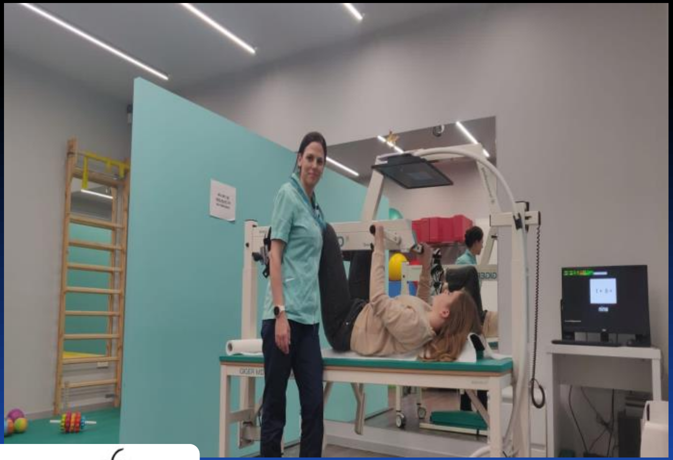
Giger MD biofeedback device



coordinated movements of arms and legs *via* hand and foot pedals, which are triggered in different phases from each other.

- A damaged neural pathway can be reorganized if it is activated by rhythmic, dynamic, and symmetrical movements of the limbs and trunk.
- The key is to activate a significantly larger area of the healthy part at the same time as the injured part. In that way, the healthy part avoids the dominance of the damaged part.
- improvement in urinary incontinence, gait speed, and bladder capacity in patients with neurogenic bladder
- harmless and can be applied in parallel with other non-surgical and surgical procedure

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Future- regenerative medicine

Review > Int J Mol Sci. 2022 Jun 7;23(12):6360. doi: 10.3390/ijms23126360.

Tissue Engineering and Regenerative Medicine in Pediatric Urology: Urethral and Urinary Bladder Reconstruction

Martina Casarin [1], Alessandro Morlacco [1], Fabrizio Dal Moro [1]

- Current surgical management (bladder augmentation using intestine) is burdened by multiple complications due to tissue heterogeneity.
- Regenerative medicine uses combinations of cells and/or biomaterials and offers an alternative for the replacement of deficient organs.
- Promising results using cell-seeded biodegradable scaffolds have been obtained in children with neurogenic bladder caused by myelomeningocele.
- Human clinical trials, governed by the US FDA, are ongoing in the USA to further evaluate the safety and efficacy of these regenerative technologies.

Augmentation Cystoplasty Using an Autologous Neo-Bladder Construct

Raghavan AM, Shenot PJ.Kidney Int. 2009

Conslusion: Neurogenic bladder

- *Early US assessment*
- *Early urodynamic and ceVUS investigation in children with risk*
- *Early start of CIC and anticholinergics*
- *Neuromodulation, biofeedback rehabilitation, new medication, Botulin toxin*
- *Continues follow up*

→ **Perservation of renal function**

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Thank you!

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

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University of Belgrade Faculty of Medicine

IPNA International Pediatric Nephrology Association
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BK POLYOMAVIRUS - ASSOCIATED NEPHROPATHY, PREVENTION AND TREATMENT. HOW MANY DIFFERENT PROTOCOLS DO WE HAVE?

Doc.dr Brankica Spasojević

UNIVERZITETSKA DEČJA KLINIKA TIRŠOVA OSNOVANA 1924.

10th SEPNWG MEETING AND TEACHING COURSE
(in Cooperation with Macedonian Pediatric Association)
Skopje, Republic of North Macedonia
1st to 3rd June 2023

Macedonian Society for Rare Diseases

LIFE with CHALLENGES Life is a puzzle, collect it.

РЕТКО Е ДА СИ РЕДОК
RRALLË ËSHTË TË JESH I RRALLË
RARE IS TO BE RARE

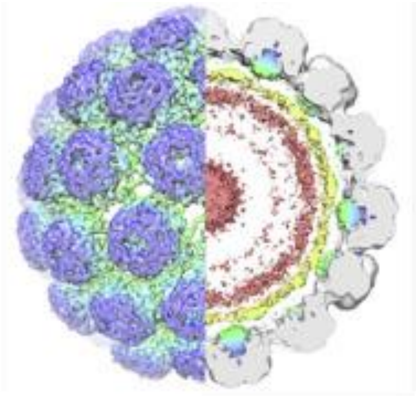
Здружение на педијатрите на Република Македонија

BK virus - History

- Named 1971.
- Sudanese KTR with ureteric stenosis
- B.K.

- JC
- SV 40
- Merckle cell virus

VP1
12 subtypes



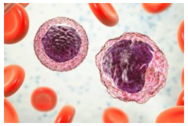
Gardner SD, Field AM, Coleman DV, et al. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet. 1971;1:1253–1257.

Cohen-Bucay A et al. Advances in BK virus complications in organ transplantation and beyond. Kidney Med 2020;2(6): 771-786.

Epidemiology

- Widespread in general population
- Seroprevalence rate of 10 to 30% in infants
- >90% by early school-age years

Lifelong persistent infection


Viruria ~ 30% KTR

Viremia ~ 12% KTR

BKVAN ~ 1-10% KTR

Clinically significant infection in KTR

Kant S et al. BK Virus Nephropathy in Kidney Transplantation: A State-of-the-art Review. Viruses 2022;14,1616

Pathogenesis

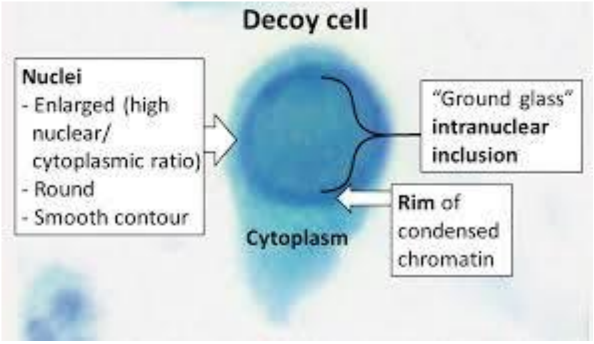
BKV infects EC of the UGT/latent

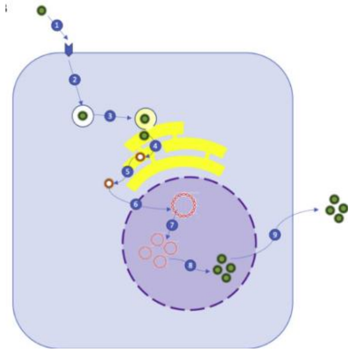
Reactivation of BKV

Viruria

Viremia

BKVAN





Necrosis and lytic destruction of the renal TI with profound inflammation

Cohen-Bucay A et al. Advances in BK virus complications in organ transplantation and beyond. Kidney Med 2020; 2(6): 771-786.

Humoral and Cellular Immune Response and Pathogenesis

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- BKV-specific nAbs may not protect against BKVAN - in 95% of cases, the replicating BKV strains are of donor origin (miss-match between the recipient`s anti-BKV-nAb and replicating BKV strain)
- Testing for antibodies against BKV before transplantation is currently not recommended
- **Cellular immunity** and in particular memory cell function is considered to be the cornestone for controlling the latent viral state and suppressing viremia and BKVAN.

Solis M et al. Neutralizing antibody-mediated response and risk of BK virus-associated nephropathy. J Am Soc Nephrol. 2018;29:326-334

Clinical manifestation/risk factors

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- BKVAN (tubulointerstitial nephritis): allograft dysfunction (↓GFR), hemathuria in 19% of patients, proteinuria in 48% of patients
- Ureteric stenosis (KTR), hemorrhagic cystitis (HSCTR)
- Several risk factors: the level of immunosuppression, the type of immunosuppressive agents

TABLE S3. **Definition of the pediatric Vasudev score**

Immunosuppressant	"Vasudev score"[1] dose per unit (mg/d)	Pediatric Vasudev score[2] dose per unit (mg/m²·d)	Immunosuppressive unit
TAC	2	1.2	1
CSA	100	58	1
EVR	2	1.2	1
SRL	2	1.2	1
MMF	500	290	1
AZA	100	58	1
Prednisone equivalent	5	2.9	1

TAC, tacrolimus; CSA, ciclosporin microemulsion; EVR, everolimus; SRL, sirolimus; MMF, mycophenolate mofetil; AZA, azathioprine.

Höcker et al. Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transpla Recipients: An International CERTAIN Registry Study. Transplantation1 2019; 03(6):1224-1233

Screening and Noninvasive diagnostic Tests
Urine and Plasma BKV PCR

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- Viruria (>1x10^7 copies/ml)

  NPV 100%, PPV 31%-67%

- Viremia (>1x10^4 copies/ml)

  NPV 100%, PPV 50%-82%

↓

BKV PCR in blood or plasma - the preferred screening method

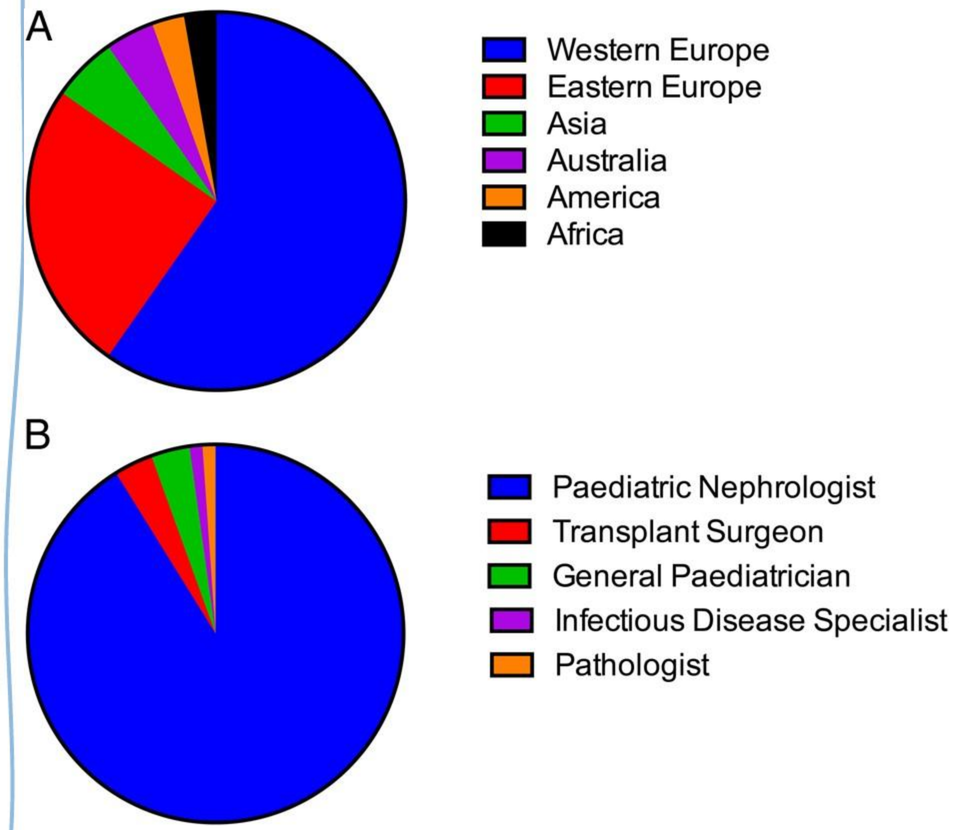
- KDIGO and AST-IDCOP

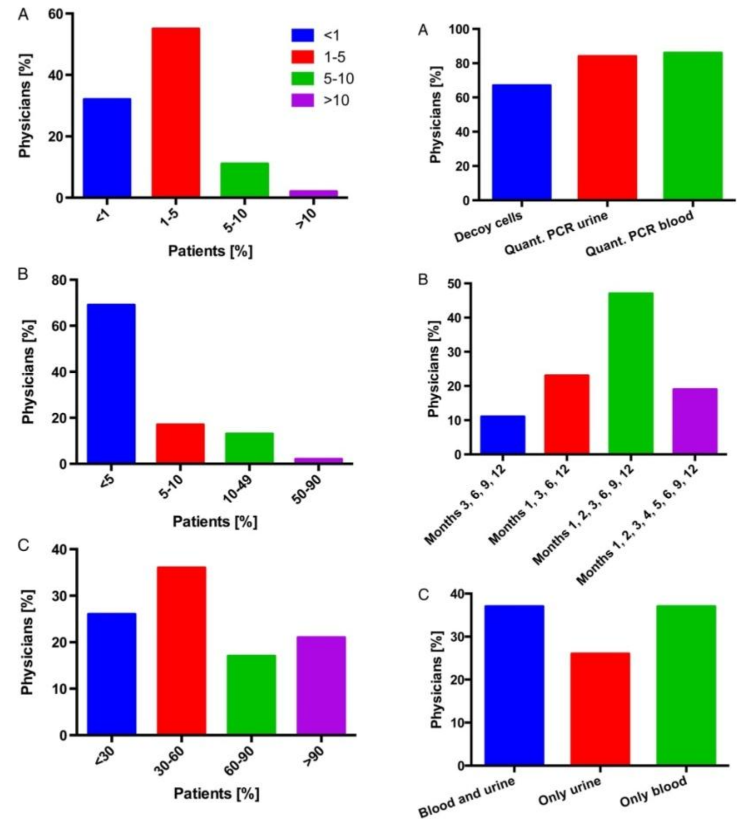
  Monthly screening for the first 6 months post-transplantation and then every 3 months for the next 18 months

- International Consensus on BKV in Kidney transplantation, April 2022, Basel

  Monthly screening for the first 9 months post TX, and then every 3 months for the next 2 years in adults and 3 years in children

BKV screening across Europe





Pape L et al. Members of the working group Transplantation of the European Society for Pediatric N. Perception, diagnosis and management of BK polyomavirus replication and disease in paediatric kidney transplant recipients in Europe. Nephrol Dual Transplant.2016;31:842-847

Transplant kidney biopsy – indication in presumed BKVAN

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- Clinical indication: raise in serum creatinine, proteinuria, hemathuria
- Persistently high BKV viremia in children
- Consider: ABOi, DSA, retransplantation, poor compliance, multi-organ transplantation, previous rejections
- Recommended immunohistochemistry: beyond SV40 - CMI (Cell mediated immunity, clone PAb416)

International Consesus Meeting on BKV in Kidney Transplantation, 7-8. April 2022, Basel

Transplant kidney biopsy

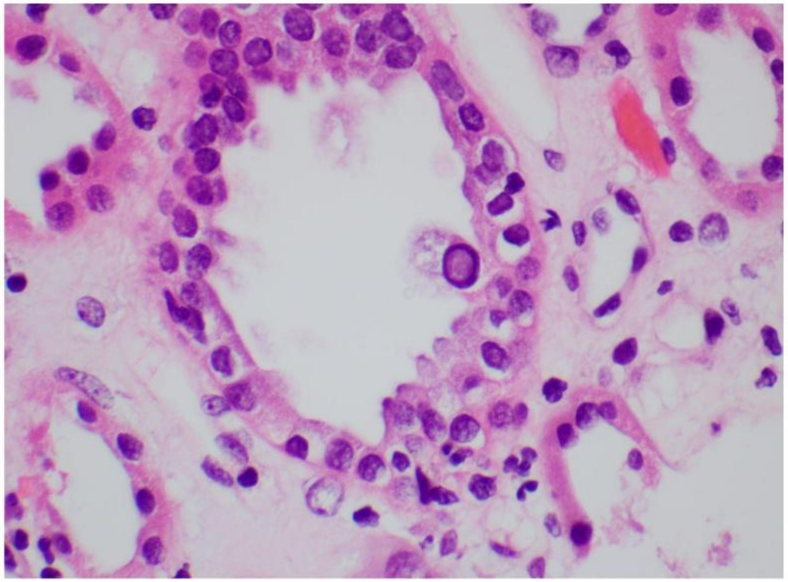

Figure 2. A tubular epithelial cell with a "ground glass" nuclear inclusion. H&E 600×.

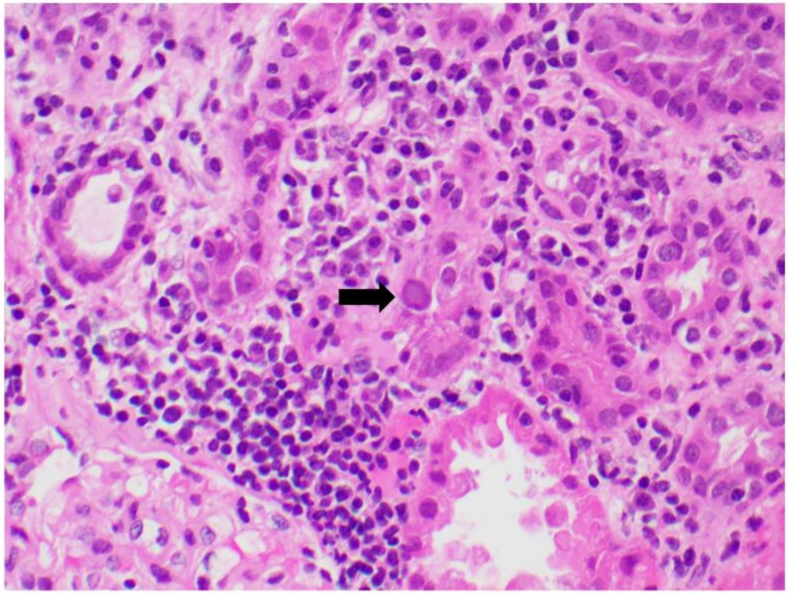

Figure 4. Lymphoplasmacytic interstitial inflammation surrounding a tubule containing an epithelial cell with a viral inclusion (arrow). H&E 400×.

Kant S et al. BK Virus Nephropathy in Kidney Transplantation: A State-of-the-art Review. Viruses 2022;14,1616

Transplant kidney biopsy – SV 40 IHC

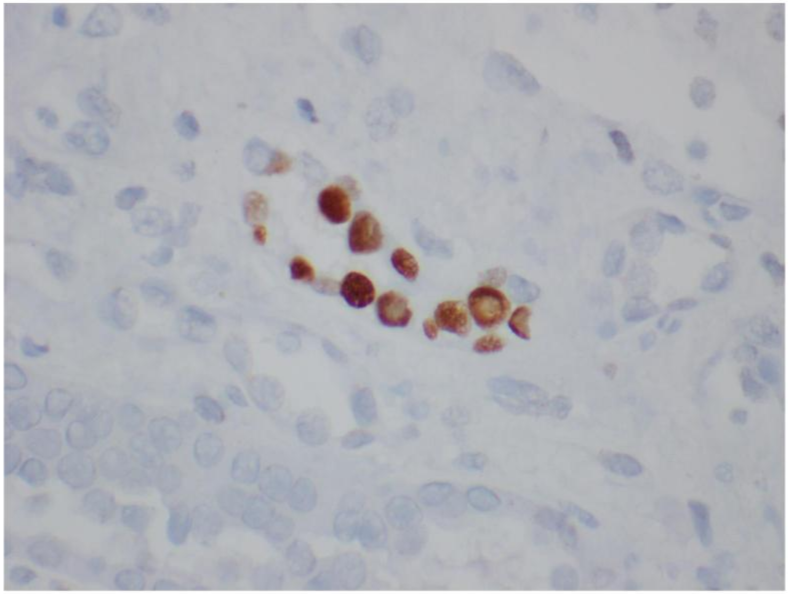

Figure 5. SV40 IHC staining highlighting infected tubular epithelial cells (600×).

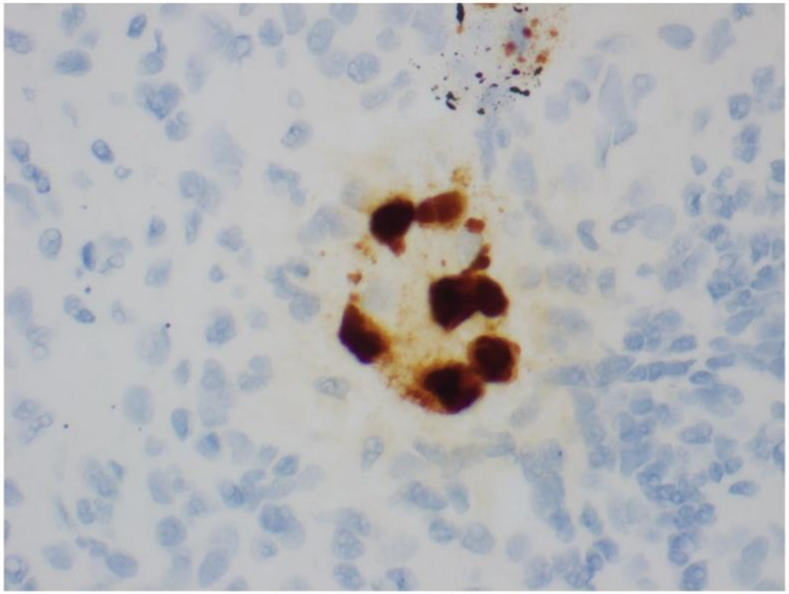

Figure 6. In situ hybridization for BK virus RNA (600×).

Kant S et al. BK Virus Nephropathy in Kidney Transplantation: A State-of-the-art Review. Viruses 2022;14,1616

Transplant kidney biopsy

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Histologic Classification System for BKV-Associated Nephropathy and Associated Outcomes

Histologic Class	Histologic Characteristics	Outcomes at 24 mo After Index Biopsy		
		Cr increase	Allograft failure	Resolution of BKV-associated nephropathy
Class 1	pvl 1 and ci ≤1	0.4 (IQR, 0-1.6) mg/dL	16%	75%
Class 2	pvl 1 and ci >1, or pvl 2 and any ci score, or pvl 3 and ci ≤1	1.0 (IQR, 0.4-4.8) mg/dL	31%	78%
Class 3	pvl 3 and ci >1	4.8 (IQR, 1.3-5.3) mg/dL	50%	50%

- ***Note:*** **pvl 1: ≤1% tubules with BKV replication, pvl 2: >1% and ≤10% of tubules with BKV replication, pvl 3: >10% of tubules with BKV replication, ci 0: interstitial fibrosis in ≤5% of cortical area; ci 1: interstitial fibrosis in >5% and ≤25% of cortical area; ci 2: interstitial fibrosis in >25% and ≤50% of cortical area; and ci 3: interstitial fibrosis in >50% of cortical area.**
- **Abbreviations: BKV, BK virus; Cr, creatinine; ci, interstitial fibrosis of cortical area; IQR, interquartile range; pvl, polyomavirus load.**

Cohen-Bucay A et al. Advances in BK virus complications in organ transplantation and beyond. Kidney Med 2(6): 771-786.

Management

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- A reduction in the intensity of immunosuppression is the overarching principle for the treatment of BK viremia and BKVAN

- Viremia ($1x10^3$ - $1x10^4$ copies/ml) twice within 2-3 weeks
- Viremia $>10^4$ copies/ml in a single measurement

International Consesus Meeting on BKV in Kidney Transplantation, 7-8. April 2022, Basel
Kant S et al. BK Virus Nephropathy in Kidney Transplantation: A State-of-the-art Review. Viruses 2022;14,1616

Management - stepwise approach to reduce immunosuppression

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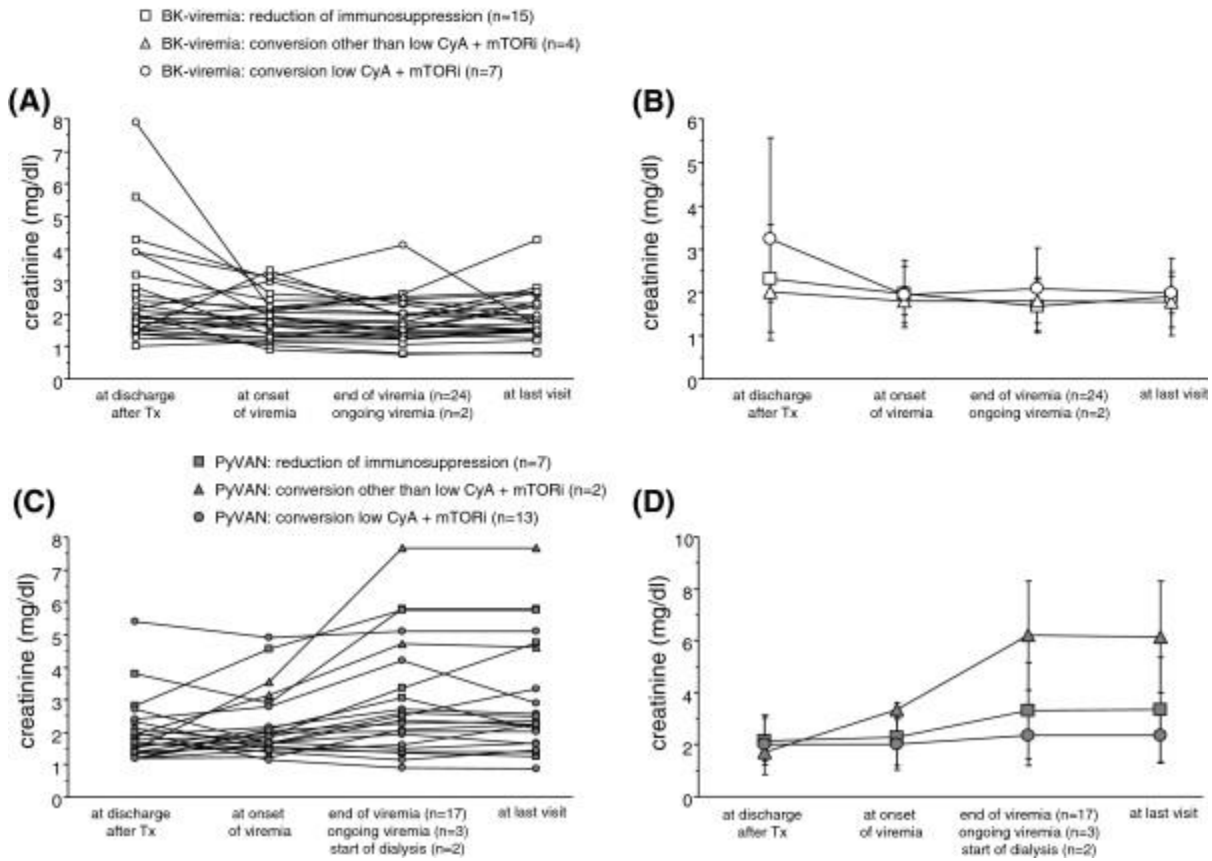
Every 2-4 weeks BKV DNA measurement

MMF reduction by 50%	CNI reduction by 25-50%
CNI reduction by 25-50%, steroids reduction /introduction to 5-10 mg	MMF reduction by 50%, steroids reduction to 5-10 mg
Stop MMF	**Stop MMF**

Improvement BKV DNA: <10x

Ahn YH and Kang HG. BK polyomavirus-associated nephropathy. Child Kidney Dis 2022;26(1):11-17.
International Consensus Meeting on BKV in Kidney Transplantation, 7-8. april, 2022, Basel

Other adjunctive therapies mTOR i



Jacobi et al. BK viremia and polyomavirus nephropathy in 352 kidney transplants: risk factors and potential role of mTOR inhibition. BMC Nephrol 2013;14:207

Other adjunctive therapies- cidofovir

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TABLE 1. Clinical characteristics of patients treated with cidofovir

Case no.	Diagnosis	Gender	Age at Tx	Time between Tx and Dx	No. of Bx before Dx	Creat at Dx (mg/dL)	Tacrolimus level at Dx (ng/mL)	Peak creat (mg/dL)	Current creat (mg/dL)	Cidofovir doses (total no.) (mg/kg/dose)
1	Renal dysplasia	M	4 yr	1 yr 10 mo	NA	1.5	10.2	7.2	1.7	1 (1)
2	Diabetic nephropathy	F	54 yr	9 mo	3	2.9	4.6	5.4	3.2	3 (0.25–0.5–1)
3	IgA nephropathy	M	29 yr	11 mo	NA	2.2	8	6.4	3	4 (3^a–3^a–3^a–1)
4	PUV	M	10 yr	12 mo	3	1.6	14.6	3.0	1.8	3 (0.5–0.5–1)

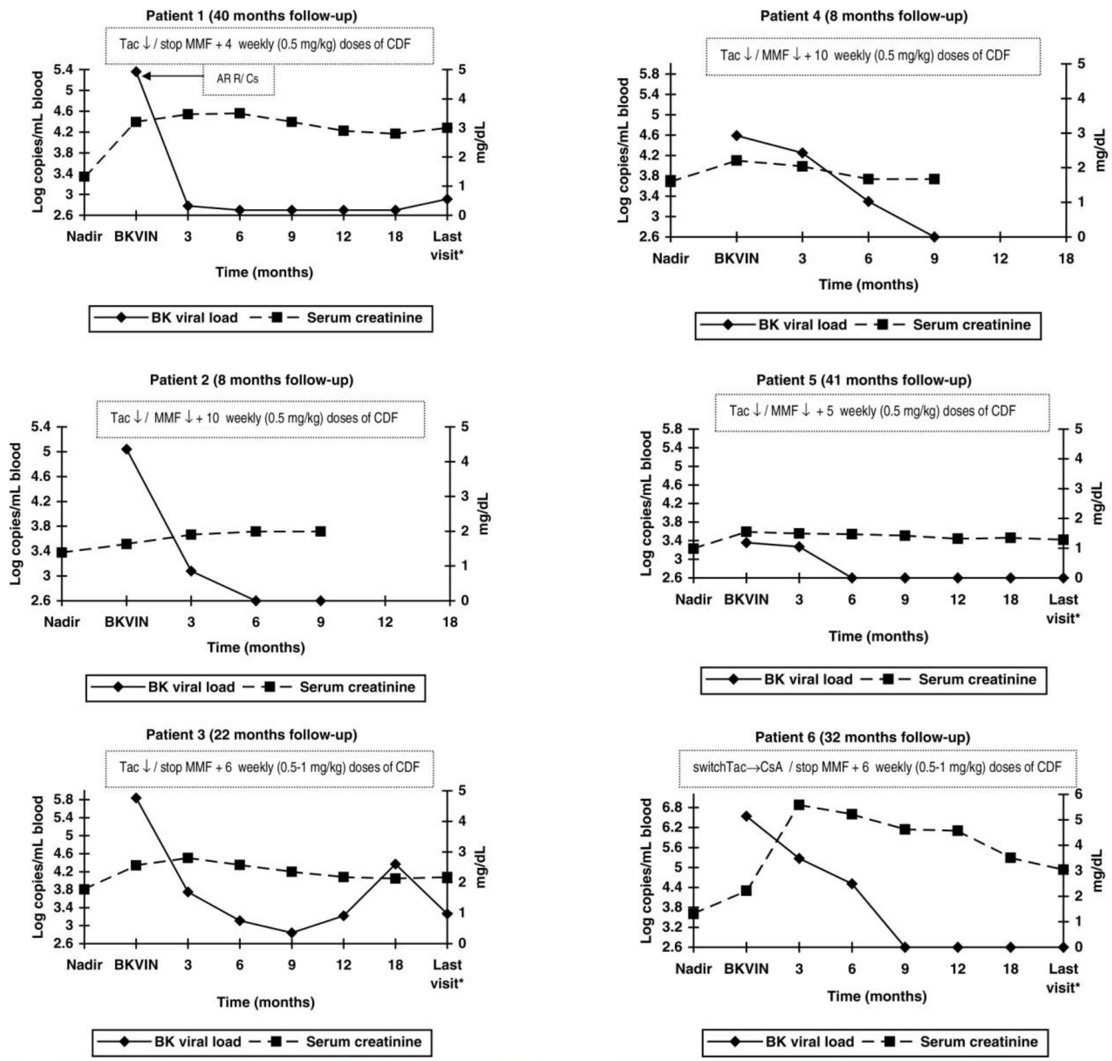
Tx, transplantation; Dx, diagnosis of BK virus-associated nephropathy; Bx, allograft renal biopsy; Creat, serum creatinine; M, male; F, female; PUV, posterior urethral valves; IgA, immunoglobulin A.

[a] Refers to three doses of cidofovir given with probenecid. All the other doses in this column refer to cidofovir therapy without probenecid.

Brincidofovir (CMX001) – a lipid conjugate of cidofovir – not commertially available – no apparent nephrotoxicity

Vats et al. Quantitative viral load monitoring and cidofovir therapy for the management of BK virus-associated nephropathy in children and adults. Transplantation 2003; 75:105-112

Other adjunctive therapies- cidofovir



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8/21 pts treated with low dose of cidofovir

9/13 pts with no cidofovir – lost graft (median 8 months)

Kuypers et al. Adjuvant Low-Dose Cidofovir Therapy for BK Polyomavirus Interstitial Nephritis in Renal Transplant Recipients. Am J Transplant. 2005;5:1997-2004.

Other adjunctive therapies-leflunomide

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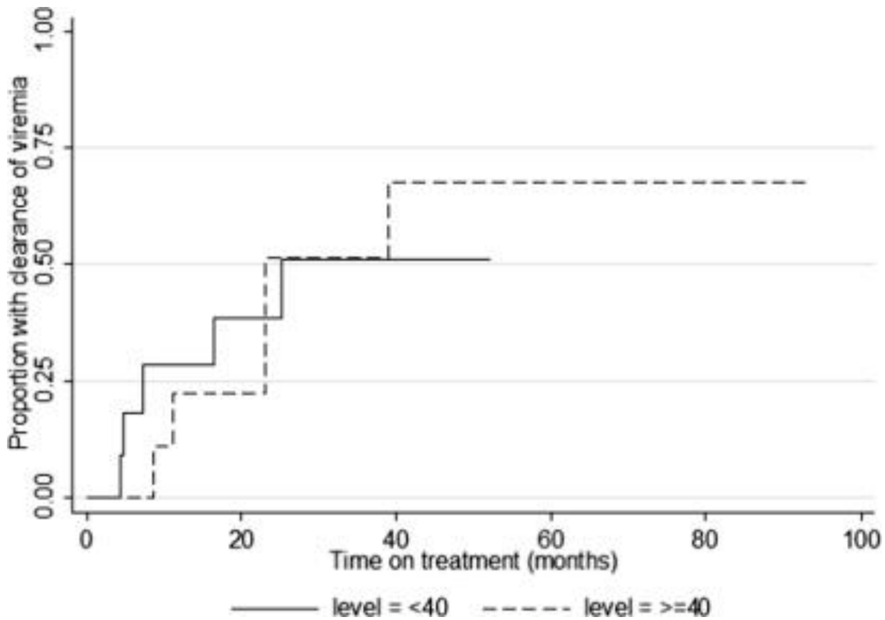
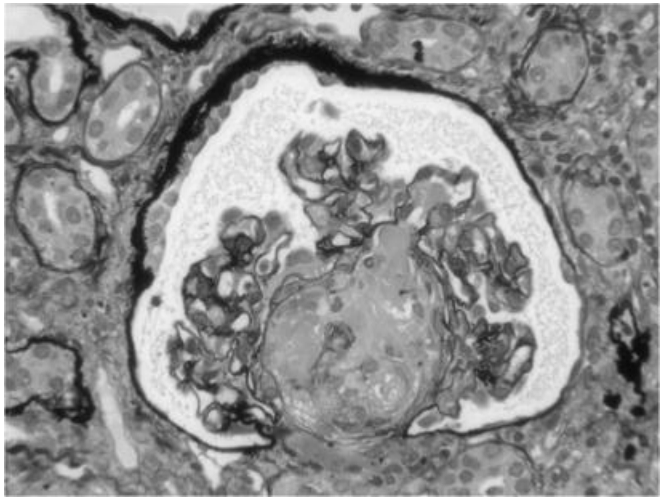
Table 3. Outcomes among patients with BK viremia without nephropathy

Outcome	Leflunomide (*n*=20)	No Leflunomide (*n*=23)	*P* Value
BK viral clearance	40	65	0.19
Rejection after BK diagnosis	10	0	0.21
Mean BK PCR during time of follow-up, copies/ml	152,930	366,614	0.47
Discontinuation of MMF within 1 mo	84	14	<0.001
Death or graft failure	15	9	0.65

Krisl et al.
Clinical Journal of the American Society of Nephrology7(6):1003-1009, June 2012. *[Leflunomide Efficacy and Pharmacodynamics for the Treatment of BK Viral Infection]*

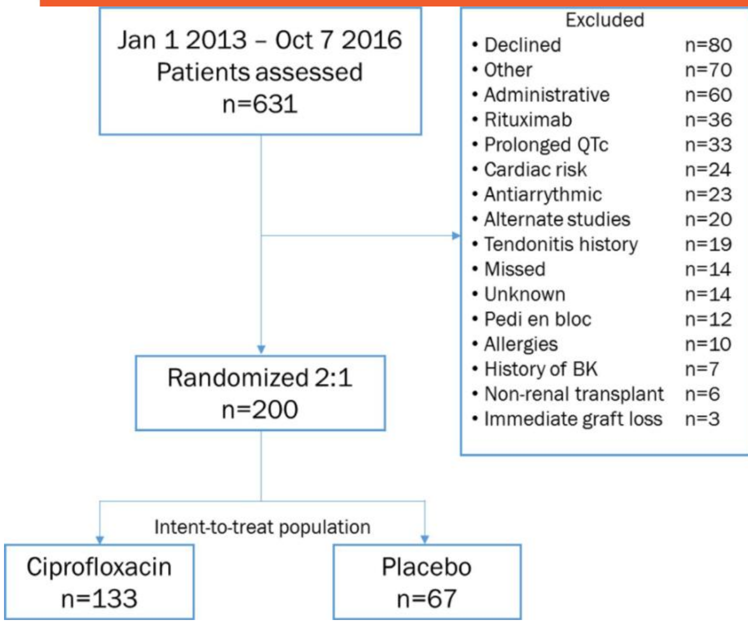


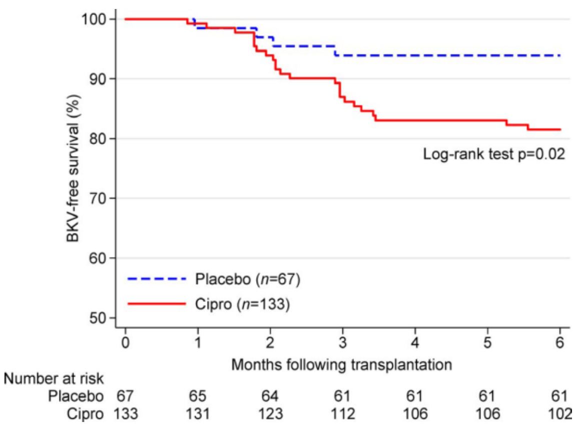


A

Leca N et al. Higher levels of leflunomide is associated with hemolysis and are not superior to lower levels for BK virus clearance in renal transplant recipients. J Am Soc Nephrol.2008;3:829-835.

Other adjunctive therapies- Quinolones



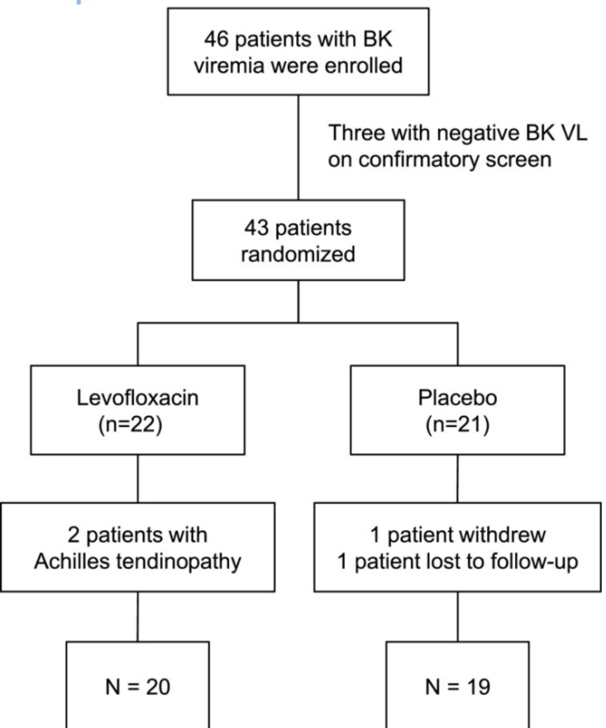


BK-related outcomes at 6- and 12-month post–kidney transplant

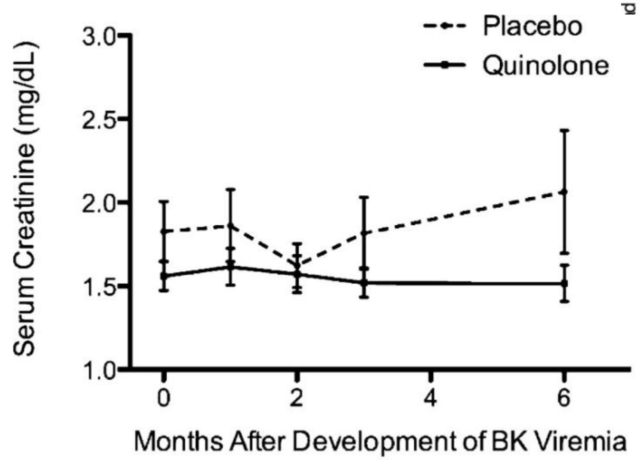
	Ciprofloxacin n = 133	Placebo n = 67	*P* value
BK viremia at month 1, n (%)	1 (0.8)	1 (1.5)	.62
BK viremia at month 3, n (%)	18 (13.5)	5 (7.5)	.20
BK viremia at month 6, n (%)	25 (18.8)	5 (7.5)	.03
BK nephropathy at month 6, n (%)	7 (5.8)b	1 (1.5)b	.26
BK viremia at month 12, n (%)	31 (23.3)	8 (11.9)	.06
BK nephropathy at month 12, n (%)	7 (5.8)b	1 (1.5)b	.26
Median time to initial BK viremia episode, d (IQR)	90 (59, 160)	76.5 (59, 295)	.74
Median PCR of initial viral load, copies/mL (IQR)	2514 (796, 8754)	1423 (724, 19 619)	.83
High-level viremia (>10 000 copies/mL), n (%)	17 (12.8)	5 (7.5)	.26

Patel SJ et al. Ciprofloxacin for BK viremia prophylaxis in kidney transplant recipients: Results of a prospective, double-blind, randomized, placebo-controlled trial Am J Transplant 2019;19(6):1831-1837

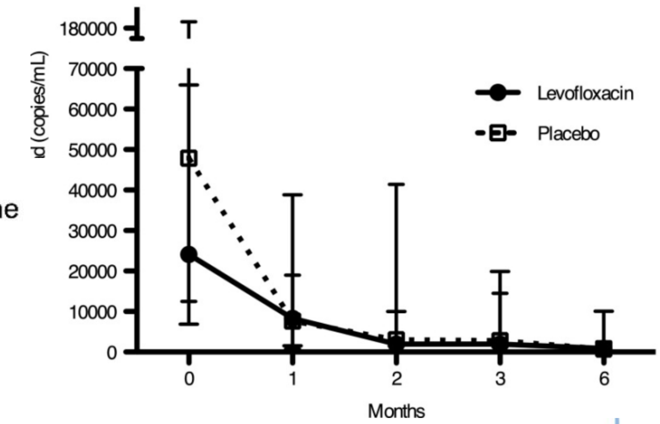
Other adjunctive therapies - levofloxacin



30 day course of levofloxacin



	Slope of sCr vs. Time	95% CI
Levofloxacin	-0.01	-0.06 to 0.03
Placebo	0.04	-0.06 to 0.14



Lee BT et al. Efficacy of levofloxacin in the treatment of BK viremia: a multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol. 2014 Mar;9(3):583-9.

Other adjunctive therapies -IVIG

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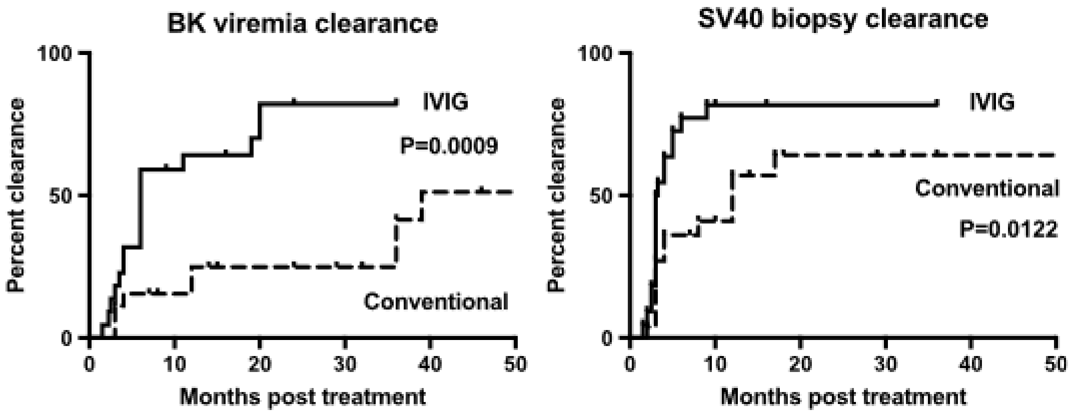
- A retrospective analysis of 50 patients with biopsy proven BKVAN – 22 of pts received 1g/kg of IVIG



Kable et al. Clearance of BK virus nephropathy by combination antiviral therapy with intravenous immunoglobulin. Transplantation Direct 2017;3:e142

Other adjunctive therapies -IVIG

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Clinical and histological outcomes for BKVAN, stratified by use of IVIG therapy

Factor	Conventional	IVIG	P
Number	28	22	
Renal transplant histology at 3 mo at later			
Banff i score inflammation	1.4 ± 0.9	1.0 ± 1.1	NS (0.14)
Banff ci fibrosis score	1.5 ± 0.9	1.1 ± 1.0	NS (0.11)
Banff ct atrophy score	1.4 ± 0.9	1.2 ± 0.9	NS (0.37)
SV40T histology	1.2 ± 0.9	0.5 ± 0.7	0.015
Final BK biopsy clearance, n (%)	14/26[a] (53.8)	18/22 (81.8)	0.041
Months to biopsy clearance	12.4 ± 12.7	6.2 ± 7.5	0.047
Virological clearance at 3 mo and beyond			
Failed clearance at high level, n (%)	12 (42.9)	4 (18.1)	
Partial SVR (<1000 copies), n (%)	6 (21.4)	4 (18.1)	
SVR (nil detected), n (%)	10 (35.7)	14 (63.3)	NS (0.07)
Quantitative BK level (×10^3 copies/mL, IQR) partial data	0.12 ± 2.6	0.15 ± 0.37	NS (0.82)
Final BK viremia clearance n (%)	9/27 (33.3)	17 (77.3)	0.044
Time to viremia clearance, mo	29.1 ± 31.8	11.3 ± 10.4	0.015
BK viremia relapse n, (%)	3/11 (27.3)	2/18 (11.1)	NS (0.72)
3 month S. creatinine, µmol/L	235 ± 108	199 ± 102	NS (0.14)
Acute renal dysfunction after immunosuppression reduction, n (%)	22 (78.6%)	13 (59.1%)	NS (0.09)
Treatment with IV methylprednisolone, n (%)	18 (64.3%)	15 (68.2%)	NS (0.78)
Late acute rejection, n (%)	16 (57.1%)	14 (63.6%)	NS (0.95)
Death-censored graft survival from BKVAN diagnosis			
1 y	96.2%	85.0%	
3 y	62.7%	65.6%	NS (0.80)
Patient survival from BKVAN diagnosis			
1 y	92.7%	95.2%	
3 y	88.7%	79.1%	NS (0.69)
Overall graft loss, n (%)	15 (53.6)	6 (27.3)	NS (0.06)
BKVAN as cause of loss, n (%)	10 (35.7)	3 (13.6)	NS (0.08)
Rejection cause of loss, n (%)	5 (17.8)	3 (13.6)	NS (0.69)
Died, n (%)	7 (25%)	4 (18.2%)	NS (0.56)
Follow-up time since BKVAN diagnosis, mo			
Mean (SD)	55.3 ± 46.7	28.5 ± 15.2	NS (0.07)
Median (IQR)	39 (18-75)	27.5 (16-39)	
Study follow-up time (months since transplantation)			
Mean (SD)	98.3 ± 74.7	46.4 ± 27.8	0.003
Median (IQR)	84 (33-138)	44.5 (28-60)	

Kable et al. Clearance of BK virus nephropathy by combination antiviral therapy with intravenous immunoglobulin. Transplantation Direct 2017;3:e142

Other adjunctive therapies - IVIG

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A retrospective study, 30 BKVAN pts, 1g/kg IVIG after IST↓ + leflunomide

90% of pts cleared viremia

1 graft loss - CR

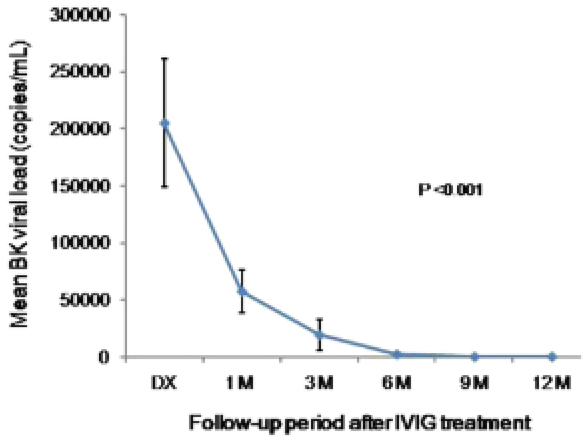


Fig 1. Mean plasma BKV DNA measured using quantitative real-time PCR assay at the time of IVIG administration (Dx) and at 1, 3, 6, 9, and 12 months after IVIG therapy.

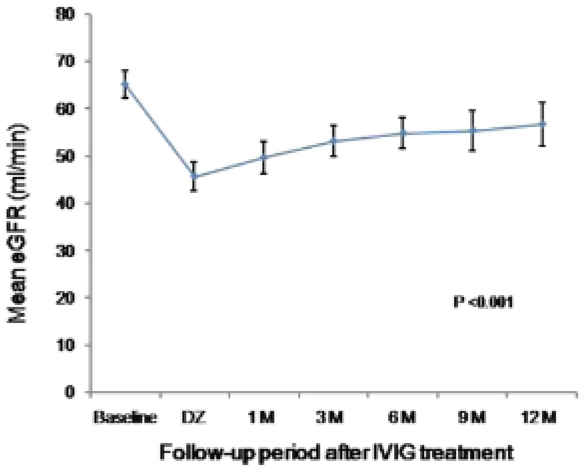
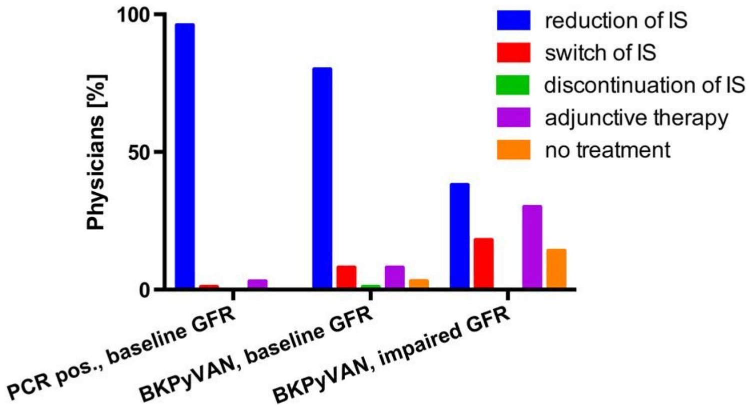
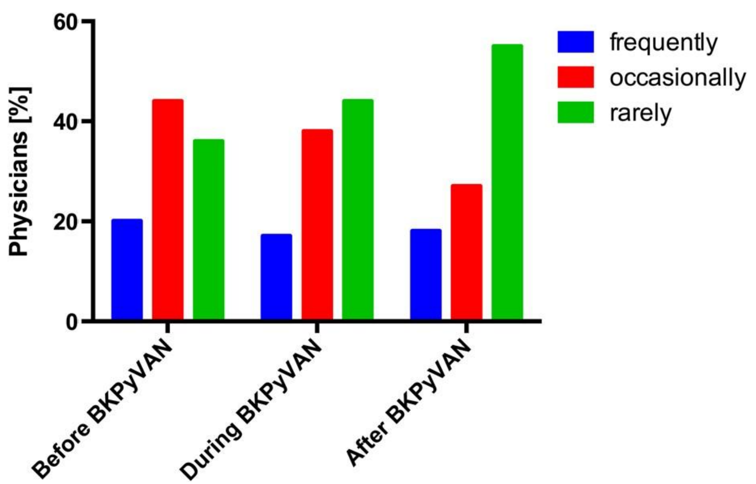


Fig 2. Mean GFR (mL/min) levels in kidney transplant recipients with BKVN. Levels were taken from patients before (baseline), at the time of IVIG administration, and at 1, 3, 6, 9, and 12 months after IVIG therapy.

Vu D et al. Efficacy of intravenous immunoglobulin in the treatment of persistent BK viremia and BK virus nephropathy in renal transplant recipients. Transplant Proc.2015;47:394-398.

Therapy –BKV across Europe





Reduction of IS

1. ↓MMF in 40%
2. ↓ CNI in 29%
3. ↓combination in 31%

Changing of IS

Discontinuation of MMF in 75%

Switching from CNI to mTORi in 52%

(48% pts with TAC, 26% pts with CsA)

In 24% pts TAC to CsA

Adjunctive th

- Cidofovir in 32%
- Leflunomide in 25%,
- Fluoroqinolones in 20%
- IVIG in 22%

Pape L et al. Members of the working group Transplantation of the European Society for Pediatric N. Perception, diagnosis and management of BK polyomavirus replication and disease in paediatric kidney transplant recipients in Europe. Nephrol Dual Transplant.2016;31:842-847

Immunosuppression and BKV infection after PKT

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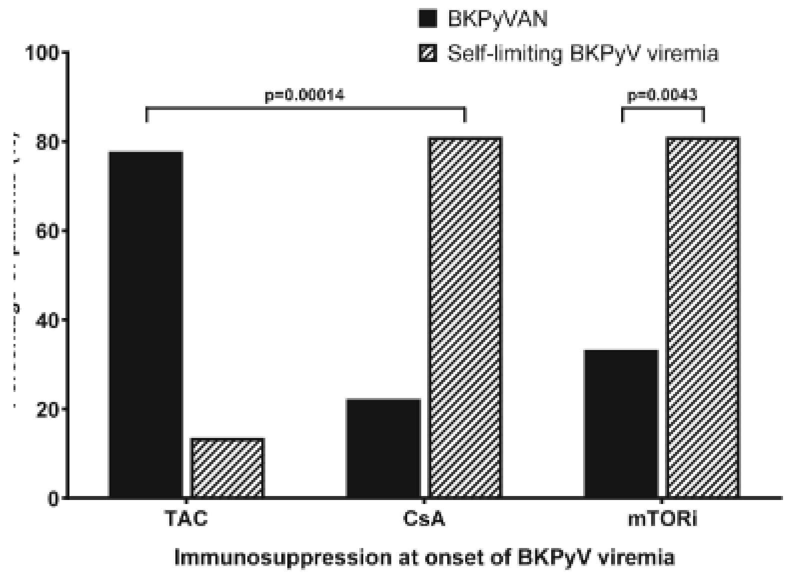
46 pts with BKV viremia

37/46 BKV specific CD4 and CD8 cells

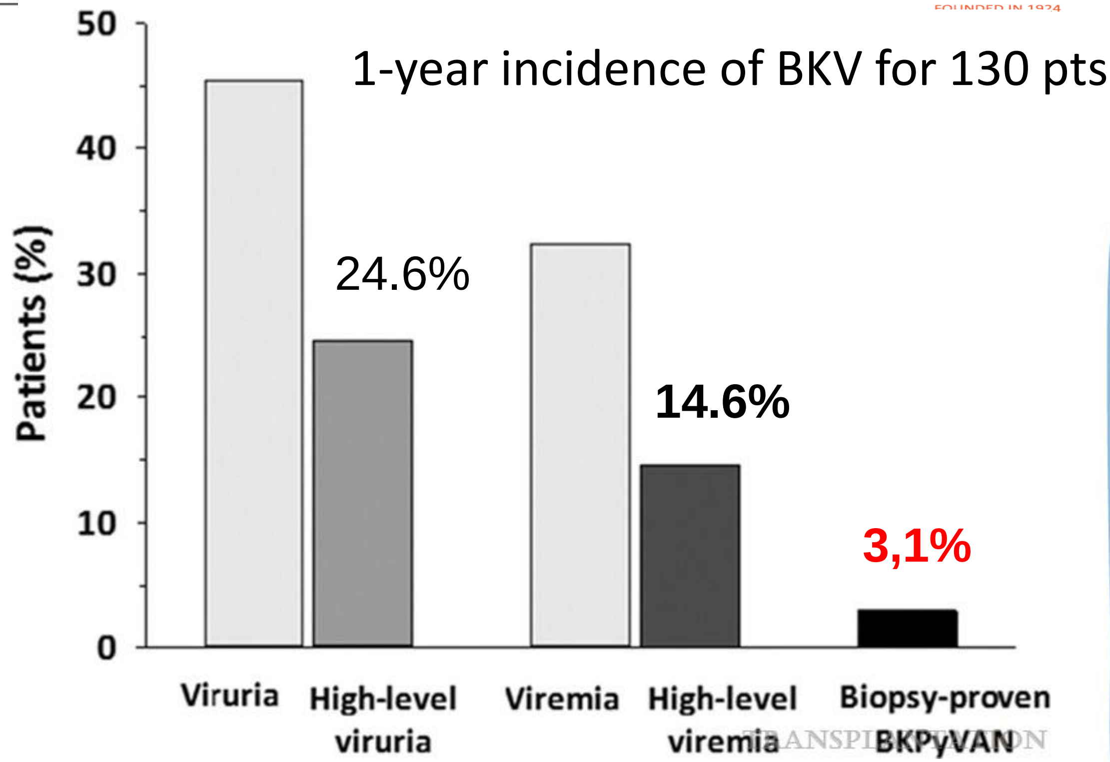
- Patients with persistent BKV viremia and BKVAN (6/6) showed lack of BKV-specific cells (<0.5 cells/uL)
- Patients with self-limiting viremia (27/31) had detectable BKV-specific cells≥0.5 cells/uL)



Ahlenstiel-Grunow T, Pape L. Immunosuppression, BK polyomavirus infections, and BK polyomavirus-specific T cells after pediatric kidney transplantation. Pediatr Nephrol 2019

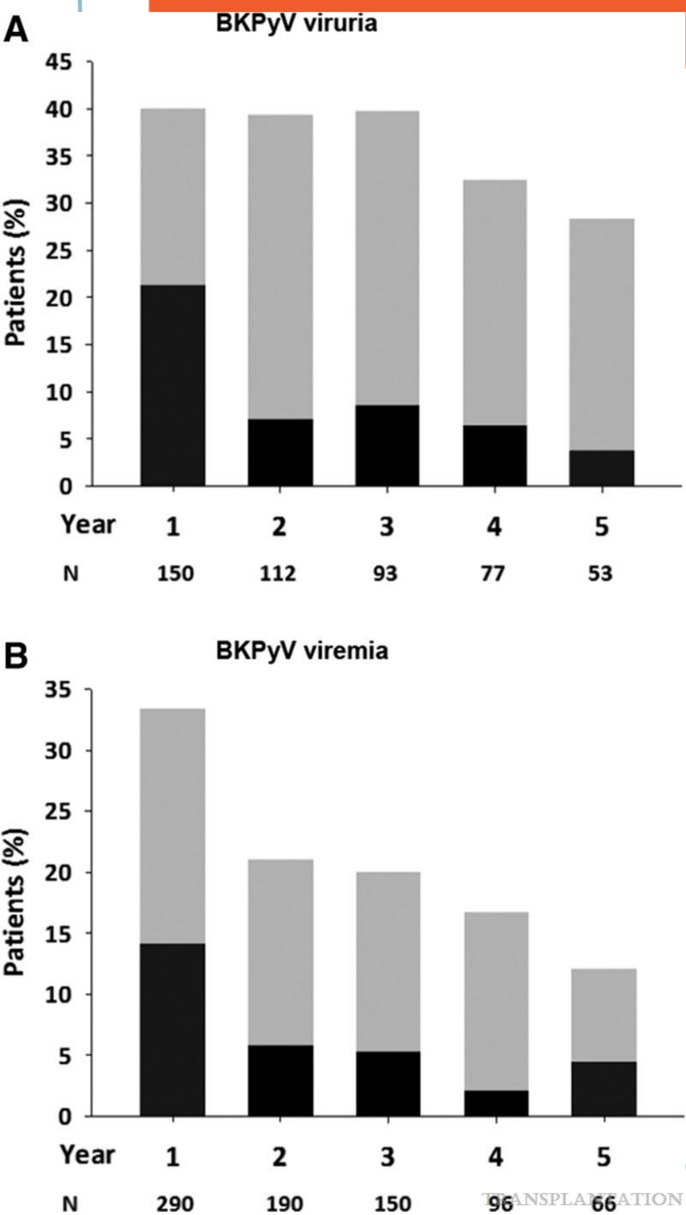
Epidemiology of and risk factors for BKV replication and nephropathy

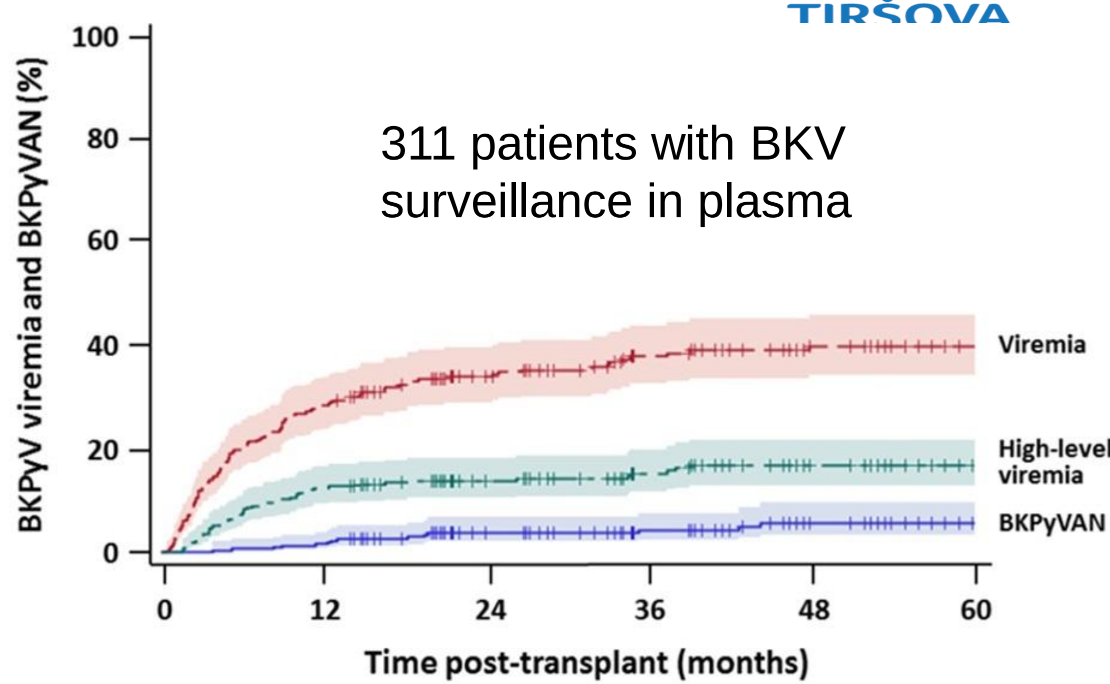
Characteristics	Patient cohort (n = 313)
Age at RTx, y	10.5 ± 5.5
Male gender, n (%)	197 (62.9)
White, n (%)	298 (95.2)
Primary kidney disease	
CAKUT, n (%)	135 (43.1)
Obstructive uropathy, n (%)	29 (9.3)
Cystic kidney disease, n (%)	54 (17.3)
FSGS, n (%)	41 (13.2)
Syndrome-related renal disease, n (%)	23 (7.3)
aHUS or MPGN, n (%)	22 (7.0)
IgA- or vasculitis-associated nephropathy, n (%)	12 (3.8)
Metabolic disorder, n (%)	10 (3.2)
Unknown cause of end-stage renal failure, n (%)	16 (5.1)
Second RTx, n (%)[b]	37 (11.8)
Living-related RTx, n (%)	106 (33.9)
HLA mismatch, n	2.7 ± 1.2
Cold ischemia time, h,	9.4 ± 6.9
eGFR, mL/min per 1.73 m^2[c]	77.4 ± 28.6
Initial immunosuppressive regimen, n (%)[d]	
IL-2 receptor antagonist, n (%)	155 (49.5)
Thymoglobulin, n (%)	20 (6.4)
TAC, n (%)	227 (72.5)
CSA, n (%)	86 (27.5)
MMF, n (%)	271 (86.6)
AZA, n (%)	9 (2.9)
EVR, n (%)	34 (10.9)
Glucocorticoids, n (%)	307 (98.1)
Pediatric Vasudev score[e,f]	14.2 ± 5.4
No. patients with BPAR, n (%)[g,h]	80 (25.6)



Höcker et al. Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transplant Recipients: An International CERTAIN Registry Study. Transplantation. 2019;103(6):1224-1233

Epidemiology of and risk factors for BKPyV replication and nephropathy





Viremia	311	223	146	101	69	48
High-level viremia	311	273	199	114	99	64
BKPyVAN	311	305	202	121	101	68

Höcker et al. Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transplant Recipients: An International CERTAIN Registry Study. Transplantation1 2019; 03(6):1224-1233

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Epidemiology of and risk factors for BKPyV replication and nephropathy

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Variables	BKPyV viruria				High-level BKPyV viruria			
	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Younger age at RTx, y	1.08 (1.02-1.15)	0.007	1.07 (1.01-1.14)	0.030	1.10 (1.03-1.18)	0.014	1.08 (1.02-1.13)	0.007
Male sex	1.72 (0.88-3.35)	0.110	n.a.[a]	—	n.a.[a]	—	n.a.[a]	—
Obstructive uropathy	n.a.[a]	—	n.a.[a]	—	2.21 (0.73-6.67)	0.160	n.a.[a]	—
Ureteral stent at RTx[b]	4.53 (1.24-16.6)	0.023	n.a.[a]	—	n.a.[a]	—	n.a.[a]	—
DD vs LD	3.17 (1.58-6.37)	0.001	3.35 (1.07-10.5)	0.038	2.41 (1.02-5.73)	0.046	n.a.[a]	—
Older donor age, y	1.03 (1.01-1.05)	0.004	n.a.[a]	—	1.03 (1.01-1.05)	0.017	n.a.[a]	—
Cold ischemia time, h	1.05 (1.00-1.09)	0.054	n.a.[a]	—	1.04 (0.99-1.10)	0.102	n.a.[a]	—
Transplant pyelonephritis	n.a.[a]	—	n.a.[a]	—	1.29 (0.97-1.72)	0.085	n.a.[a]	—
Induction therapy[c]	1.65 (0.84-3.25)	0.146	n.a.[a]	—	n.a.[a]	—	n.a.[a]	—
TAC vs CSA	n.a.[a]	—	n.a.[a]	—	3.00 (0.66-13.7)	0.156	n.a.[a]	—
EVR vs MMF	n.a.[a]	—	n.a.[a]	—	n.a.[a]	—	n.a.[a]	—
Pediatric Vasudev score[d]	n.a.[a]	—	n.a.[a]	—	1.08 (0.97-1.21)	0.180	n.a.[a]	—

Variables	BKPyV viremia				High-level BKPyV viremia			
	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Younger age at RTx, y	1.06 (1.01-1.10)	0.014	1.07 (1.01-1.13)	0.019	1.10 (1.04-1.17)	0.001	1.13 (1.04-1.22)	0.002
Male sex	1.42 (0.88-2.31)	0.153	n.a.[a]	—	1.79 (0.91-3.54)	0.093	n.a.[a]	—
Obstructive uropathy	1.95 (0.91-4.20)	0.088	n.a.[a]	—	2.72 (1.16-6.40)	0.022	n.a.[a]	—
Ureteral stent at RTx[b]	3.75 (1.54-9.16)	0.004	n.a.[a]	—	3.21 (1.28-8.06)	0.013	n.a.[a]	
DD vs LD	1.53 (0.92-2.53)	0.102	n.a.[a]	—	n.a.[a]	—	n.a.[a]	—
Older donor age, y	1.02 (1.00-1.03)	0.035	n.a.[a]	—	n.a.[a]	—	n.a.[a]	—
Cold ischemia time, h	1.03 (1.00-1.07)	0.089	n.a.[a]	—	1.04 (1.00-1.09)	0.060	n.a.[a]	—
Transplant pyelonephritis	n.a.[a]	—	n.a.[a]	—	1.29 (0.99-1.69)	0.061	n.a.[a]	—
Induction therapy[c]	n.a.[a]	—	n.a.[a]	—	1.97 (1.06-3.67)	0.032	n.a.[a]	—
TAC vs CSA[d]	3.30 (1.75-6.25)	<0.001	3.63 (1.51-8.76)	0.004	4.21 (1.46-12.1)	0.008	4.55 (1.15-18.1)	0.031
EVR vs MMF[d]	0.45 (0.22-0.93)	0.031	n.a.[a]	—	0.31 (0.09-1.03)	0.055	n.a.[a]	—
Pediatric Vasudev score[e]	1.11 (1.02-1.20)	0.018	n.a.[a]	—	1.28 (1.16-1.43)	< 0.001	1.32 (1.15-1.51)	<0.001

Höcker et al. Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transplant Recipients: An International CERTAIN Registry Study. Transplantation2019;103(6):1224-1233

Epidemiology of and risk factors for BKV replication and nephropathy

BKV viremia

Variables	Unadjusted OR (95% CI)[a]	P
TAC/MMF (n = 201) vs CSA/MMF (n = 43)[b]	2.52 (1.18-5.39)	0.017
TAC/MMF (n = 201) vs CSA/EVR (n = 31)[b]	5.15 (1.74-15.3)	0.003
TAC/MMF (n = 201) vs TAC/AZA (n = 9)[b]	1.74 (0.45-6.67)	0.421
TAC/MMF (n = 201) vs TAC/EVR (n = 15)[b]	1.04 (0.35-3.12)	0.940
CSA/MMF (n = 43) vs CSA/EVR (n = 31)[b]	2.05 (0.58-7.26)	0.268

BKVAN

Variables	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Younger age at RTx, y	1.08 (0.98-1.20)	0.122		
Male sex	3.70 (0.81-16.8)	0.091		
Obstructive uropathy	9.00 (2.88-28.2)	<0.001	12.4 (2.95-52.3)	0.001
Transplant pyelonephritis	1.53 (1.11-2.11)	0.009		
Acute rejection	4.06 (1.24-13.2)	0.020		
Pediatric Vasudev score[a]	1.26 (1.10-1.45)	<0.001	1.27 (1.07-1.50)	0.006

BKV viremia occuring later than 1-year posttransplant

Variable	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Cold ischemia time, h	1.05 (0.99-1.11)	0.092		
Obstructive uropathy	2.37 (0.72-7.91)	0.153		
IL-2R antagonist induction[a]	2.12 (0.880-5.10)	0.094		
TAC vs CSA	5.50 (1.26-24.0)	0.024	8.17 (1.05-63.9)	0.045
Pediatric Vasudev score[b]	1.13 (0.99-1.29)	0.081		

[a] Induction therapy, defined as induction with thymoglobulin or IL-2R antagonist, did not prove to be significantly associated with the development of BKPyV viremia beyond the first year posttransplant.
[b] According to reference.[35,36]
BKPyV, BK polyomavirus; CI, confidence interval; CSA, ciclosporin microemulsion; IL-2, interleukin-2; OR, odds ratio; TAC, tacrolimus.

TRANSPLANTATION

Höcker et al. Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transplant Recipients: An International CERTAIN Registry Study. Transplantation103(6): 1224-1233, June 2019. doi: 10.1097/TP.0000000000002414

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BKVAN - Prognosis

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- Allograft loss rates : 15-38%
- Half due to the rejection episodes in the setting of reduced immunosuppression due to BKVAN

Cohen-Bucay A et al. Advances in BK virus complications in organ transplantation and beyond. Kidney Med 2020; 2(6): 771-786.

- BKVAN – associated with the development of class II de novo DSA
- An induvidualized approach to immunosuppression modifications (close monitoring of GFR, BK viremia and DSA)

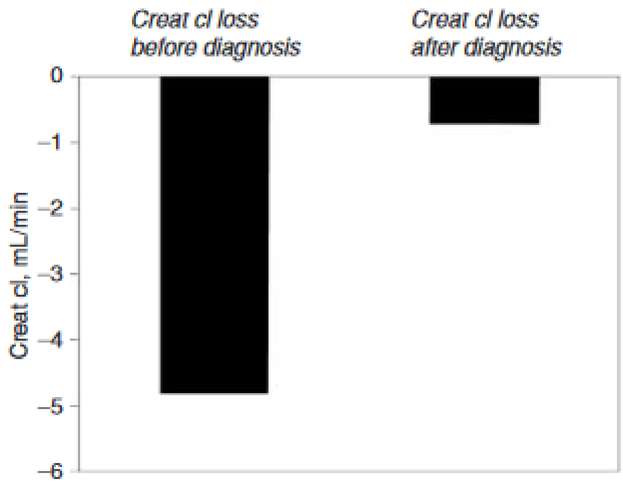
Sawinski et al. Persistent BK viremia does not increase intermediate-term graft loss bit is associated with de novo donor-specific antibodies. J Am Soc Nephrol. 2014.

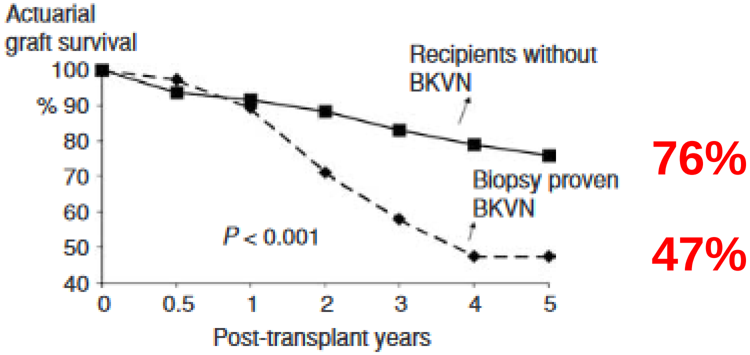
BKV nephritis: Risk factors, timing and outcome

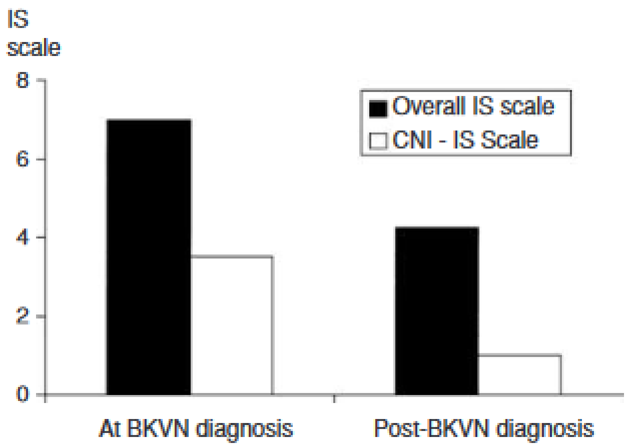
I group (until 2001)- 16 pts dg with biopsy

II group (2001-2003) – 25 pts diagnosed

with blood PCR BKV

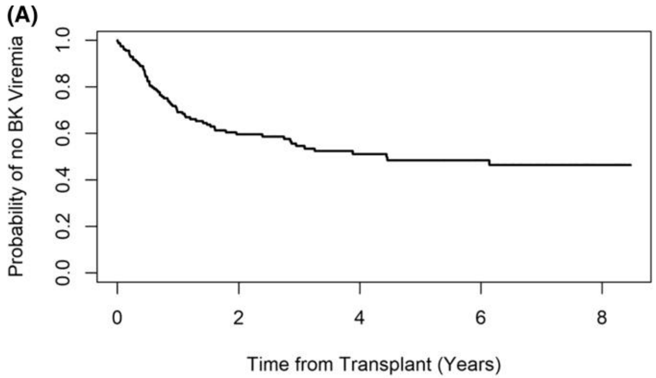


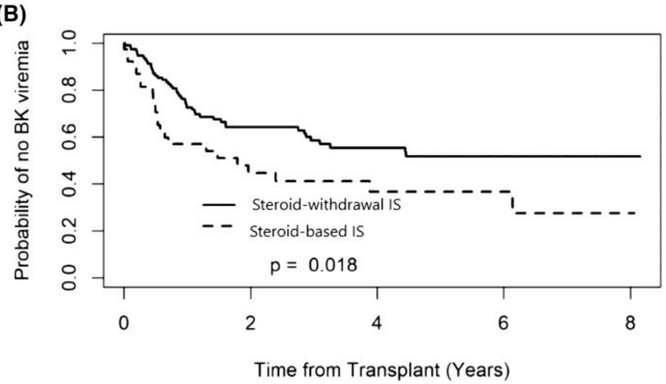


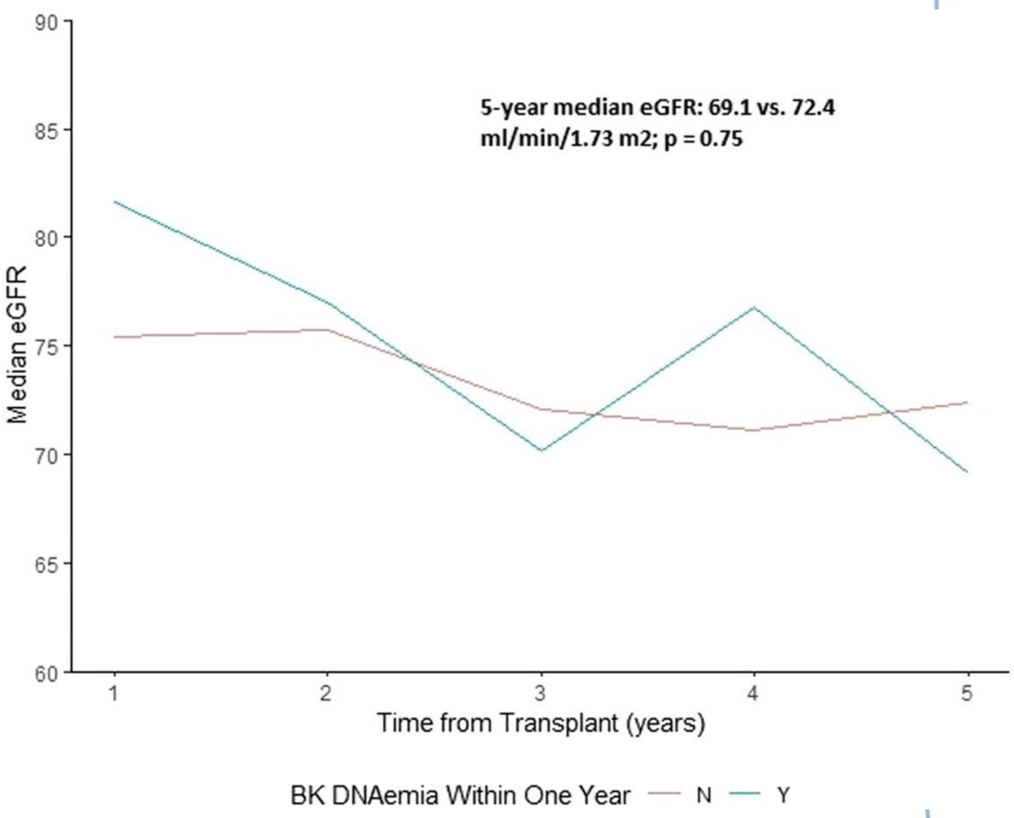


Vaseduv B. et al. BK virus nephritis: Risk factors, timing, and outcome in renal transplant recipients. Kidney Inter 2005;68:1834-1839

BKV viremia in PKTR – predictors and outcomes







Schoephoerster J et al. BK DNAemia in pediatric kidney transplant recipients: Predictors and outcome. Pediatric Transplantation.2023;27:e14372.

Retransplantation after graft loss

- Safe procedure
- To wait until viremia resolution before retransplantation
- Graft nephrectomy before retransplantation – a controversial approach

Cohen-Bucay A et al. Advances in BK virus complications in organ transplantation and beyond. Kidney Med 2(6): 771-786

Monitoring and management strategy for BKVAN

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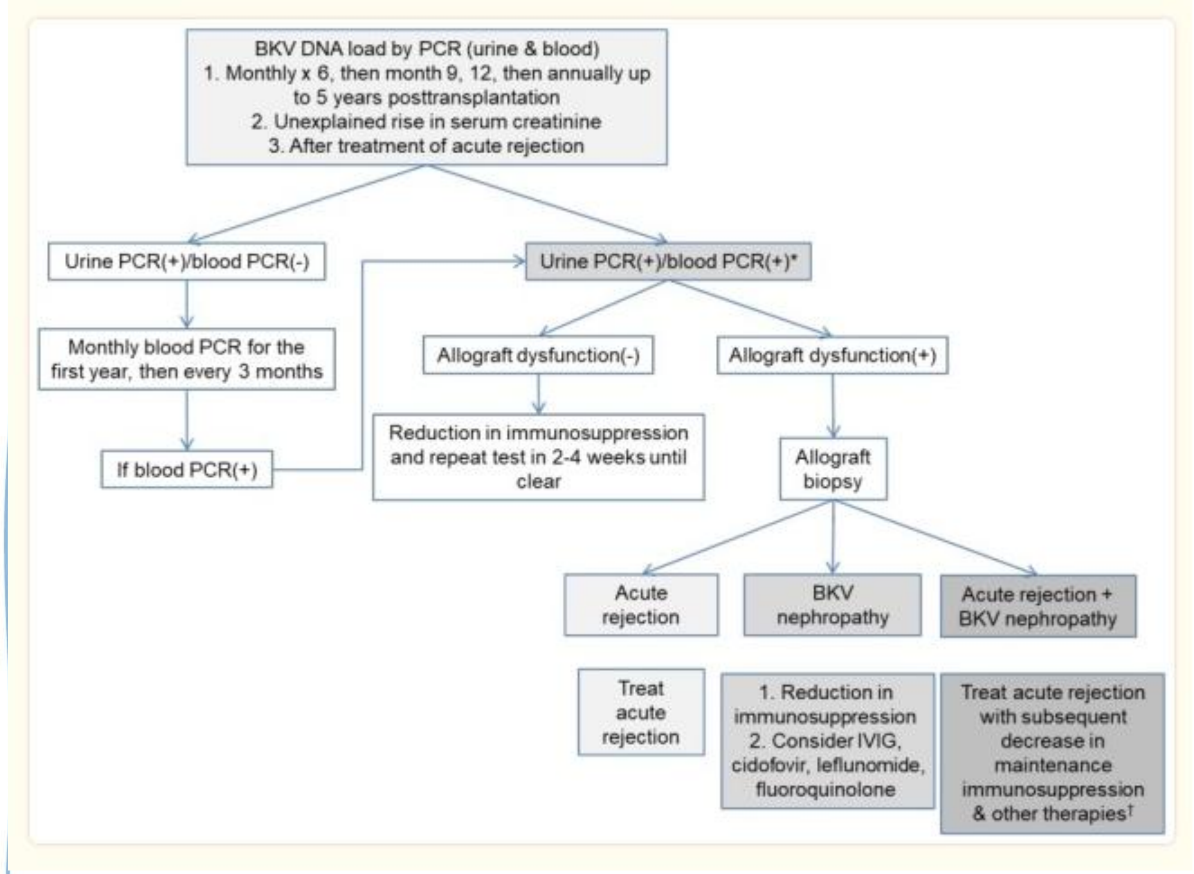

Before reducing immunosupression consider: BKV-specific T cells (BKV-Tvis)

BKV-CD4>0.7 cells/uL
BKV-CD8 Tvis>0.5 cells/uL
↓
PPP 0.96 and NPV 0.75
For self-limiting viremia

Ahlenstiel-Grunow T. and Pape L, Pediatr Nephrol 2020;35:375-382

Cho MH. Monitoring BK virus infection in pediatric kidney transplant recipients. Korean J Pediatr 2019;62(11):414-415

Conclusion

UNIVERSITY CHILDREN'S HOSPITAL TIRŠOVA FOUNDED IN 1924

- The cornestone of BKVAN and prophylaxis is the reduction of immunosuppressive therapy
- There is no uniform strategy how immunosuppressive therapy should be decreased
- No established antiviral treatment is currently available
- Screening and early diagnosis of viral replication and BKVAN are of paramount importance to allow effective management strategies - **the best treatment is prevention**

Thank you for your atention!

Contact us:
brankica.spasojevic@udk.bg.ac.rs
dijaliza @udk.bg.ac.rs

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FOUNDED IN 1924

Nephrolithiasis in children: a practical approach

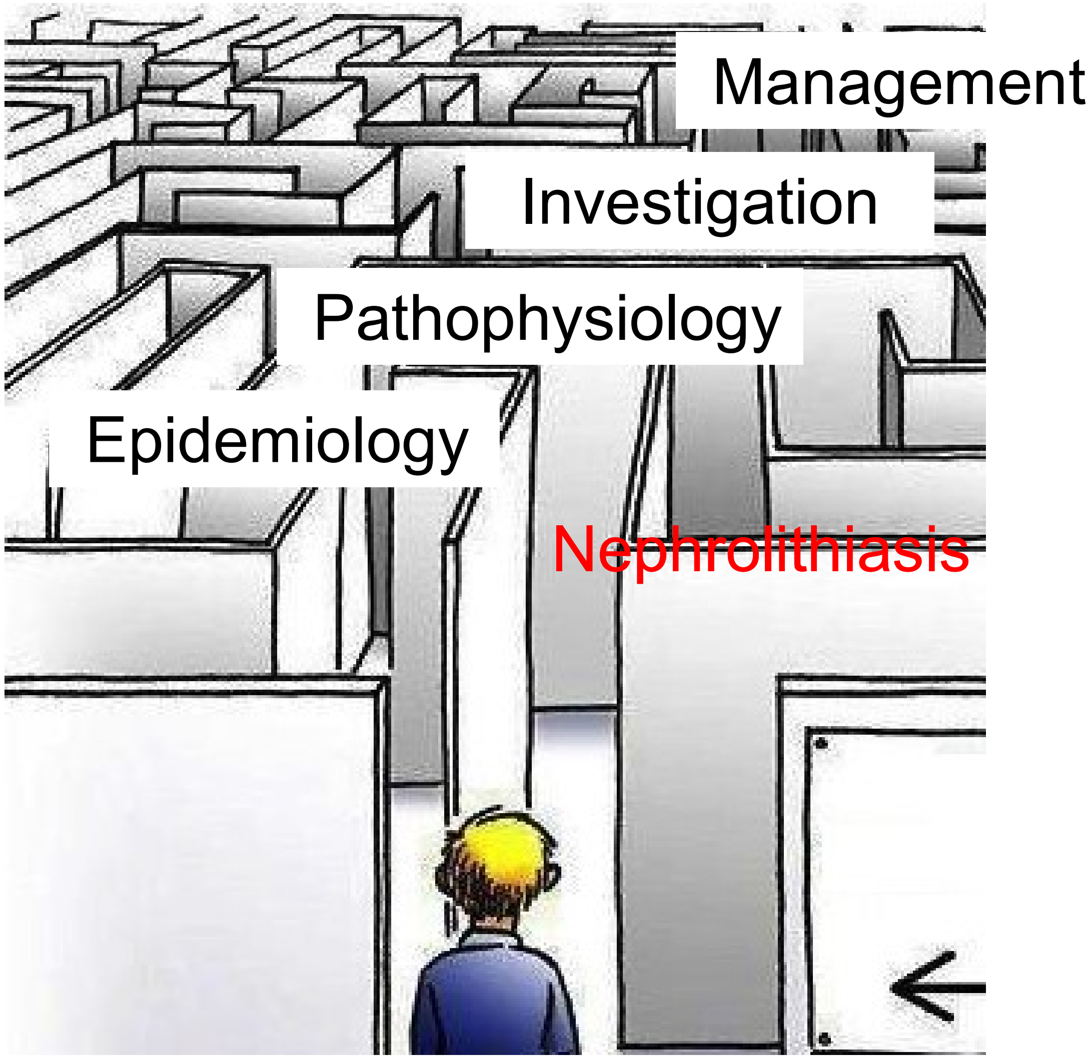
Constantinos J. Stefanidis, MD, PhD, FESPN

Head of Pediatric Nephrology
“MITERA” Children’s Hospital, Athens, Greece

10th SEPNWG Meeting

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

Nephrolithiasis in children: a practical approach



Prevalence of kidney stones (KS) (NHANES*)

*National Health and Nutrition Examination Survey

1 in 11 people in the US will have KS during their life

	2003	2012
Men:	6.3%	10.6%
Women:	4.1%	7.1%

Stamatelou KK, et al. Kidney Int. 2003

Scales CD, et al. Eur Urol 2012

Kidney stones (KS) in adults

Up to 50% of individuals will experience a second kidney stone within 10 years of their initial presentation.

Pearle MS, et al. J Urol 2001

Recurrent stone disease is linked to renal function decline.

Patients with:

- Frequent urinary tract infections (struvite stones)
- Urinary malformations
- Malabsorptive bowel conditions
- Some monogenic disorders

Gambaro G, et al. J Urol. 2017

Urolithiasis incidence per 100 000 population

https://www.cookmedical.com/urology/world-kidney-day-a-global-look-at-a-growing-concern/

Incidence of nephrolithiasis in children

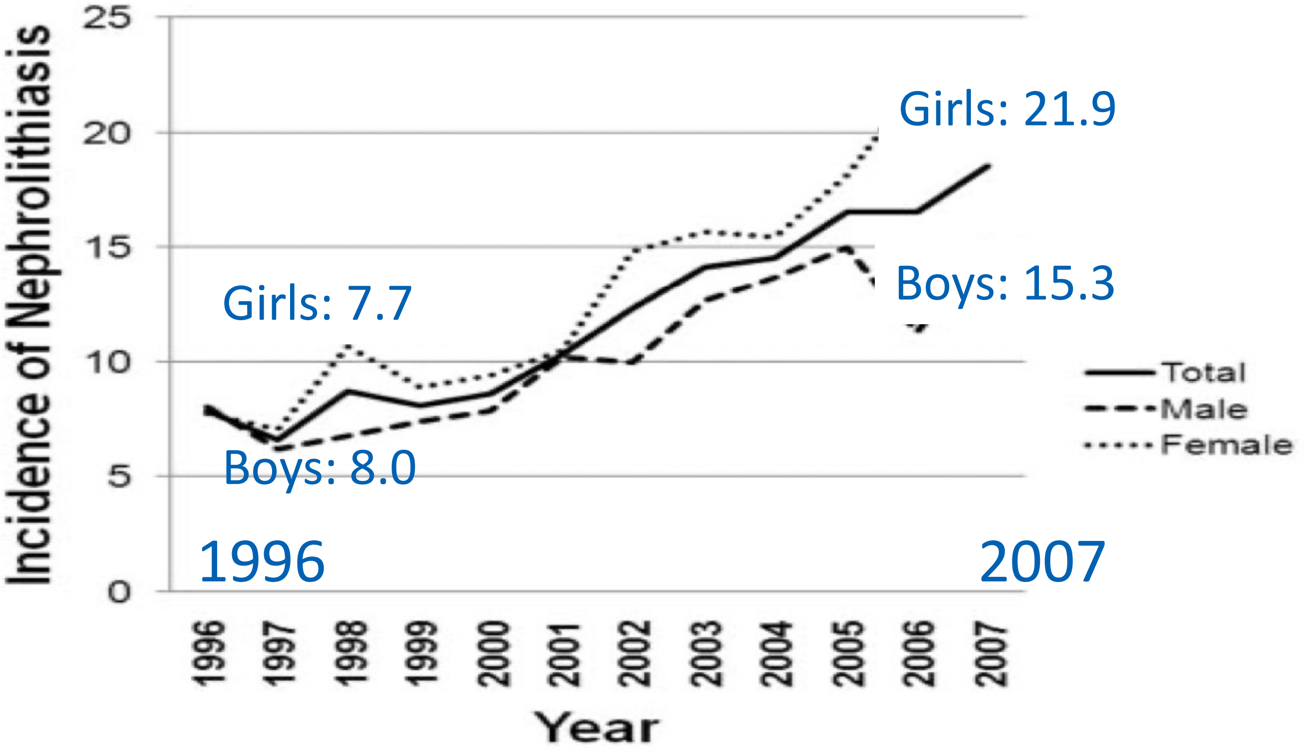
North America and Europe:

Yearly incidence in children:
<10 per 100.000 population

Pediatric nephrolithiasis is a rare disease
(<10 cases/ 100,000 population)

Incidence of pediatric nephrolithiasis (S. Carolina)

per 100,000 children

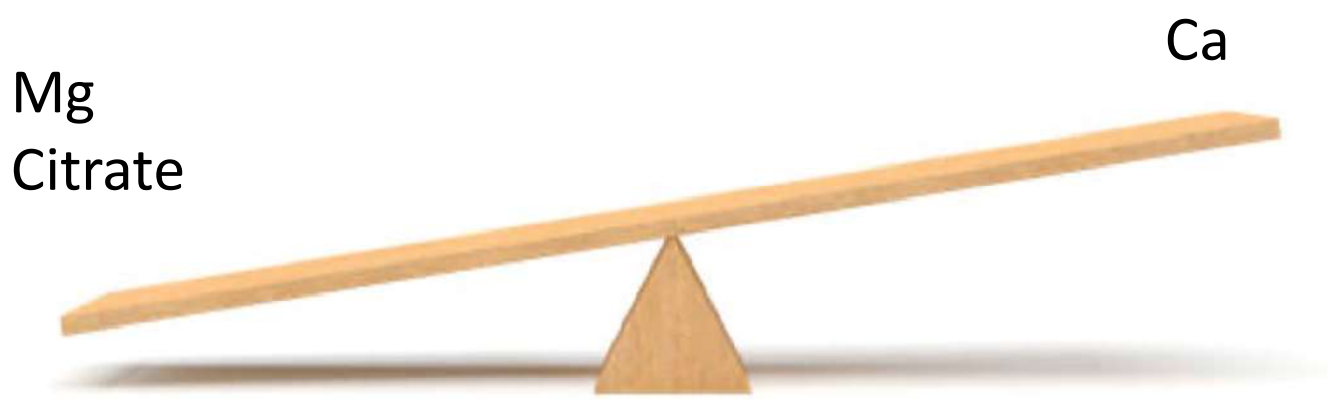


Sas DJ, et al. J Pediatr, 2010

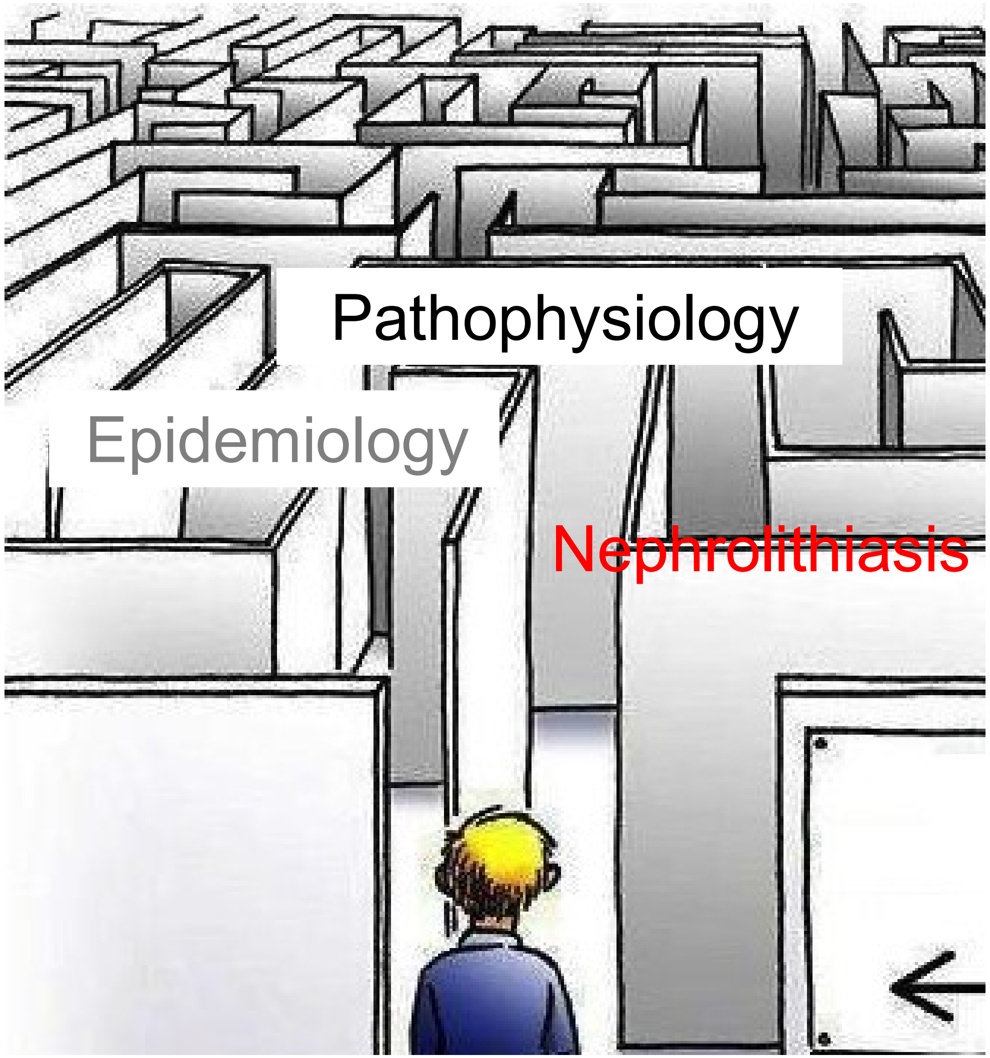
Why children have lower incidence of KS?

Children have a higher urine concentration of calcium, but have also a higher concentration of inhibitors of crystallization (Mg, citrate)

Miyake OA et al. Urology 2001



Nephrolithiasis in children: a practical approach

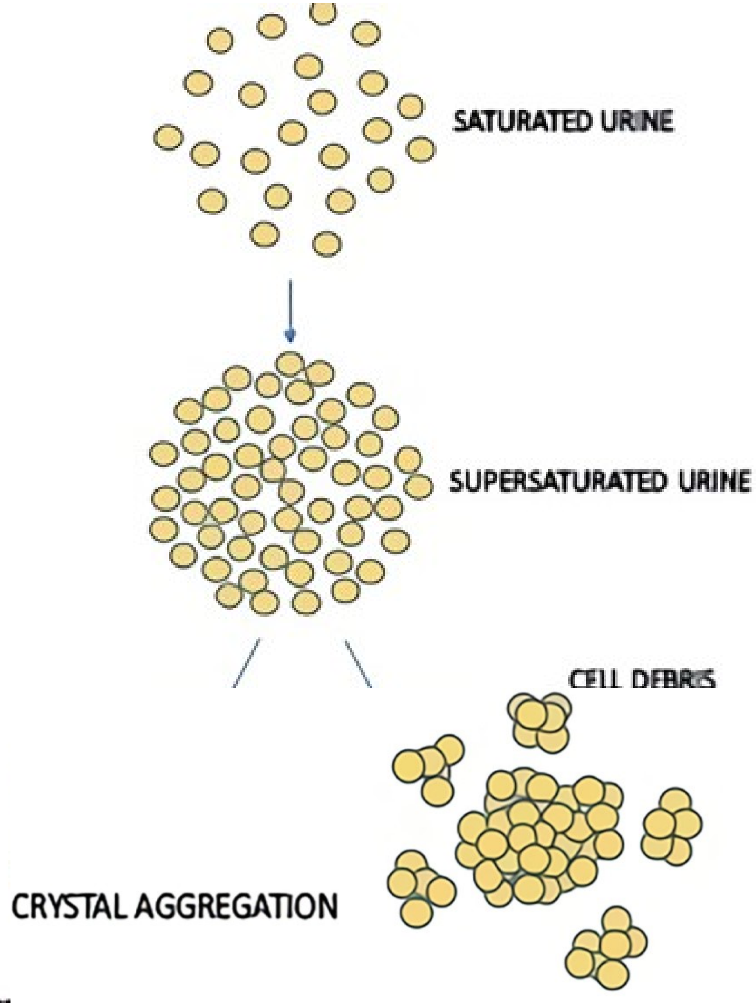


Supersaturation and crystallization

Urine: complex solution containing Ca and Ox and other ions and macromolecules that can interact with Ca and/or Ox and modulate:

Supersaturation

Crystallization

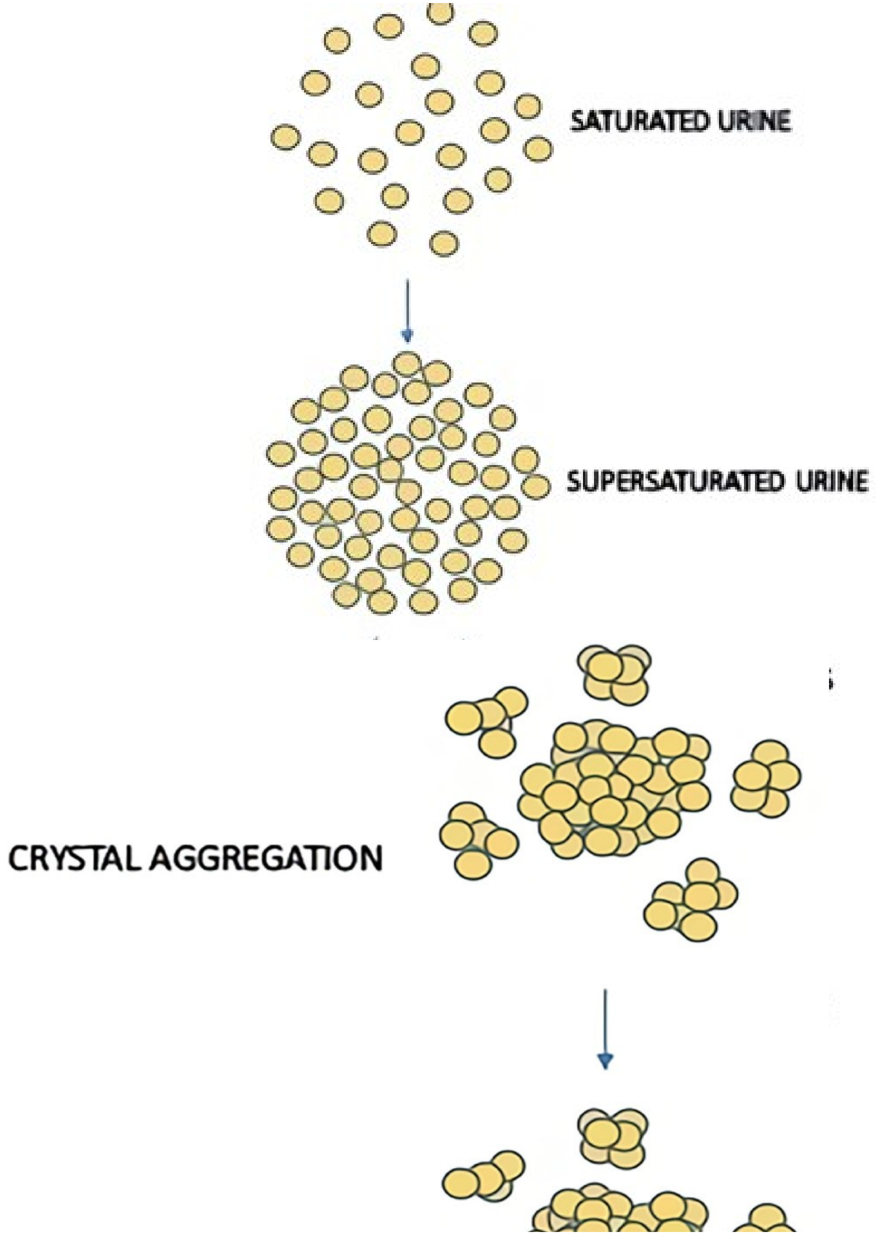


Khan SR. Urol Res 2006

Supersaturation and crystallization

Millions of urinary crystals are excreted daily indicating transient supersaturation

Supersaturation, it is only one step in the process of stone formation

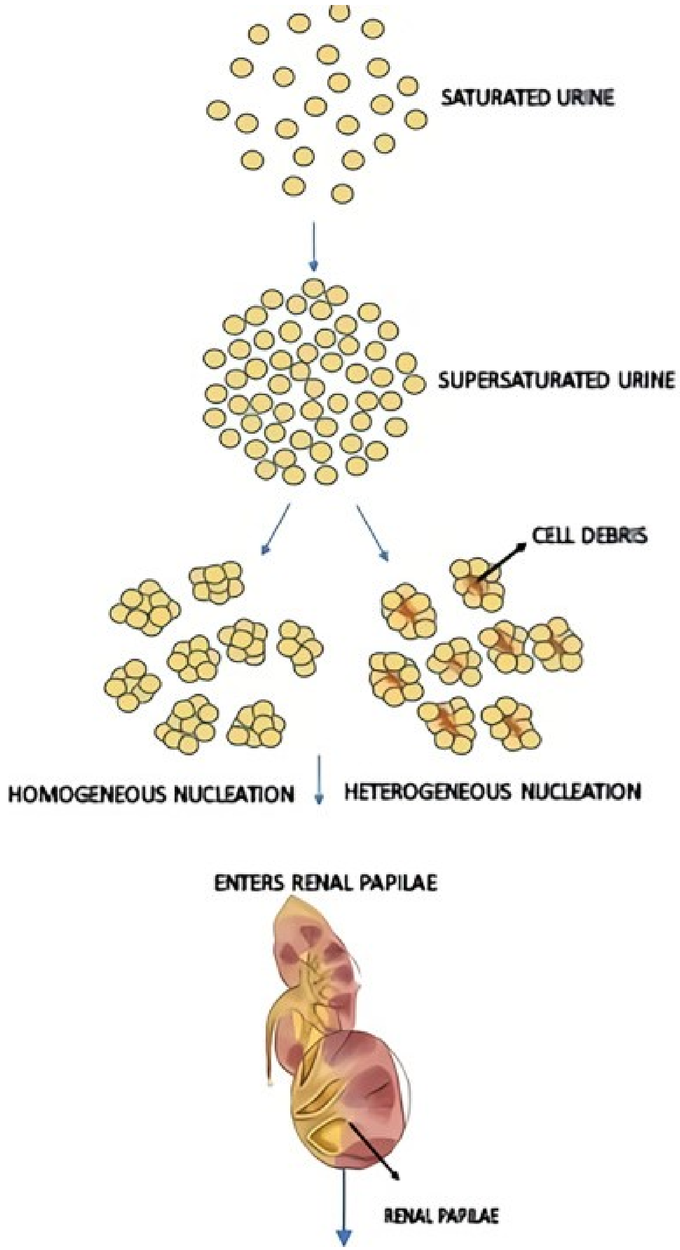


Khan SR. Urol Res 2006

Renal epithelial attachment

Crystal retention by attachment to renal epithelial cells

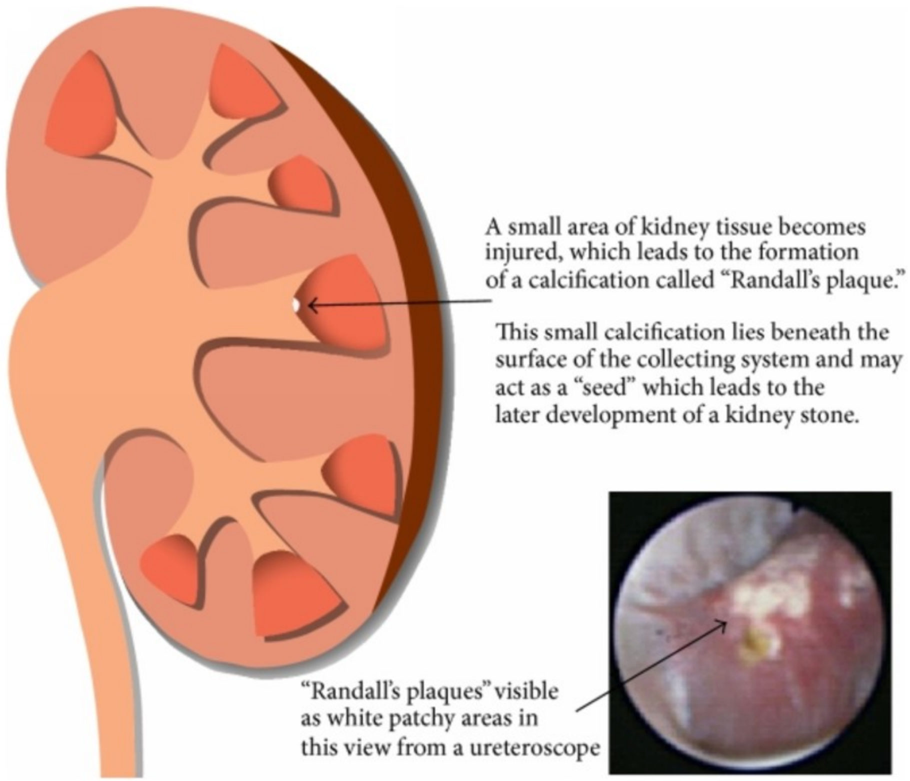
The epithelial production of several urinary macromolecules modulate the nucleation, aggregation and retention of crystals in the interstitium of the kidneys



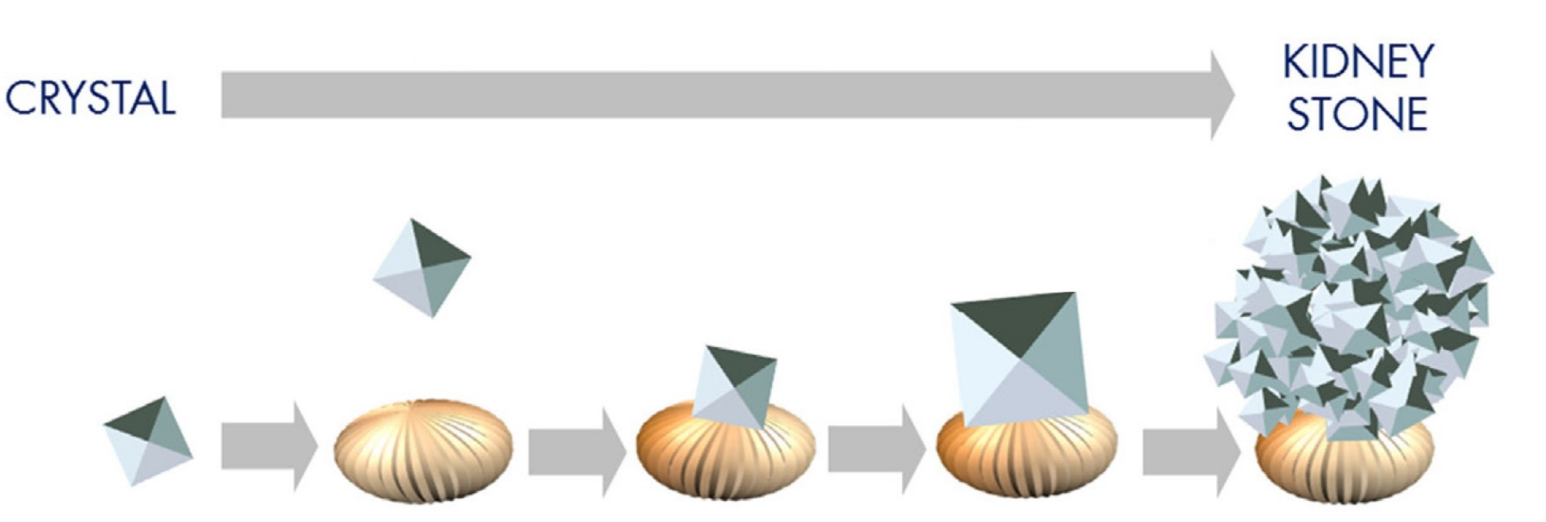
Khan SR. Urol Res 2006

Randall’s plaques

In order for stone to be formed, crystals should be located at renal papillary surface to ulcerate and form a stone nidus



Lithogenesis

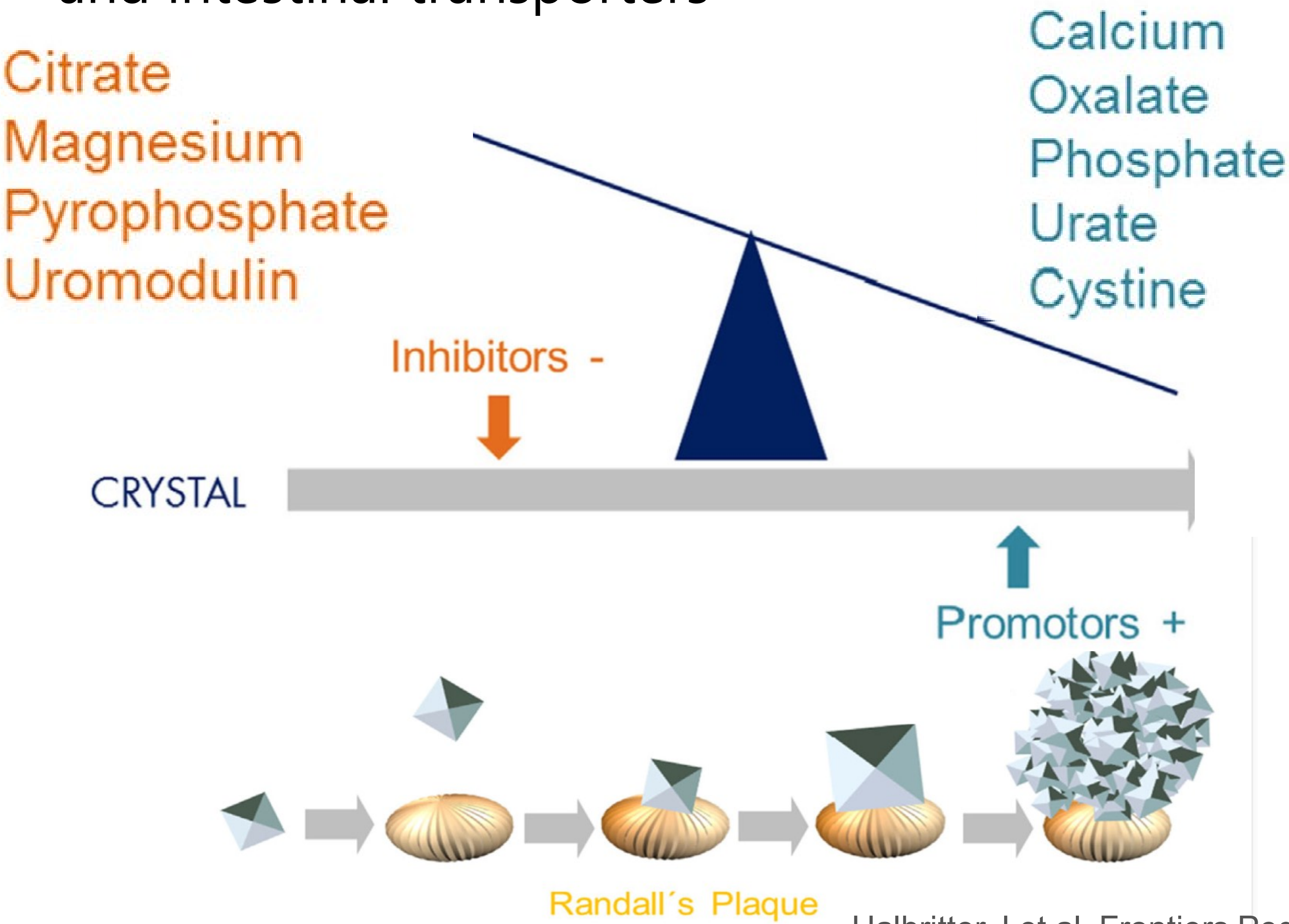


Randall's plaque

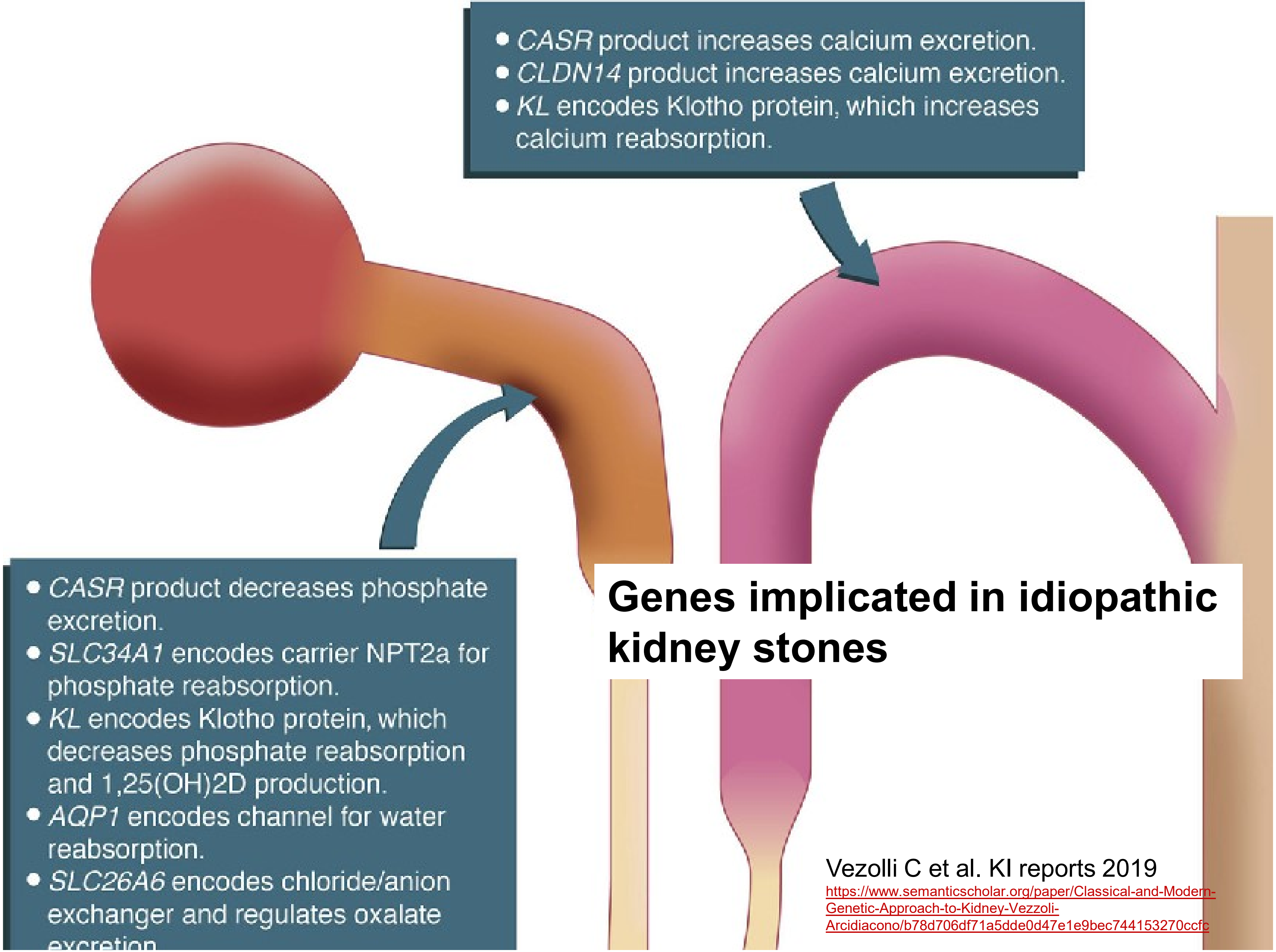
Halbritter J et al. Frontiers Ped 2018

Imbalance of inhibitors and promotors of crystallization

Urinary inhibitors and promotors are controlled by renal and intestinal transporters



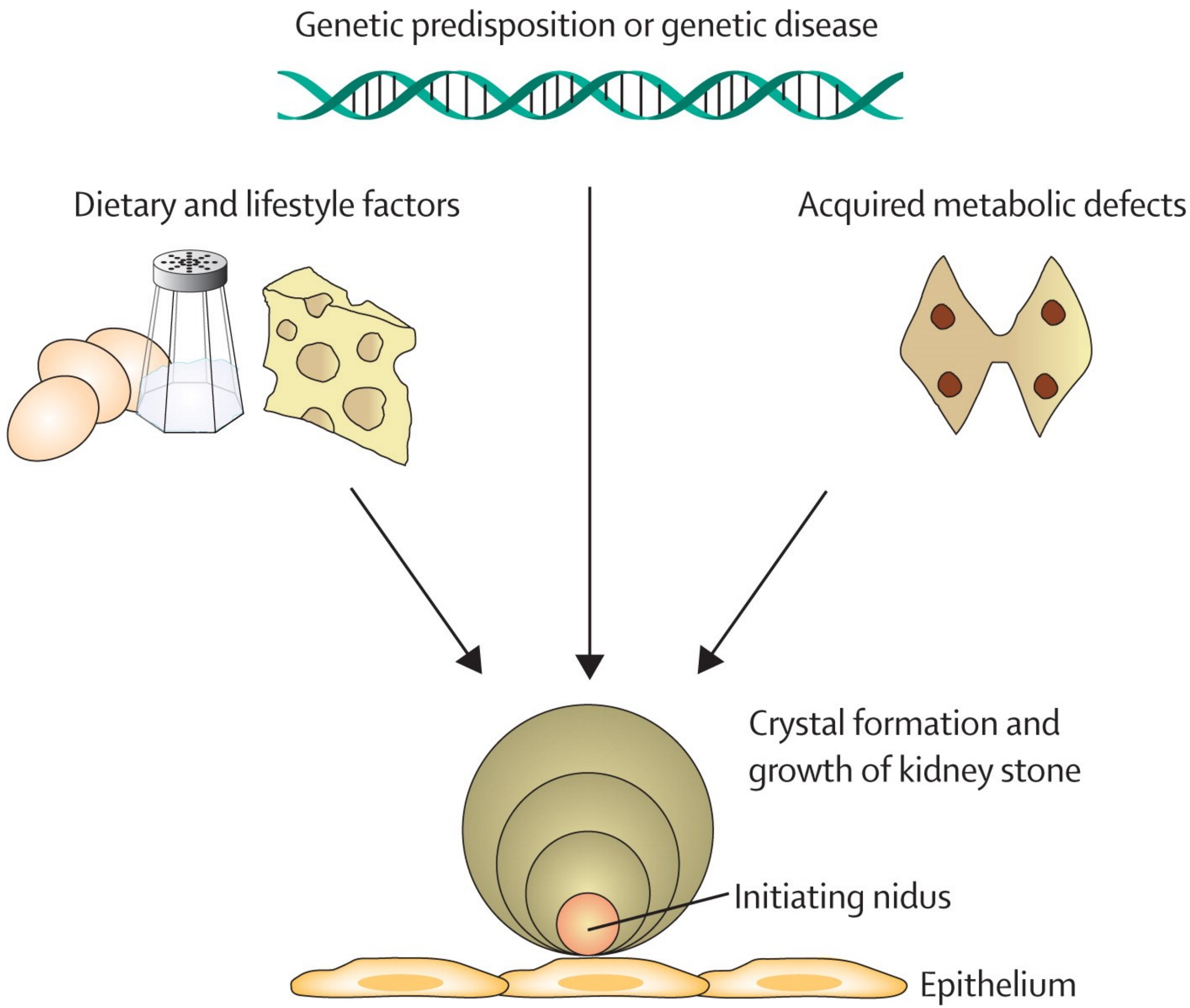
Halbritter J et al. Frontiers Ped 2018



Genes implicated in idiopathic kidney stones

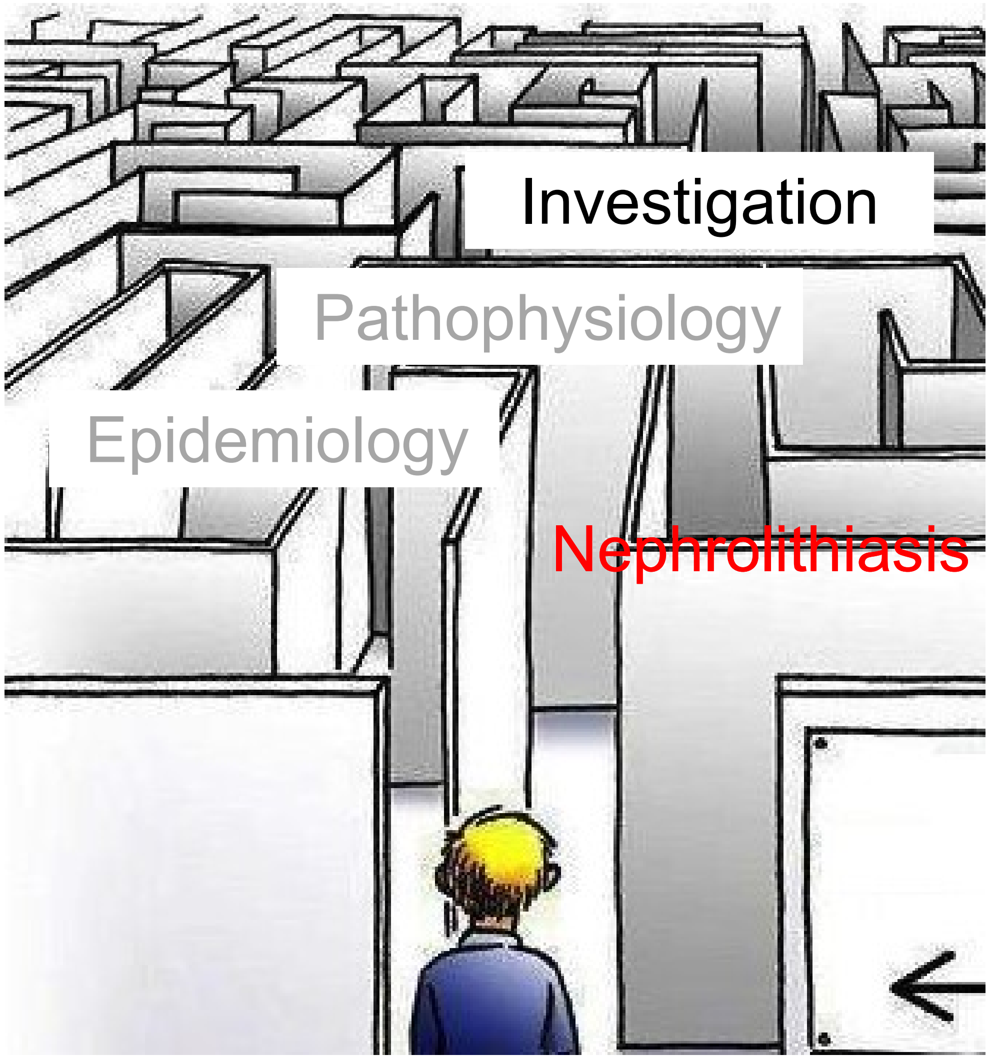
Vezolli C et al. KI reports 2019
https://www.semanticscholar.org/paper/Classical-and-Modern-Genetic-Approach-to-Kidney-Vezzoli-Arcidiacono/b78d706df71a5dde0d47e1e9bec744153270ccfc

Etiology of calcium stones

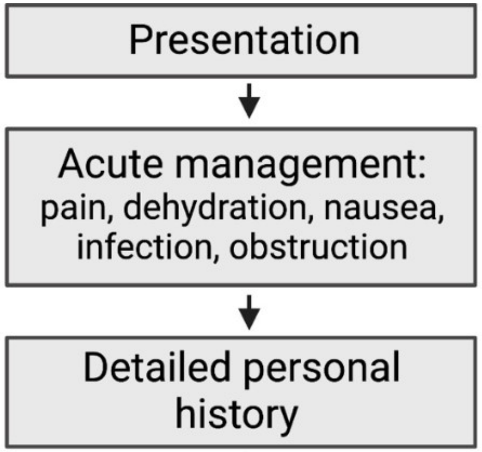


Moe OW. Lancet 2006

Nephrolithiasis in children: a practical approach



Investigation of nephrolithiasis



Risk factors for kidney stones in children

Inadequate hydration

Increase in dietary Na intake

produces higher urinary Ca excretion

High intake of proteins

↑ Ca, UA, Ox excretion

↓ urinary pH, which ↑ precipitation of UA and CaOx.

↓ urinary citrate

Obesity?

Marra G J Nephrol 2018

Risk factors for kidney stones in children

History of CAKUT

UTIs caused by a urease-producing organism (Proteus or Klebsiella)

Perinatal medical history (prematurity, vitamin D supplementation)

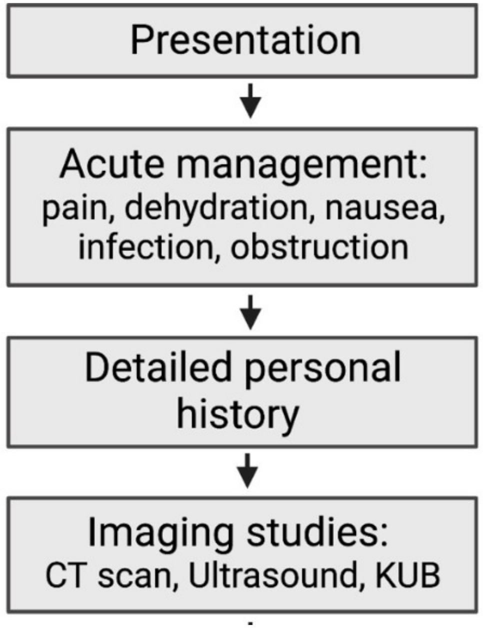
Conditions leading to immobilization

Medications associated with stone formation

Malabsorptive intestinal diseases and conditions

Marra G J Nephrol 2018

Management of nephrolithiasis

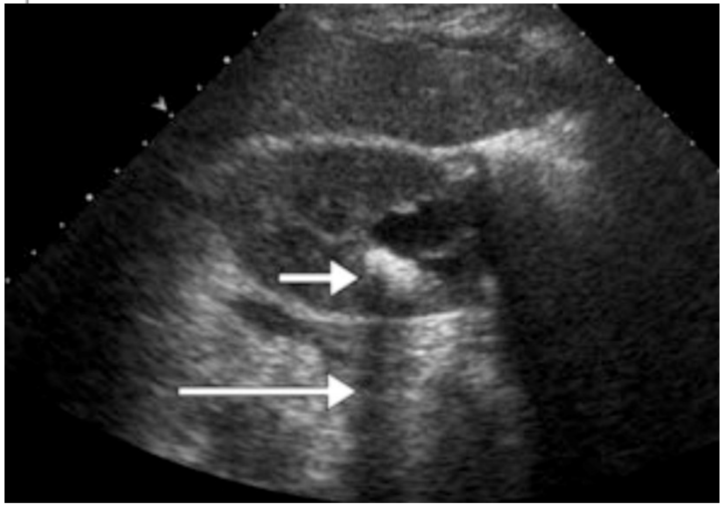


Imaging

KUB X-ray

Radio density	
Radio-opaque	Calcium oxalate Carbonate apatite $Ca_5(PO_4)_3\ 2H_20$ Brushite $CaHPO_4\ 2H_20$
Intermediate	Cystine Struvite $MgNH_4PO_4\ 6H20$
Radiolucent	Uric acid Xanthine 2,8 Dihydroxyadenine

Renal ultrasound



Edvardsson V. Ped Nephrol 2016

Imaging

KUB X-ray

Renal ultrasound

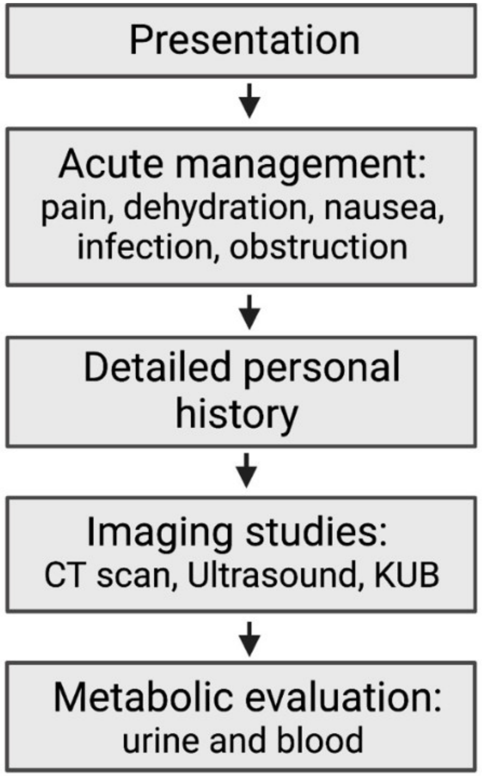
CT scan

In 50 patients 13 KS were not diagnosed by US
12 stones < 5 mm
3 stones in ureter

Passerotti C et al. J Urol 2009

Edvardsson V. Ped Nephrol 2016

Management of nephrolithiasis



First-line tests in pediatric nephrolithiasis

Urine collection	Once	Oxalates and amino acids
	3 times	Creatinine, proteins, beta2 microglobulins, Na, K, Cl, Ca, P, Mg, uric acid, citrate
Urine microscopic examination	3 times	Crystals and urinary sediment
Blood test	Once	Urea, creatinine, uric acid, Na, K, Cl, Ca, P, Mg, EAB

Marra G et al. J Nephrol 2018

Stone risk in as many as one in four children may be misclassified if normative values of only a single 24-hour urine are used.

733 pediatric patients

Ellison JS et al. J Pediatr Urol 2017

Metabolic risk factors present in children with stones

	No. Totals (%)	No. Neurogenic Bladder (%)	No. Anatomical Abnormality (%)	No. Isolated (%)
None	14 (31.1)	2 (22.2)	1 (33.3)	11 (33.3)
Hypocitraturia	13 (28.9)	4 (44.4)	0	9 (27.3)
Hypercalciuria	6 (13.3)	1 (11.1)	1 (33.3)	4 (12.1)
Hyperoxaluria	2 (4.4)	0	0	2 (6.1)
Hyperuricosuria	1 (2.2)	0	0	1 (3.0)
Hypocitraturia + hypercalciuria	3 (6.7)	1 (11.1)	0	2 (6.1)
Hypercalciuria + hyperoxaluria	4 (8.9)	1 (11.1)	0	3 (9.1)
Hypocitraturia + hypercalciuria + hyperoxaluria	2 (4.4)	0	1 (33.3)	1 (3.0)
Totals	45	9	3	33

Kovacevic L, et al. J Urol 2012

Limited metabolic assessment

Hypercalciuria and low urine volume were considered the most common abnormalities in pediatric stone formers

Recent studies noted that hypocitraturia was more common

Hypocitraturia corresponds to a low consumption of potassium and magnesium

Chan KH et al. J Pediatr Urol 2018

Limited metabolic assessment

Retrospective study 2005-2015
410 patients <18 years, 380 were excluded this left
80 patients

Low urine volume <1ml/kg/hour,

Elevated	24-hour calcium	>4.0 (1 mol) mg/kg
Decreased	24-hour citrate	<4.2 mg (27 mol) /kg
Elevated	24-hour oxalate	>52 mg (0.58 mmol)/1.73m2
Elevated	24-hour uric acid	>20 mg (0.12 mmol) /kg
Decreased	24-hour Mg	<4.5 mg (0.2 mmol) /kg

Chan KH et al. J Pediatr Urol 2018

Limited metabolic assessment

would have detected almost all clinically significant metabolic abnormalities

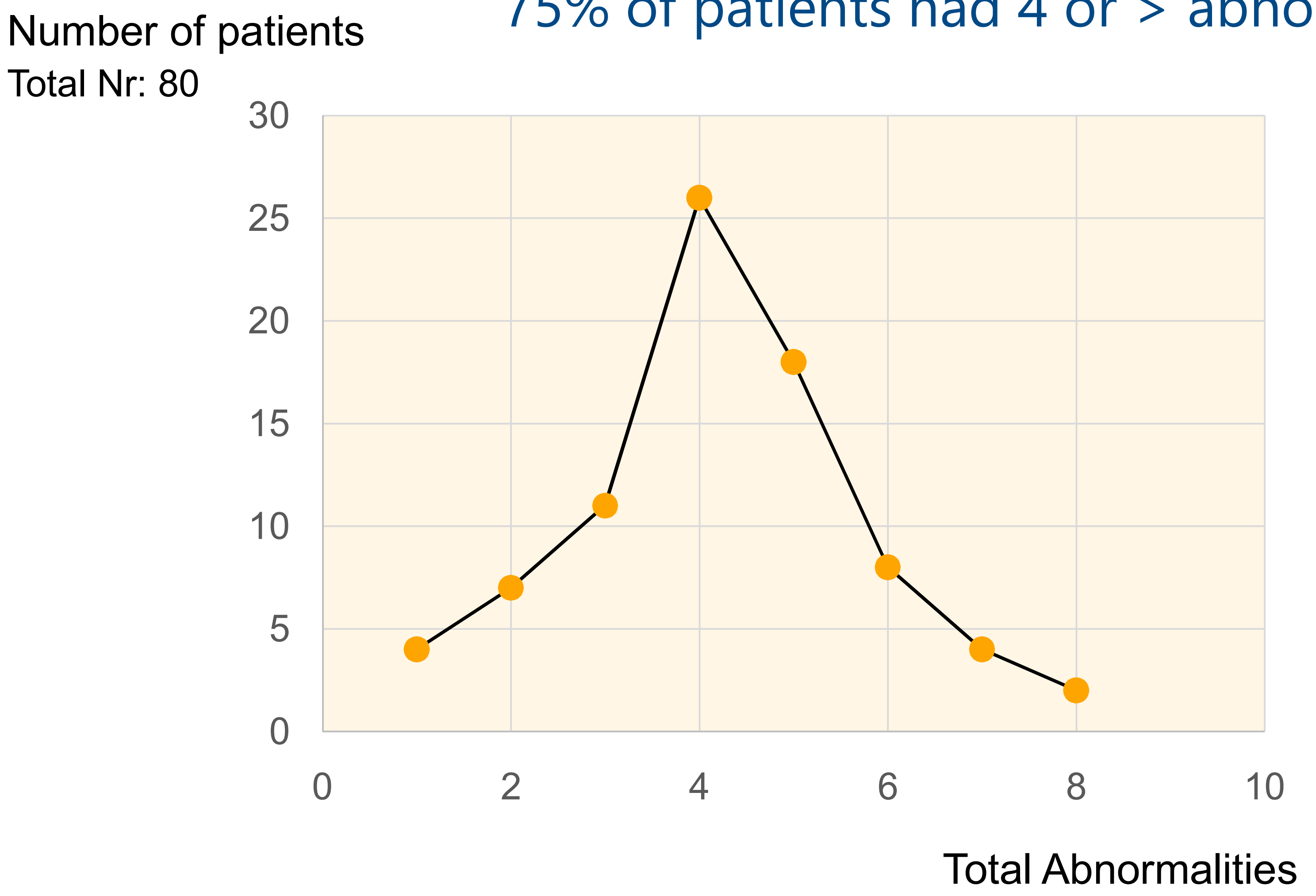
- Potassium (low) 61 (76.3%)
- Magnesium (low) 57 (71.3%)
- Citrate (low) 55 (69.6%)
- Low urine volume 42 (52.5%)
- Calcium (high) 18 (22.5%)
- Oxalate (high) 12 (15.0%)
- Uric acid (high) 2 (2.5%)

- pH (high) 27 (33.8%)
- Sodium (high) 20 (25.0%)
- Phosphorus (low) 14 (17.5%)
- pH (low) 12 (15.0%)
- Phosphorus (high) 7 (8.8%)
- Sodium (low) 2 (2.5%)

Chan KH et al. J Pediatr Urol 2018

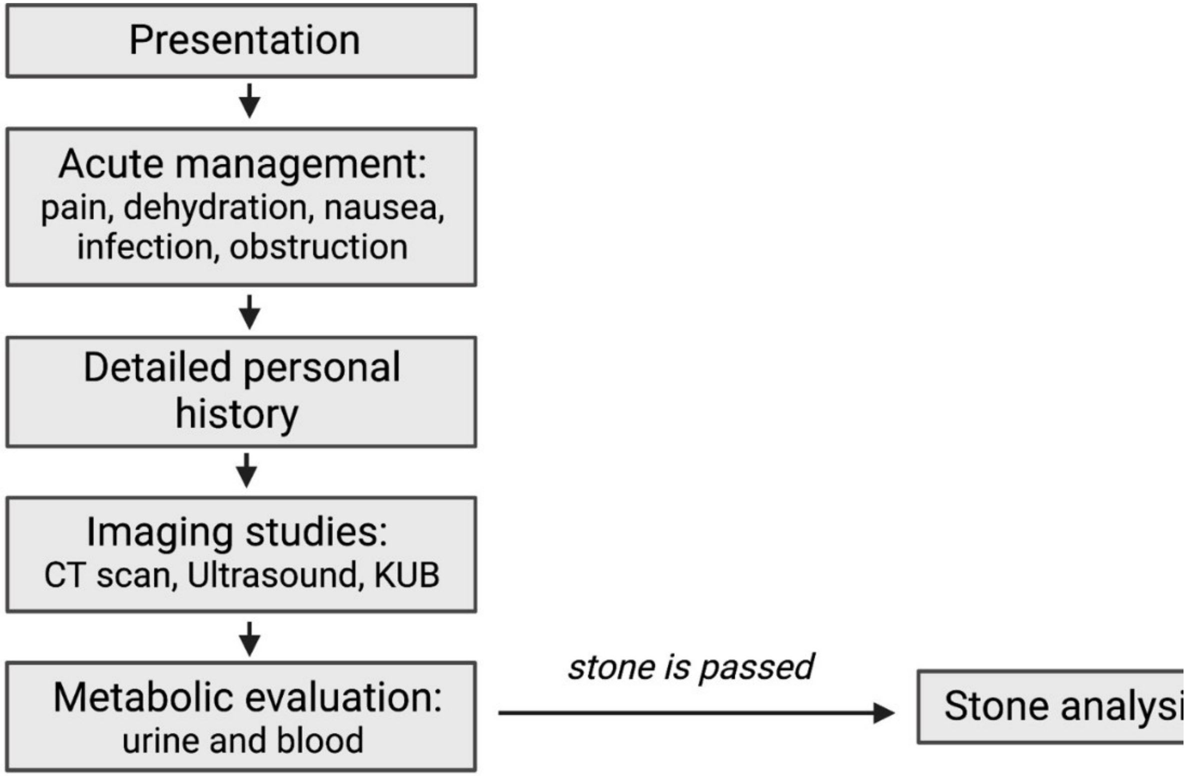
Limited metabolic assessment

75% of patients had 4 or > abnormalities



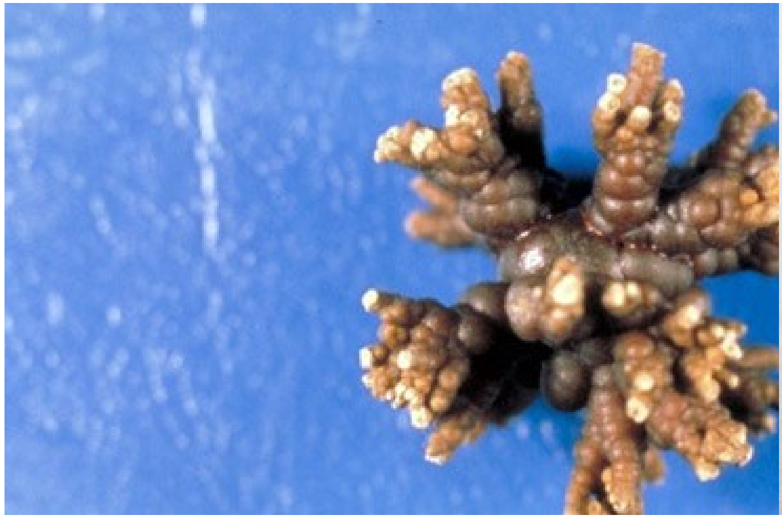
Chan KH et al. J Pediatr Urol 2018

Management of nephrolithiasis



Calcium oxalate stones

Urine pH < 5.5
Hypercalciuria
Enteric or idiopathic hyperoxaluria




Brusite stones (Calcium phosphate)

Urine pH > 6.7
Hypercalciuria
RTA
Dent's disease


Uric acid stones

pH ούρων <5.5

Icreased protein intake
Tumor lysis syndrome
Lesch-Nyhan syndrome: Deficiency of HPRT*

*Hypoxanthine-guanine phosophoribosyltransferase

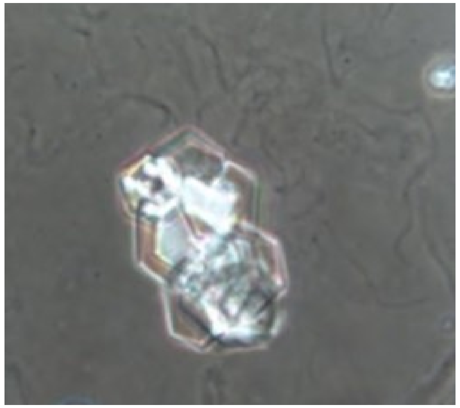
Cystine stones

pH ούρων <5.5

Therapeutic target:

Urine cystine < 250 mg/L (~ 1 mmol/L)

Hexagonal crystals



Large, branched staghorn calculus

Struvite stones $MgNH_4PO_4 6H20$

pH ούρων >7
Urease producing bacterium

Risk factors for struvite stones:

Younger age

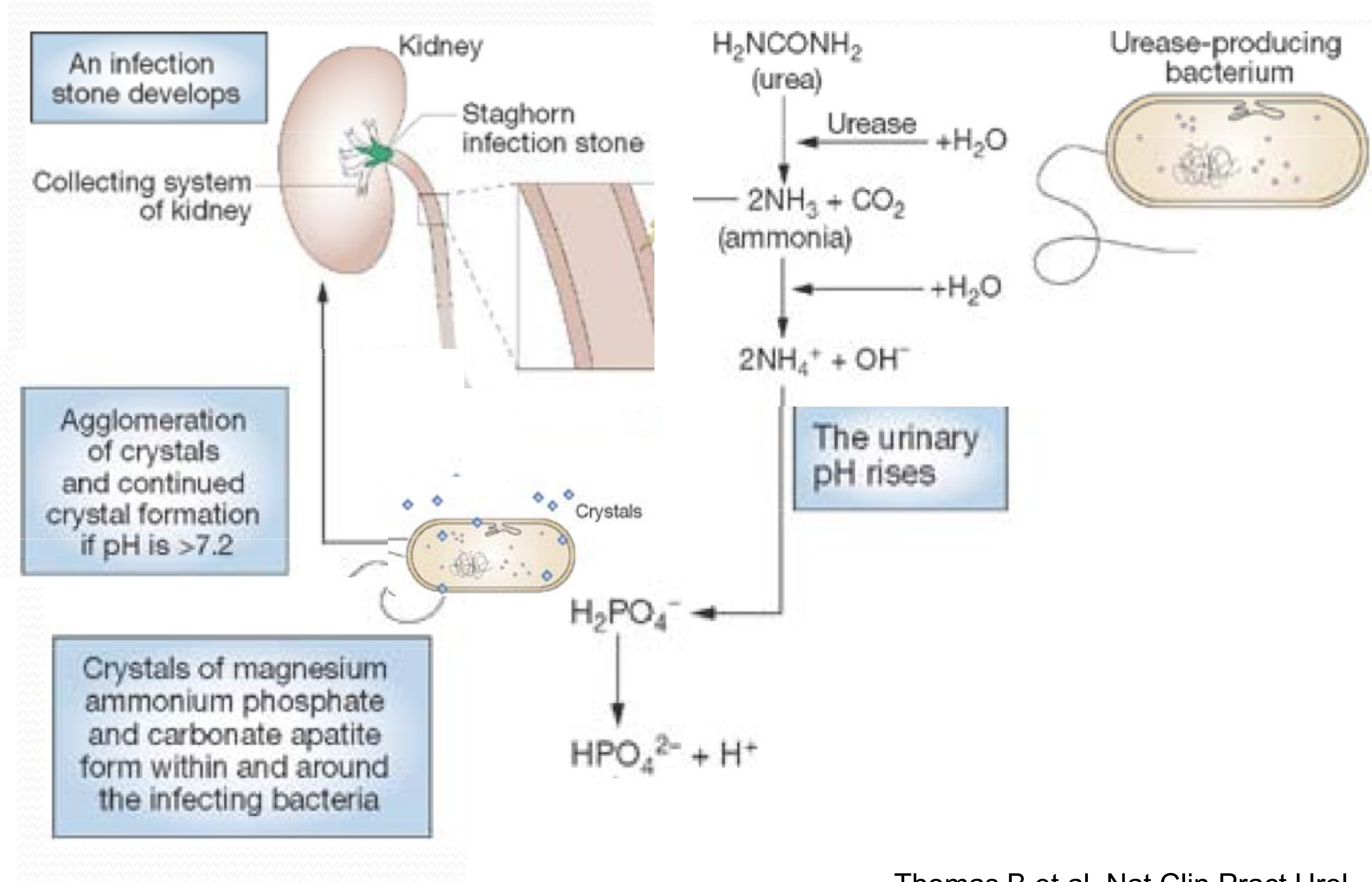
Obstructive uropathy

Urinary diversion

Neurogenic bladder

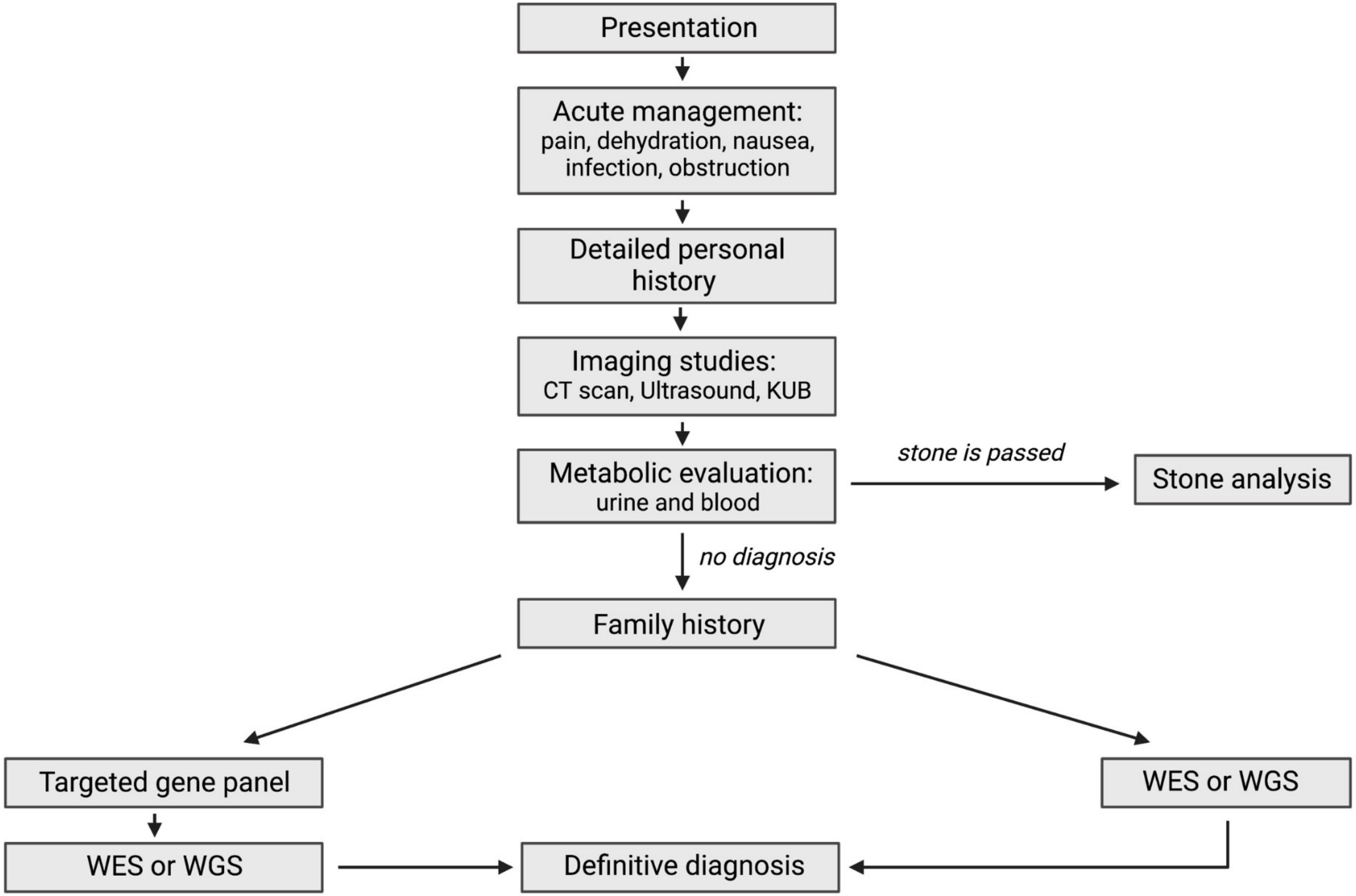
Prior urologic surgeries

Struvite stones $MgNH_4PO_4\ 6H20$



Thomas B et al. Nat Clin Pract Urol 2008

Management of nephrolithiasis



Schott C et al. Frontiers Urol. 2022
https://www.frontiersin.org/articles/10.3389/fruro.2022.1075711/full

When to suspect rare causes of kidney stones?

Currently, there are 41 known genes with monogenic causation for nephrolithiasis

History	Family history of nephrocalcinosis Growth retardation, rickets, CKD
Imaging	Nephrocalcinosis Radiolucent kidney stones Multiple stones, bilateral stones
Lab results	Unexplained kidney failure Mild-moderate proteinuria Increased urine b2 microglobulin

Type 1 hyperoxaluria (PH1)

Kidney stone in a child

Recurrent lithiasis

Nephrocalcinosis

Family history of stones

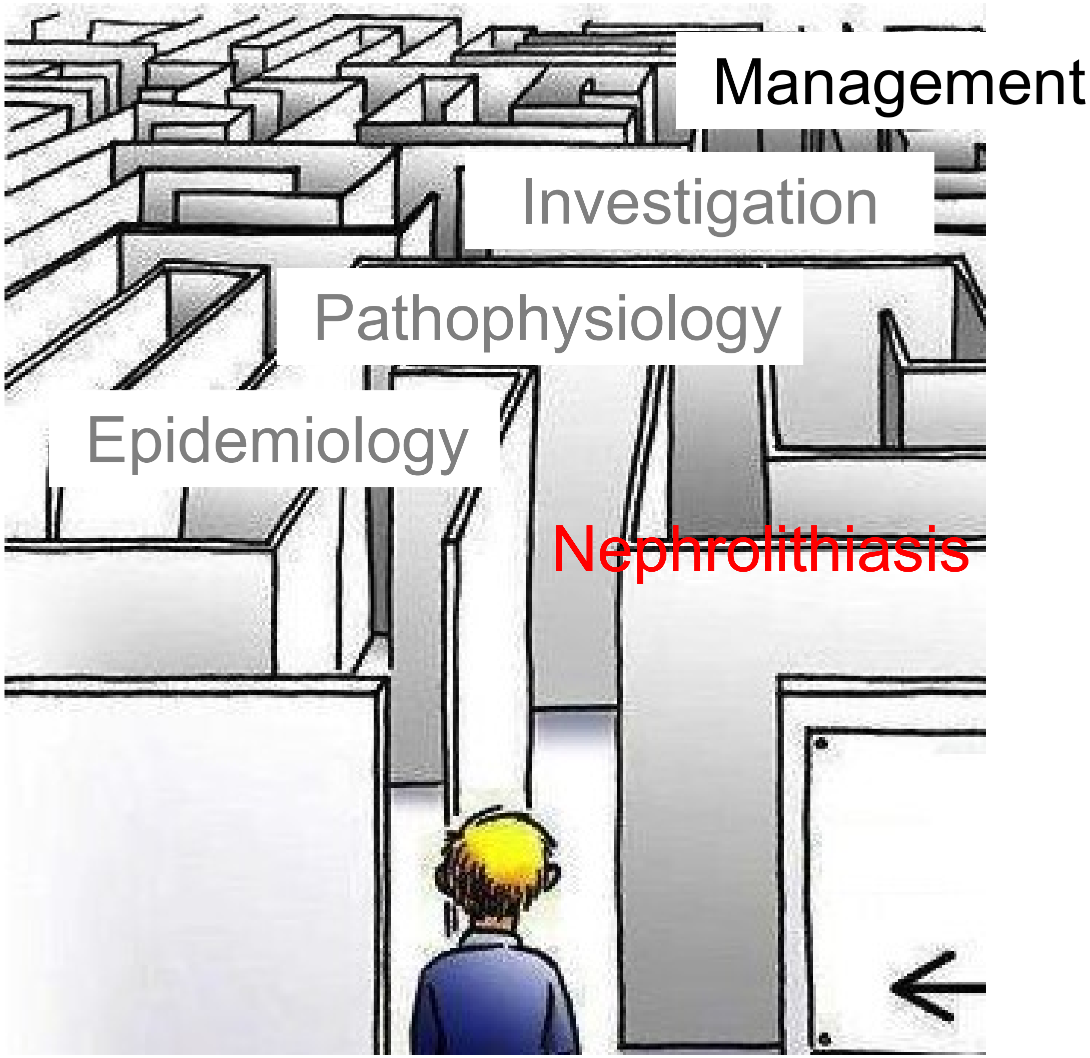
Failure to thrive in infancy

Progressive kidney function decline that commonly progresses to ESRD

Monogenic kidney stone disease

Phenotype	Disorders	Genes
Hypercalciuria	Familial hypercalciuria Autosomal dominant hypocalcaemia Bartter syndrome Dent disease Hypophosphatemic rickets Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis Infantile hypercalcaemia	*ADCY10, VDR* *CASR, GNA11* *NKCC2, ROMK, CLCNKB, BSND, CASR, CLCN5* *CLCN5, OCRL* *SLC34A1, SLC34A3, SLC9A3R1* *CLDN16, CLDN19* *CYP24A1, SLC34A1*
Cystinuria	Cystinuria	*SLC3A1, SLC7A9*
Hyperuricosuria	Hereditary hyperuricosuria	*HRPT1, PRPS1, SLC22A12, SLC2A9*
Xanthinuria	Hereditary xanthinuria	*XDH, MOCOS, MOCS1, MOCS2, GPHN*
Failed urinary acidification	Distal renal tubular acidosis	*SLC4A1, [illegible]6VB1, ATP6VA4, CA2*
Hyperoxaluria	Primary hyperoxaluria	*AGXT, GRHPR, HOGA1, SLC26A1*
Dihydroxyadenine crystals	Dihydroxyadenine crystals	*APRT*

Nephrolithiasis in children: a practical approach



Prevention of KS recurrence

Fluids intake 2 – 2.5 L/1.73m^2/24hrs

Nutrition

Ca intake: as recommended for normal children

Animal protein and salt restriction

High intake of potassium

K Citrate 2-4 mEq/kg/24hrs 25 mEq (2.7 g) /package

Target Urine pH ~ 6.5

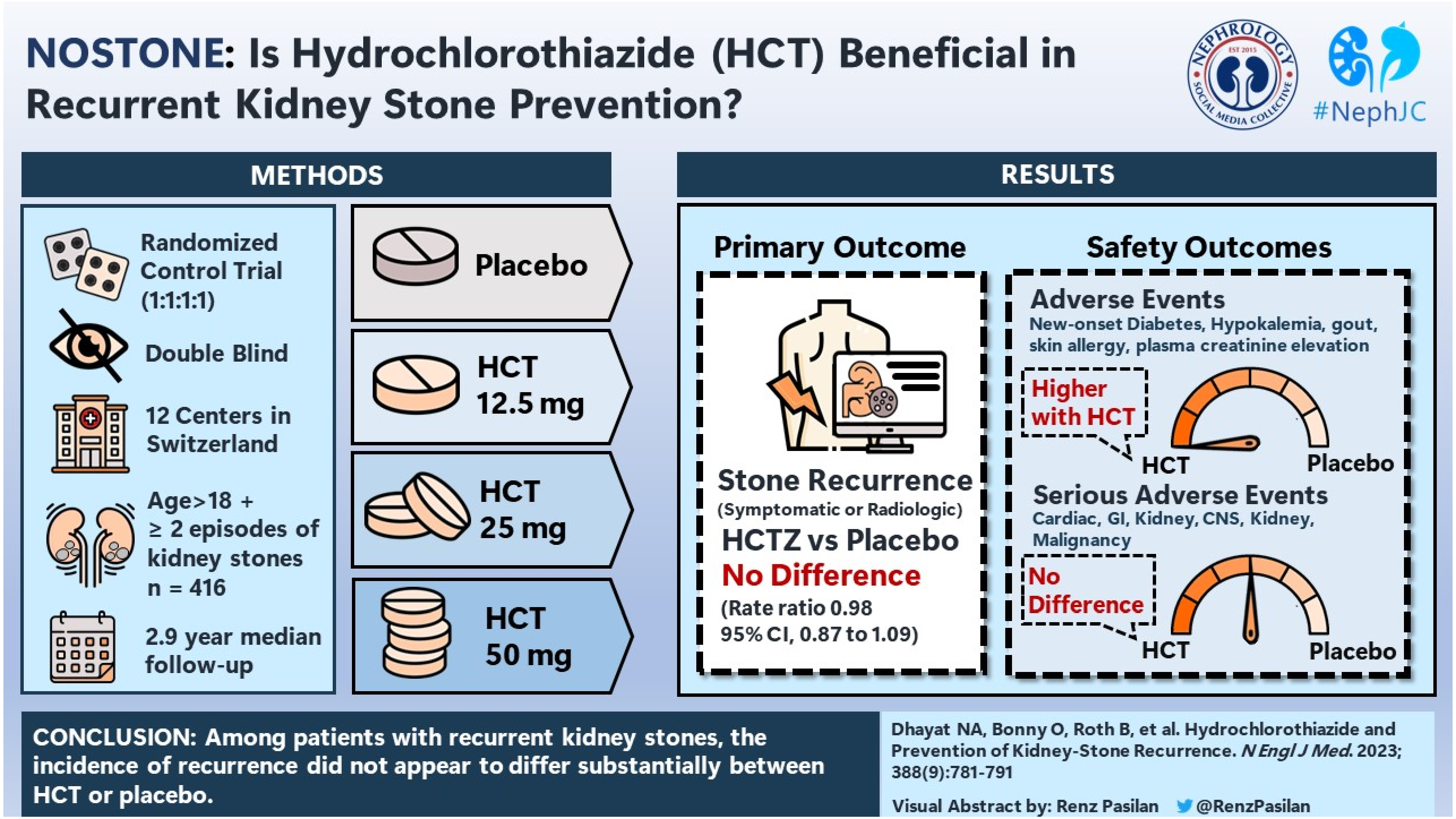
Urine pH > 7 to 7.5 promotes Ca phosphate stones

Normal values of urine phosphate

Boys		<40 mmol (1.24 g)/1.73m^2/24hrs
Girls	2-6 years	<45 mmol (1.40 g)/1.73m^2/24hrs
	6-10	<40 mmol (1.24 g)/1.73m^2/24hrs
	10-14	<35 mmol (1.08 g)/1.73m^2/24hrs
	> 14	<30 mmol (0.93 g)/1.73m^2/24hrs

Wasilewska A. et al. Acta Pediatr 2017

Do Thiazides Reduce the Risk of KS Recurrence?



Dhayat NA, et al. N Engl J Med 2023

Do Thiazides Reduce the Risk of KS Recurrence?

There was a lower urinary calcium excretion among patients in the hydrochlorothiazide groups than among those in the placebo group

The patients in the hydrochlorothiazide groups also had increased urinary oxalate excretion

Thiazide therapy is related with frequent side effects, including
hypokalemia, hyponatremia, hypercalcemia, hyperuricemia, dysglycemia, and dyslipidemia

Dhayat NA, et al. N Engl J Med 2023

Take home messages

A stepwise approach is recommended for the management of pediatric kidney stones

Early diagnosis of monogenic diseases is a priority

Management should be individualized

MECHANISMS OF OBESITY-RELATED RENAL DISEASE

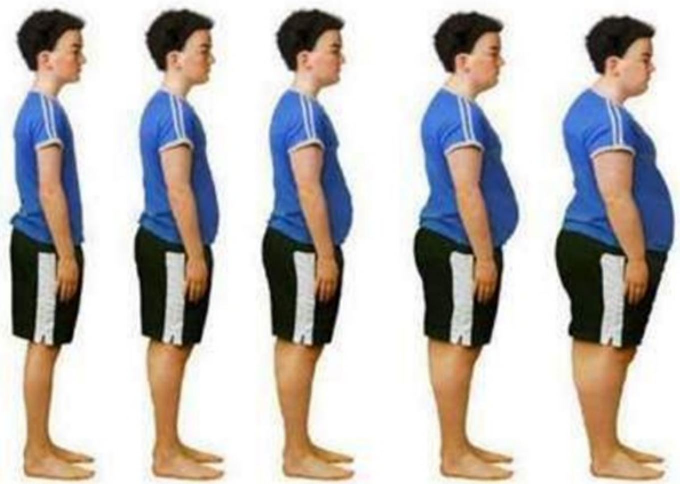
Danka Pokrajac

University Clinical Centre, Department of Pediatric Nephrology, Sarajevo, Bosnia and Herzegovina

10th SEPNWG MEETING AND TEACHING COURSE, 1st-3rd June 2023, Ohrid, Republic of North Macedonia

INTRODUCTION

Obesity (obesitas, adipositas) is a chronic metabolic disease which in recent years recognizes as one of the leaders health problems throughout world.

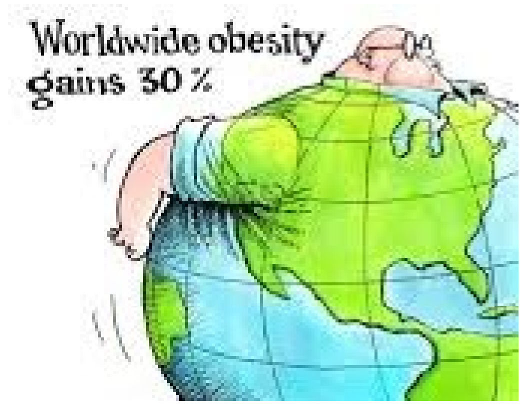


INTRODUCTION

In the last decades, WHO has declared overweight and obesity as **"A global pandemic of the new millennium "**.

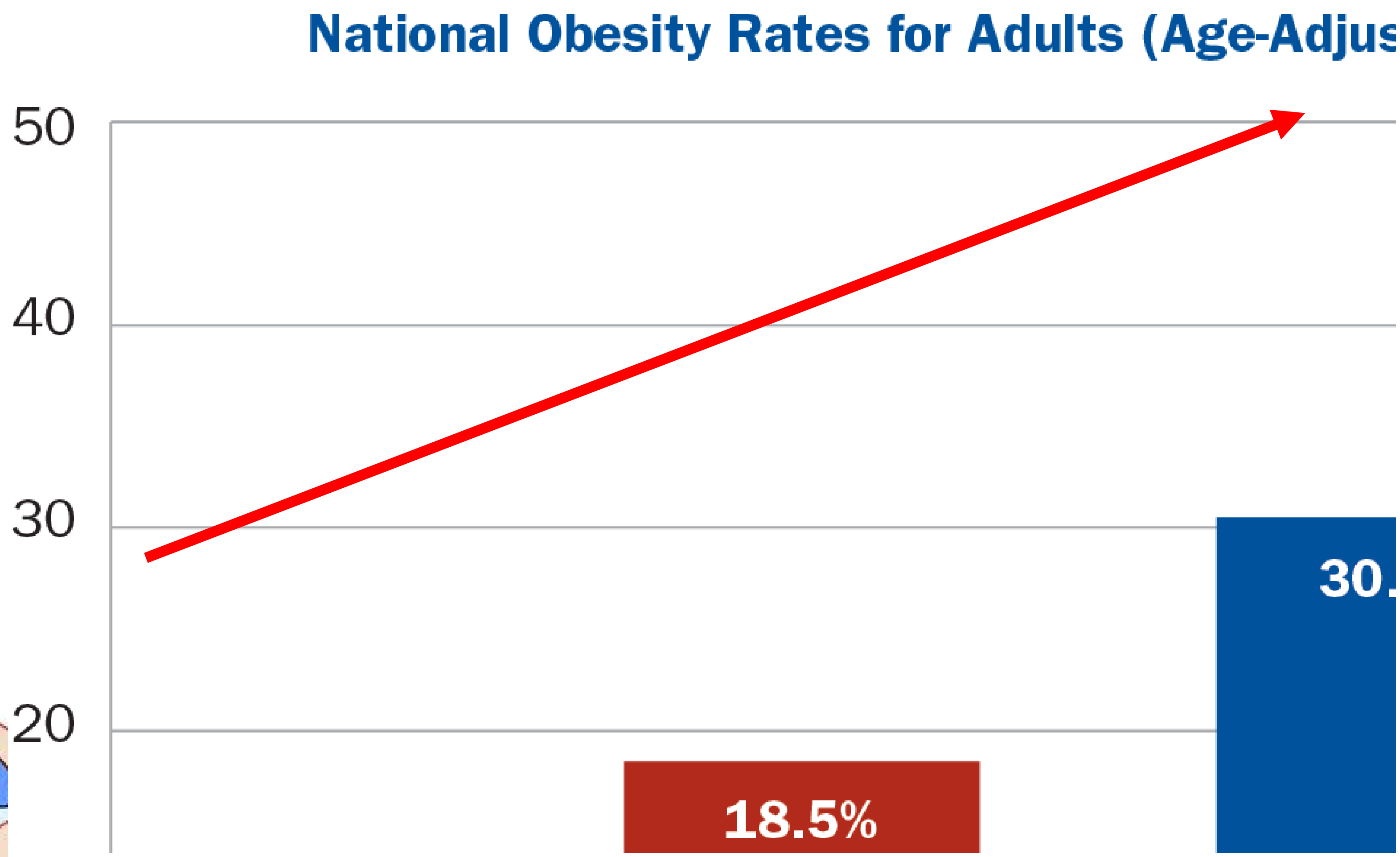
PREVALENCE AND INCIDENCE OF OBESITY

- Around **30 percent of all people** on Earth are overweight or obese.

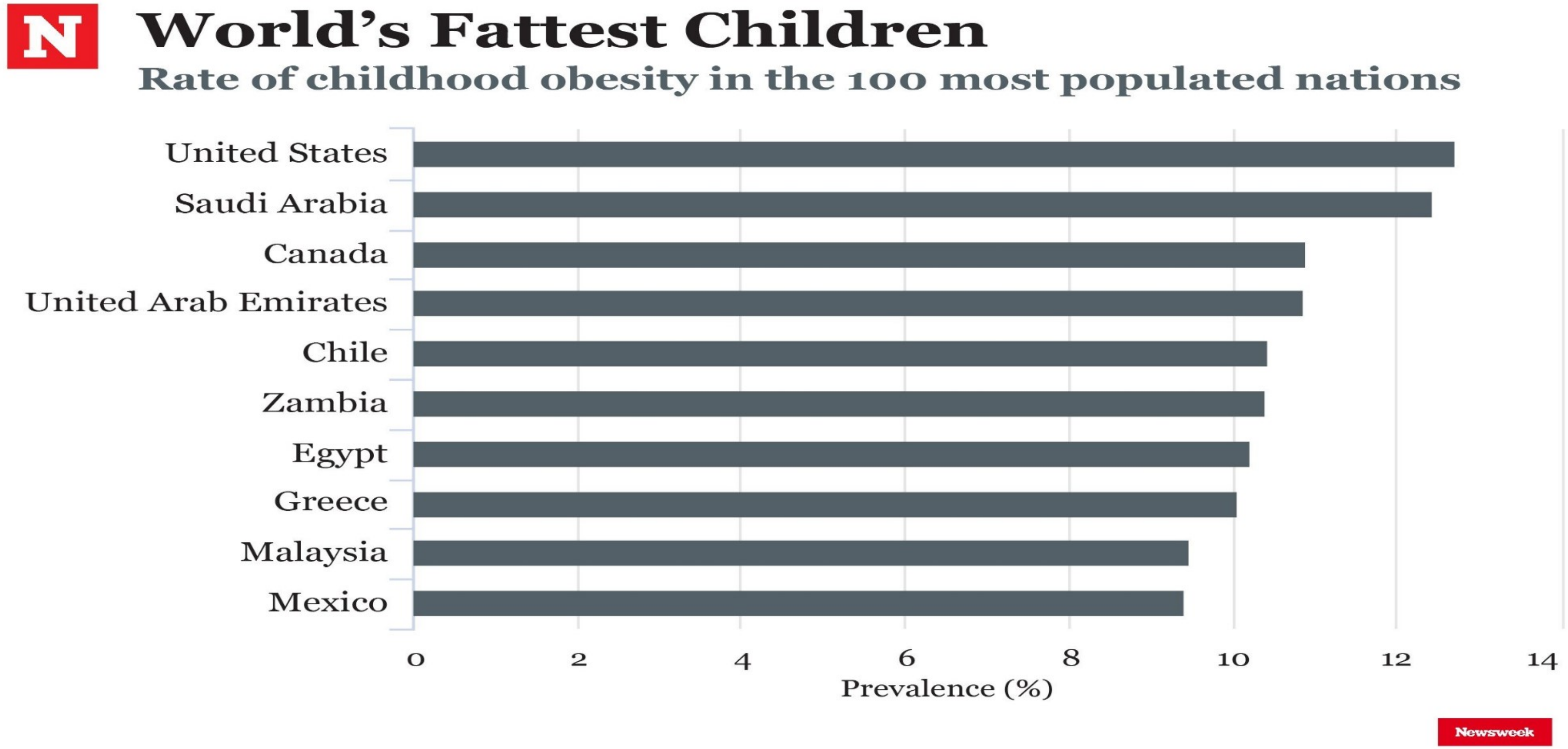


- **Since 1980 to today**, the prevalence of **obesity has doubled in more than 70 countries** and has continuously increased in most other countries.

PREVALENCE AND INCIDENCE OF OBESITY



PREVALENCE AND INCIDENCE OF OBESITY



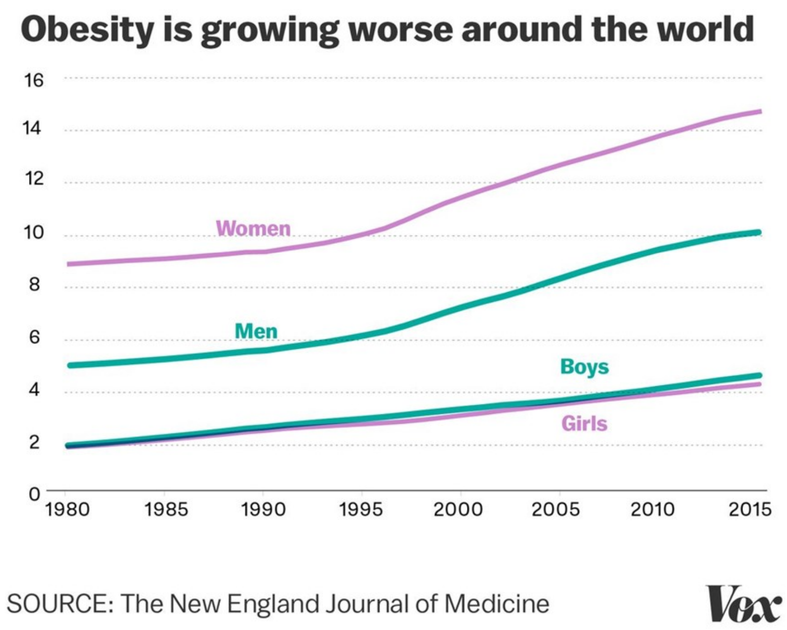
Graphic showing the countries with **the highest levels of obesity** within the 100 most populated nations. **NEWSWEEK (DECEMBER, 2017**)

PREVALENCE AND INCIDENCE OF OBESITY

The 2015 updated analysis of the Global Burden Disease Study reported:

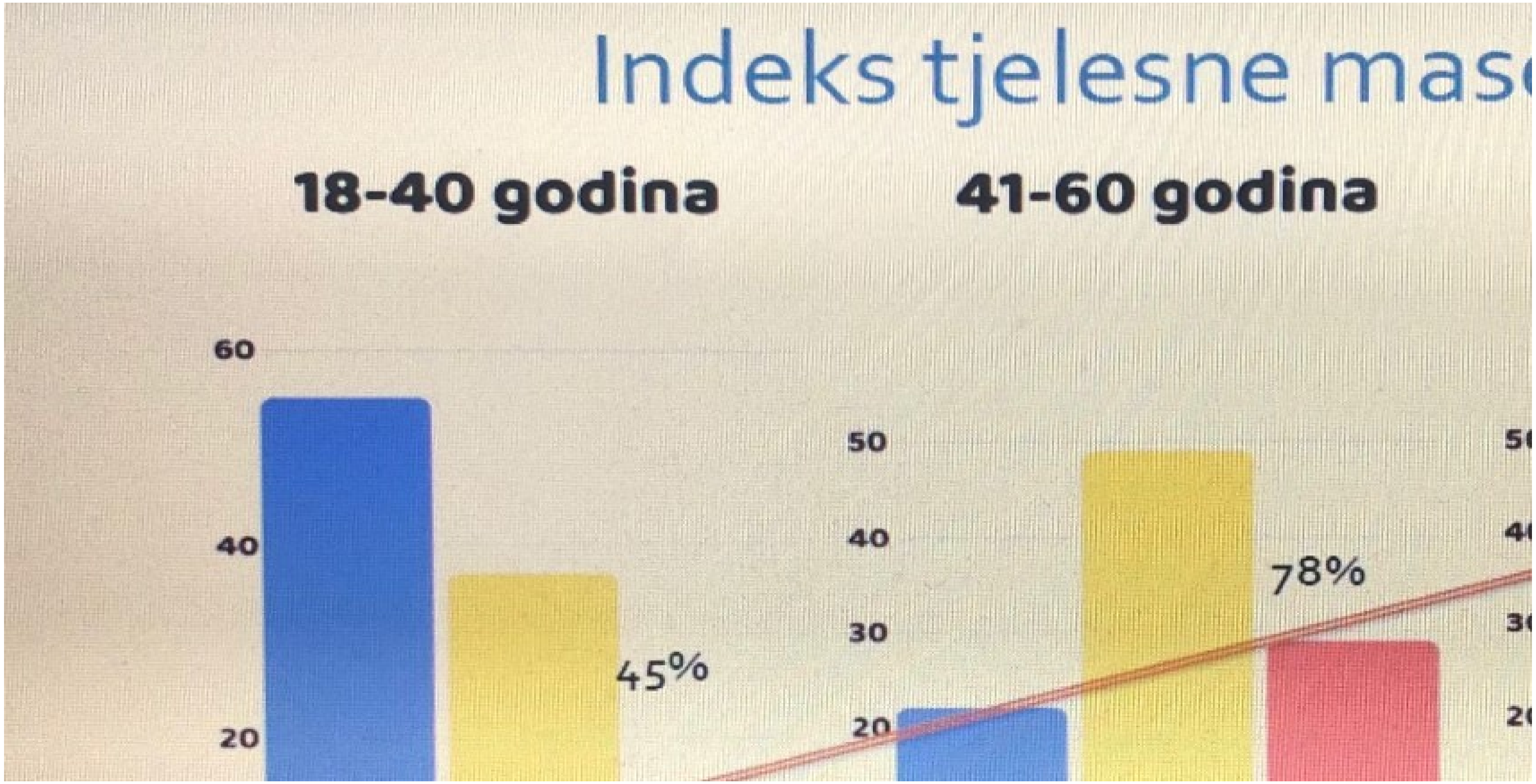
- **107.7 million obese children and**

- **603.7 million obese adults.**



GBD 2015 Obesity Collaborators, Afshin A et al. ***N Engl J Med*** **2017;377: 13–27**

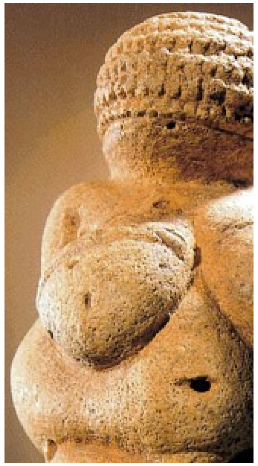
PREVALENCE AND INCIDENCE OF OBESITY



Federal Office of Statistics, Federation of Bosnia and Herzegovina, December 2017

THE IMPORTANCE OF THE OBESITY PROBLEM

The problem of obesity is not only personal problem of the individual.

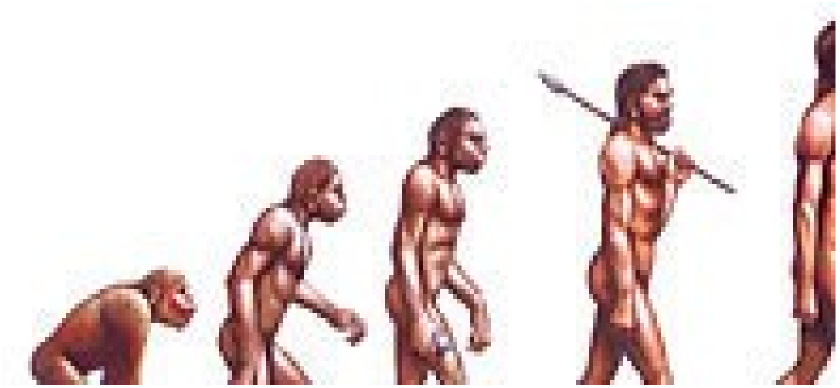


Venus of Willendorf

Venus of Milos

Obesity is a significant

- **health**
- **social**
- **national and**
- **economic problem**



WHAT IS OVERWEIGHT AND OBESITY?

Overweight is defined as the gender and age crossing of the 95th percentile on the growth map.

Overweight can come from:

- -muscles
- -bones
- -adipose tissue
- -body water

Obesity persons have larger proportion of body fat.

ADIPOSE TISSUE

The adipose tissue **is the largest ENDOCRINE ORGAN**.

It is made of:

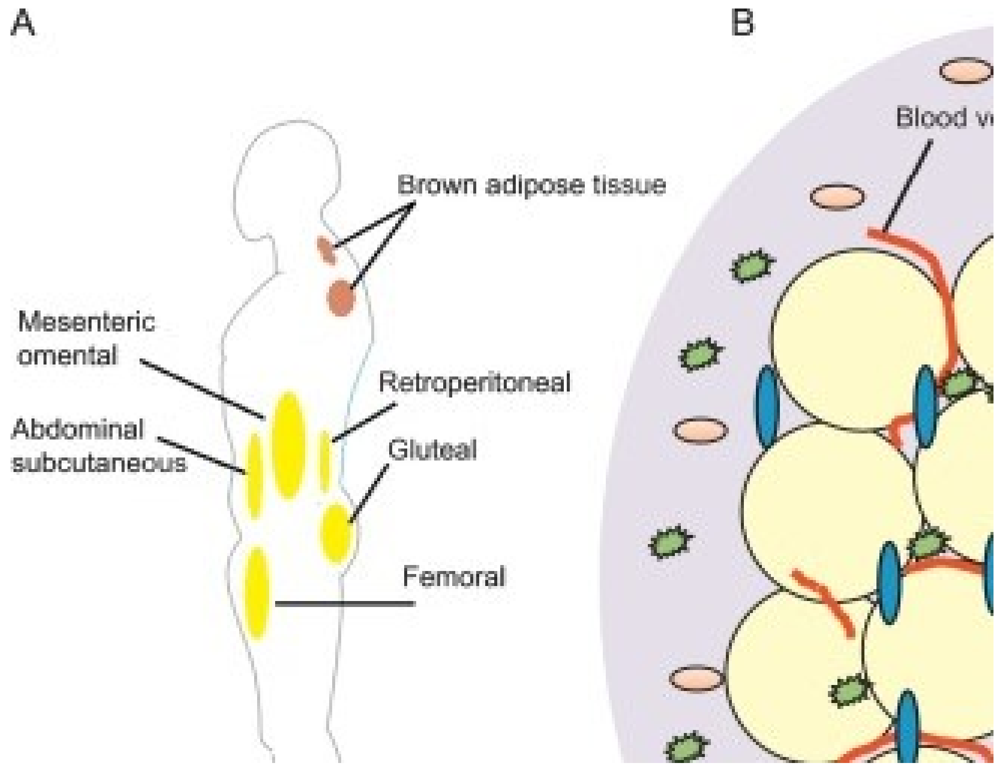
-adipocytes

-preadipocytes

-vascular cells

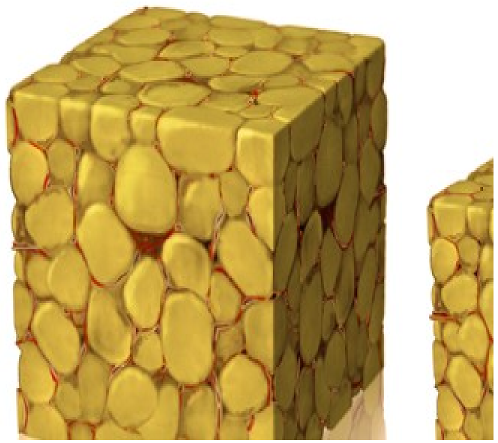
-fibroblasts

-macrophages



ADIPOSE TISSUE

Normal adult person has **30 billion of fat cell**.

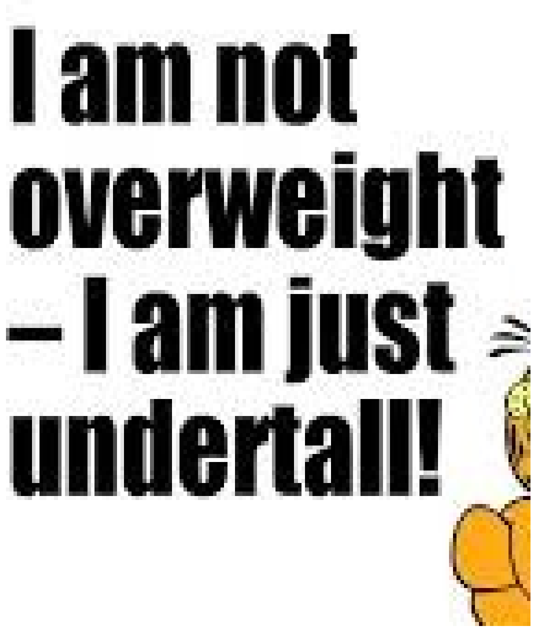


Obese people have **100-200 billion of fat cells**.

HOW DETERMINES THE HEALTH RISKS ASSOCIATED WITH BODY WEIGHT?

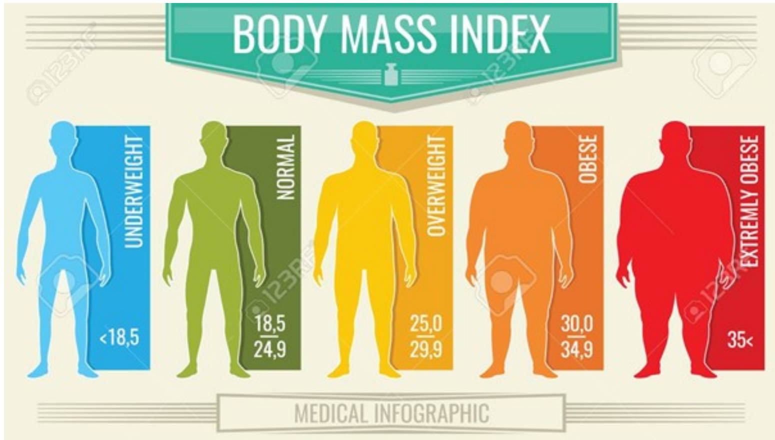
The healthcare profession recommends application **body mass index (BMI)** as simple the criterion of obesity.

BMI = BW(kg)/BH(m²)



HOW DETERMINES THE HEALTH RISKS ASSOCIATED WITH BODY WEIGHT?

BMI>25 = overweight
BMI 25-29.9 = "pre-obese"
BMI>30 = obesity



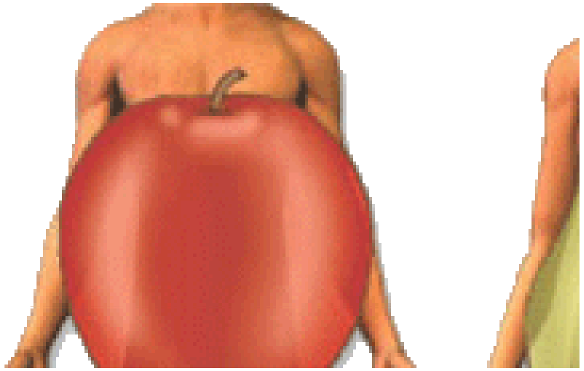
Subcategories of obesity:

The first degree of obesity: 30.0-34.9 = moderate
The second degree of obesity: 35.0-39.9 = severe
The third degree of obesity: 40+ = very severe

World Health Organization. Obesity: Preventing and Managing the Global Epidemic. *Technical Report Series no. 894. WHO, Geneva, 2000*

WHEN IS A PERSON OBESE?

It is important to distinguish the so-called female and male obesity.



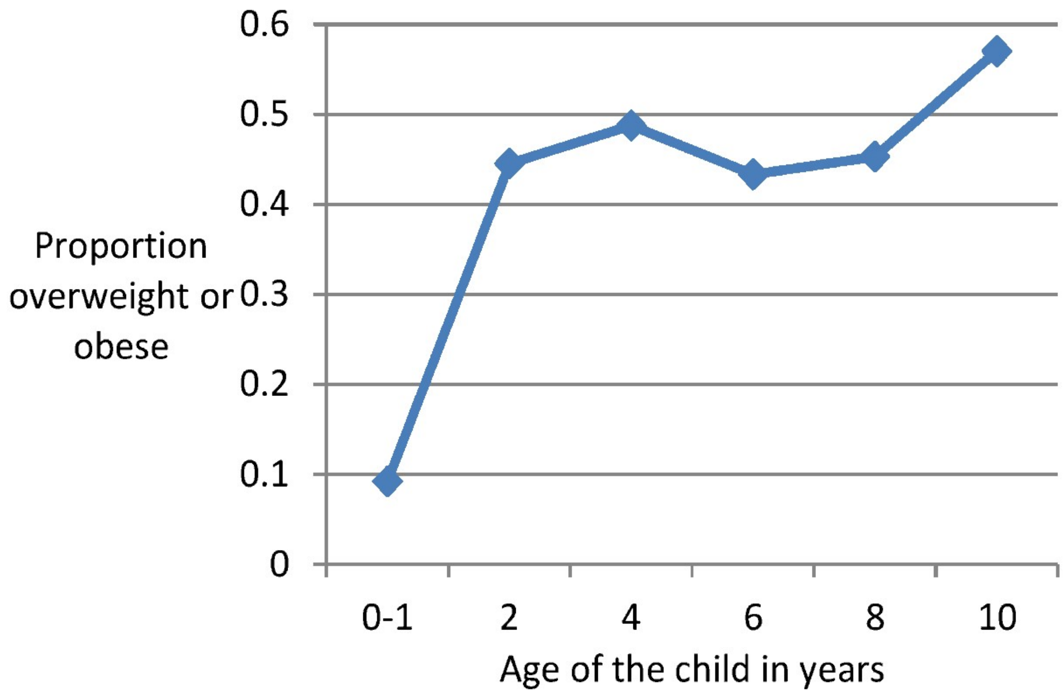
Female type fat on the hips.

Male type fatty tissue around the waist - diseases heart, blood vessels, type 2 diabetes, increased levels of fat and blood glucose, microalbuminuria.

In adults, waist circumference of ♂ **> 102 cm**, and for ♀ **> 88 cm** prognostically worse sign.

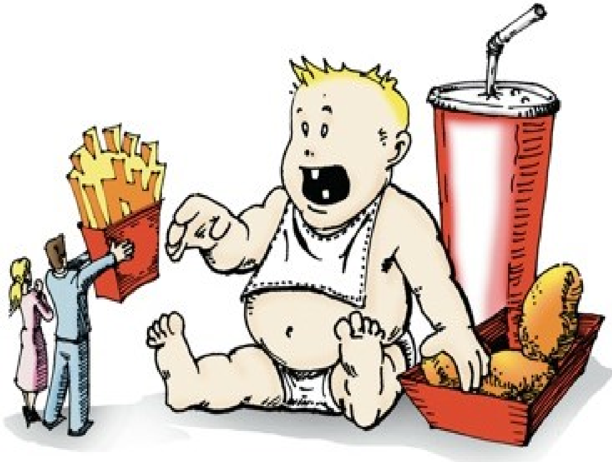
RISK LIFE PERIOD FOR OBESITY

- **Prenatal age**
- **Preschool (4 to 6 years)**
- **Adolescence**



CAUSES OF OBESITY

- Inadequate nutrition (95%),
- Eating too many calories,
- Physical inactivity,
- Obstructions in the growth and development of the fetus,
- Endocrine, genetic, and emotional and diencephalic damage (5% obesity).



CONSEQUENCES OF OBESITY

Obesity is a major generator **of metabolic syndrome (dysmetabolic syndrome, insulin resistant syndrome and syndrome X)**, that is, **obesity is a phenotypic characteristic of metabolic syndrome**:

- increased waist circumference
- high fasting glucose
- insulin resistance
- dyslipidemia
- high blood pressure
- chronic inflammation
- prothrombotic condition
- MS is associated with high cardiovascular risk

Kul S et al. *Nutr Metab Cardiovasc Dis* 2014;24:176-82

Abd Elaziz KM et al. *J Public Health (Oxf)* 2015;37:612-7

CONSEQUENCES OF OBESITY

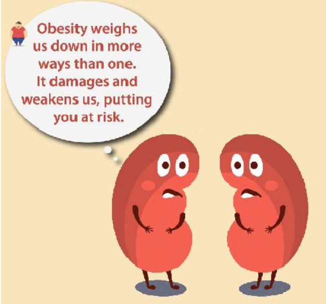
Obesity is a RISK FACTOR for

1. Type 2 diabetes
2. Cardiovascular diseases
3. High cholesterol
4. Certain types of cancer (breast, colorectal endometrial and renal)
5. Musculoskeletal disorders (osteoarthritis)
6. Lung diseases (asthma)
7. Hepatic steatosis
8. Sleep apnea

CONSEQUENCES OF OBESITY

OBESITY IS ALSO ASSOCIATED WITH:

-Complications in pregnancy
-Menstrual problems
-Hirsutism
-Stress incontinence
-Increased risks during operations
-Increased mortality
-Psychological disorders (depression) - obese children are the subject of early and systematic discrimination.



CONSEQUENCES OF OBESITY

WHAT ABOUT RENAL DISEASES?

The aim of this lecture is to raise awareness of the importance of **chronic kidney disease (CKD) in obese persons**.

In each decade of the last two, the number of people with terminal kidney disease has doubled.

35 years ago **Weisinger et al. described FSGS** with nephrotic syndrome in 4 extremely obese patient.

Weisinger JR et al. *Ann Intern Med*. 1974; 81: 440–447

OBESITY AND KIDNEY DISEASE

Barry Brenner found that maternal malnutrition, followed by postnatal **catch up growth**, causes a smaller number of nephrons, which is the same in patients with **essential hypertension**. These are associated with a **higher risk of insulin resistance** and **obesity.**

Dr. Barker was examination in Helsinki a woman in aged of 40 who had a myocardial infarction and found that BW in newborn period was low, but after that was been very rapid growth. **So cardiovascular as well as renal risk starts in part in utero**.

Barry M. Brenner et al. ***American Journal of Hypertension 1988; 1(4):*** **335–347**
Barker DJ, Osmond C. ***BMJ*****. 1988; 297(6641): 134–135**

OBESITY AND KIDNEY DISEASE

The current studies show a dramatic increase in histologically proven renal diseases in obese persons in the absence of diabetes.

- **40% higher risk of kidney damage** than normal-weight person.

- **60% of transplant patients are obese**.

- This is confirmed by the systematic review and meta-analysis from ***2017 by Garofalo and colleagues*** in the general adult population (600,000 participants).

Garofalo C et al. Kidney Int 2017;91:1224–1235

OBESITY AND KIDNEY DISEASE

- **Scientific pediatric nephrology community confirm a similar trend among obesity children as in adults with CKD**:

- increased **CKD** and end stage renal disease (**ESRD**).
- and increased **risk of death** among children.

OBESITY AND KIDNEY DISEASE

- In 2013, a study about the European pediatric population **under renal replacement therapy** found more than **30% of the children were overweight or obese**.

Bonthuis M et al. *Nephrol Dial Transpl* 2013; 28(suppl 4):195–204.

OBESITY AND KIDNEY DISEASE

- **CKD** is currently **a worldwide public health problem** (affects individuals early in their productive years and brings negative consequences for quality of life).

- **arterial hypertension (SAH)** and **diabetes mellitus (DM)** the main causes of CKD (70% of cases of CKD). **The role of metabolic syndrome (MS) as a cause of CKD has been little discussed**.

OBESITY AND KIDNEY DISEASE

- Persons with MS have a 2-to-3 fold higher risk of developing **microalbuminuria** than those without MS.
- Microalbuminuria is **the first clinical sign of kidney damage** in obese children and **sign of generalized endothelial dysfunction**.

Song YM et al. *Clin Exp Nephrol* 2015;19:887-94

OBESITY AND KIDNEY DISEASE

- **Central obesity seems to be more important than body mass index (BMI) as a risk factor for cardiovascular diseases and CKD.**

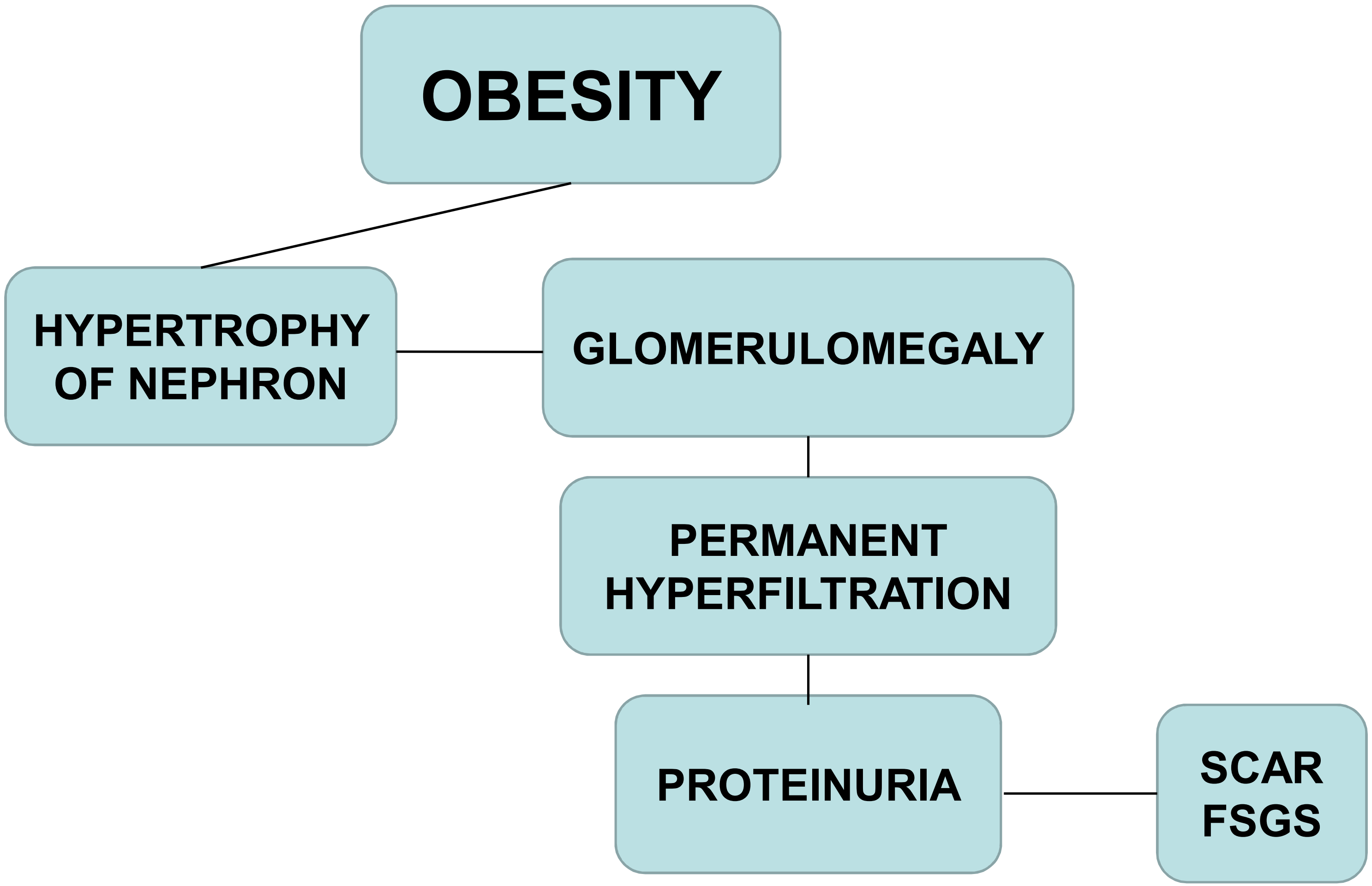
- Several renal disorders are associated with overweight, obesity and metabolic syndrome, as summarized in *Table 1*.

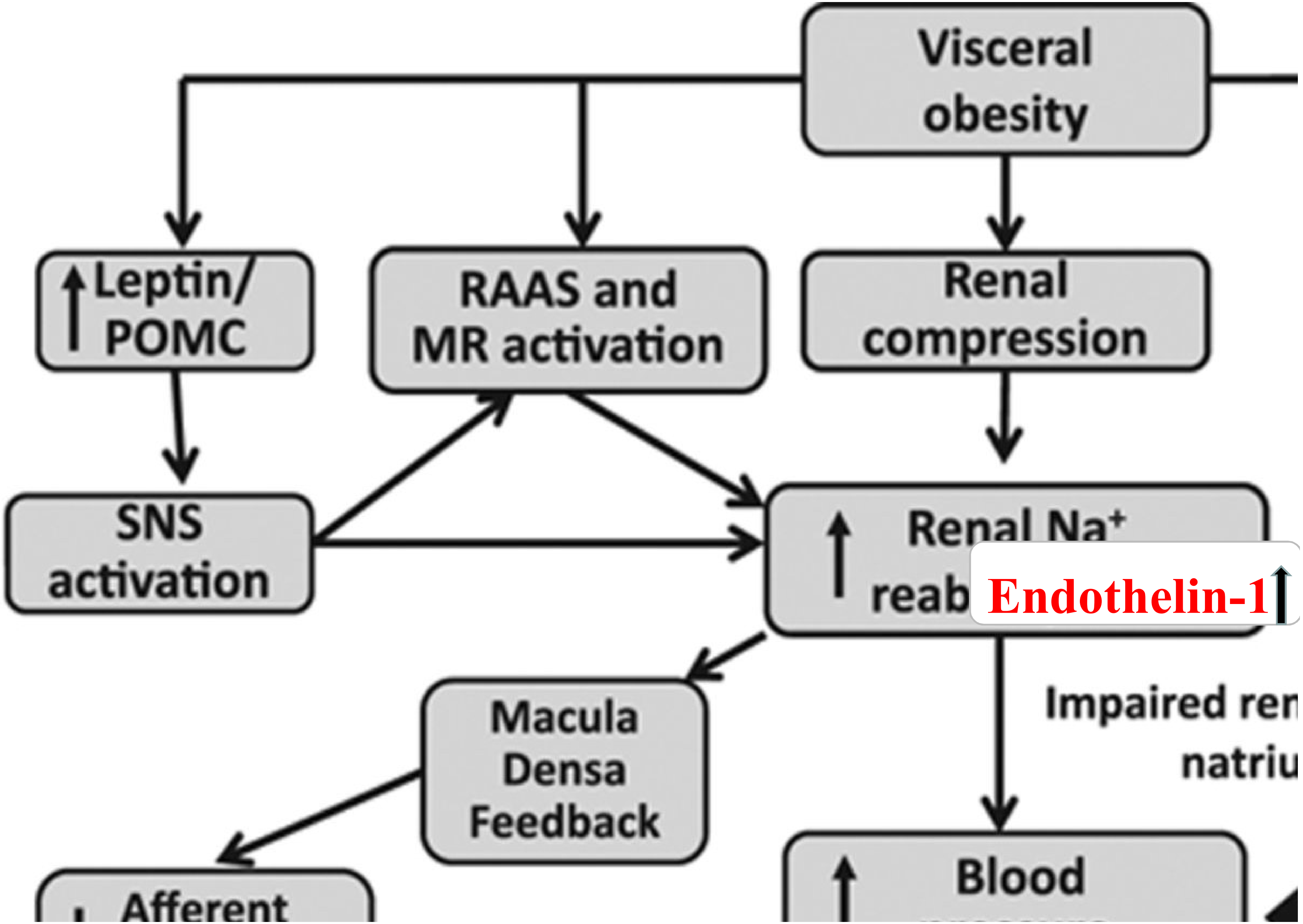
OBESITY AND KIDNEY DISEASE

***Table 1*. Renal abnormalities associated with overweight, obesity and metabolic syndrome** (**Adapted from Kopple & Feroze. *J Ren Nutr* 2011;21:66-71**)

Hemodynamic/Physiologic changes	Increase effective plasmatic flow, GFR, filtration fraction and albuminuria.
Anatomic changes	Increase kidneys' weight, glomeruls, glomerular basement membrane and mesangial matrix. Mesangial cell proliferation. Decrease in the number of podocytes.
Pathology	Increase in the number of glomeruli with segmental and global **sclerosis**, Obesity-associated glomerulopathy/FSGS
Chronic kidney disease/ Glomerulopathies	Diabetic nephropathy, Hypertensive nephrosclerosis, FSGS, IgA nephropathy
Other renal/urologic complications	Higher incidence of renal carcinoma, nephrolithiasis (uric acid and calcium oxalate), surgical complications and graft loss in the context of kidney transplantation.
End-stage renal disease	Higher incidence of ESRD

OBESITY AND KIDNEY DISEASE





Visceral obesity
Leptin/ POMC
RAAS and MR activation
Renal compression
SNS activation
Renal Na+ reab
Endothelin-1
Macula Densa Feedback
Impaired ren
natriu
Afferent
Blood

OBESITY AND KIDNEY DISEASE

Adipose tissue is not only a fat reservoir, but is also an immune organ

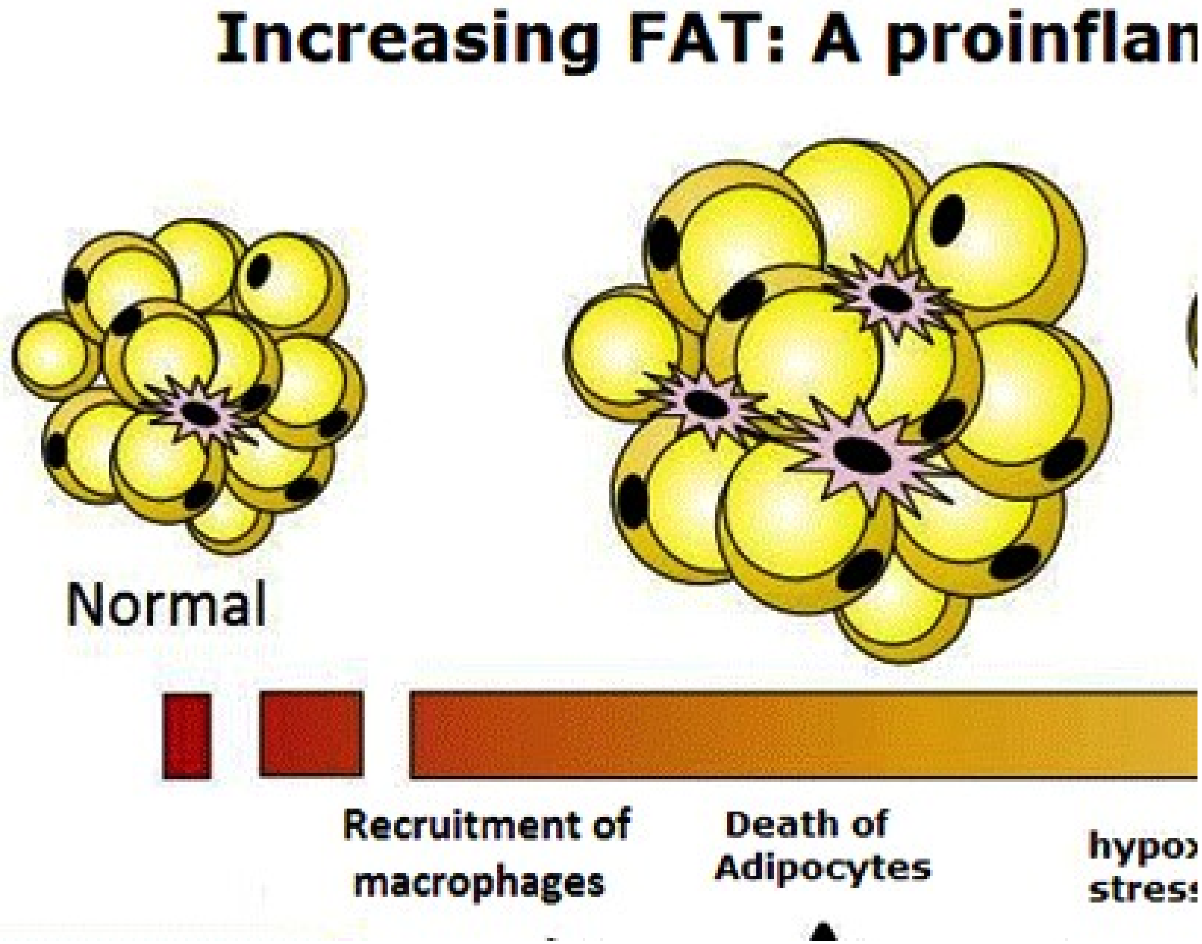
- **secretes immunomodulators**: cytokines, leptin, adiponectin, resistin, tumor necrosis factor-α, monocyte chemoattractant protein-1, transforming growth factor-β and interleukins.

-causes chronic kidney inflammation

Inflammation itself is a risk factor for renal function loss.

Declèves AE, Sharma K. *Curr Opin Nephrol Hypertens* 2015;24:28-36

OBESITY AND KIDNEY DISEASE



OBESITY AND KIDNEY DISEASE

Hormones, cytokines and growth factors which produces adipose tissue

Leptin	a hormone with many effects
Adiponectin	development of insulin resistance and DM type2
11 ß hydroxysteroid dehydrogenase	an enzyme that converts cortisone to cortisol, which affects the distribution of body fat (increases central fat)
Interleukin-6	elevated IL-6 is a sign of cardiovascular damage
Plasminogen activator inhibitor -1 (PAI -1)	onset of thrombosis and coronary disease
Angiotensinogen	hypertrophy and hyperplasia of smooth muscle cells leading to fibrosis
TNF-α	induction of proinflammatory cytokines
TGF-ß	inflammatory cytokine
Resistin	leads to fibrosis

OBESITY AND KIDNEY DISEASE

LIPOTOXIC KIDNEY DAMAGE

In obesity, **fatty acids damage cells** and lead to **apoptosis** of cells.

Part of the **fatty acids bind to albumin in the proximal tubule** and causes **tubulointerstitial inflammation** and **fibrosis**.

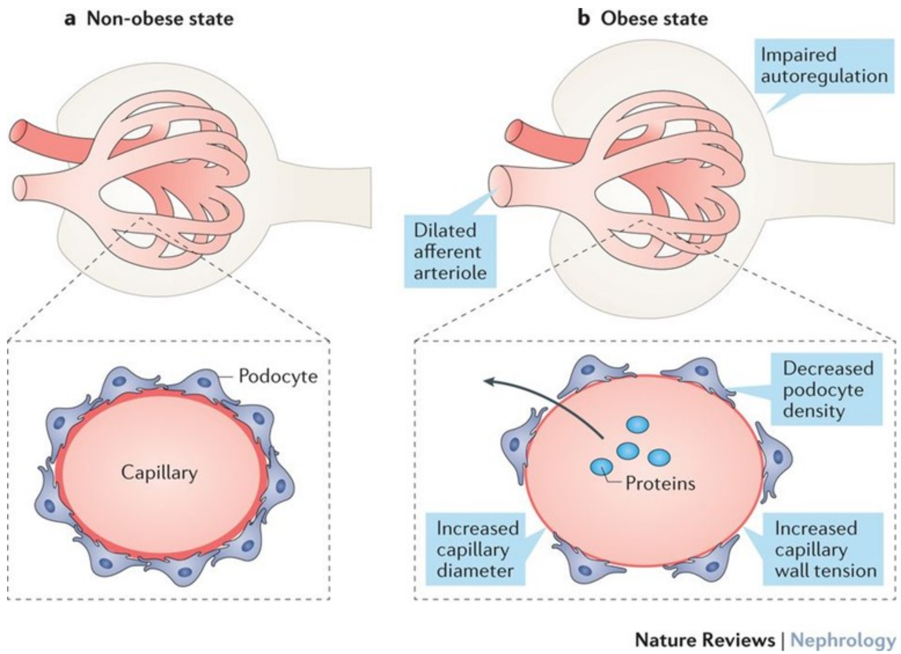
OBESITY AND KIDNEY DISEASE

- There is also evidence that obesity itself **increases albumin excretion**, and, in rare cases, can lead to **nephrotic syndrome** and renal progression in patients with **IgA nephropathy** and **FSGS**.

Praga M et al. *Kidney Int* 2000;58:2111-8

OBESITY AND KIDNEY DISEASE

Obesity-related glomerulopathy is a secondary form of **focal segmental glomerulosclerosis (FSGS)**, which was **first described in 1975 by Cohen**.



Cohen AH. *Am J Pathol* 1975;81:117–130

OBESITY AND KIDNEY DISEASE

PH findings are characterized by glomerulomegaly and FSGS

	Glomerulopathy in obesity	Idiopathic FSGS
Enlargement of almost all glomeruli	+++	+
Proteinuria	+	+++
Changes on podocytes	+	++
Serum albumin	almost N	decreased
Edema	+	+++
Cholesterol	almost N	increased

OBESITY AND KIDNEY DISEASE

- The association between **obesity**, **MS** and **nephrolithiasis** has been observed in some studies, mainly due to **increased serum uric acid levels** in obese people.

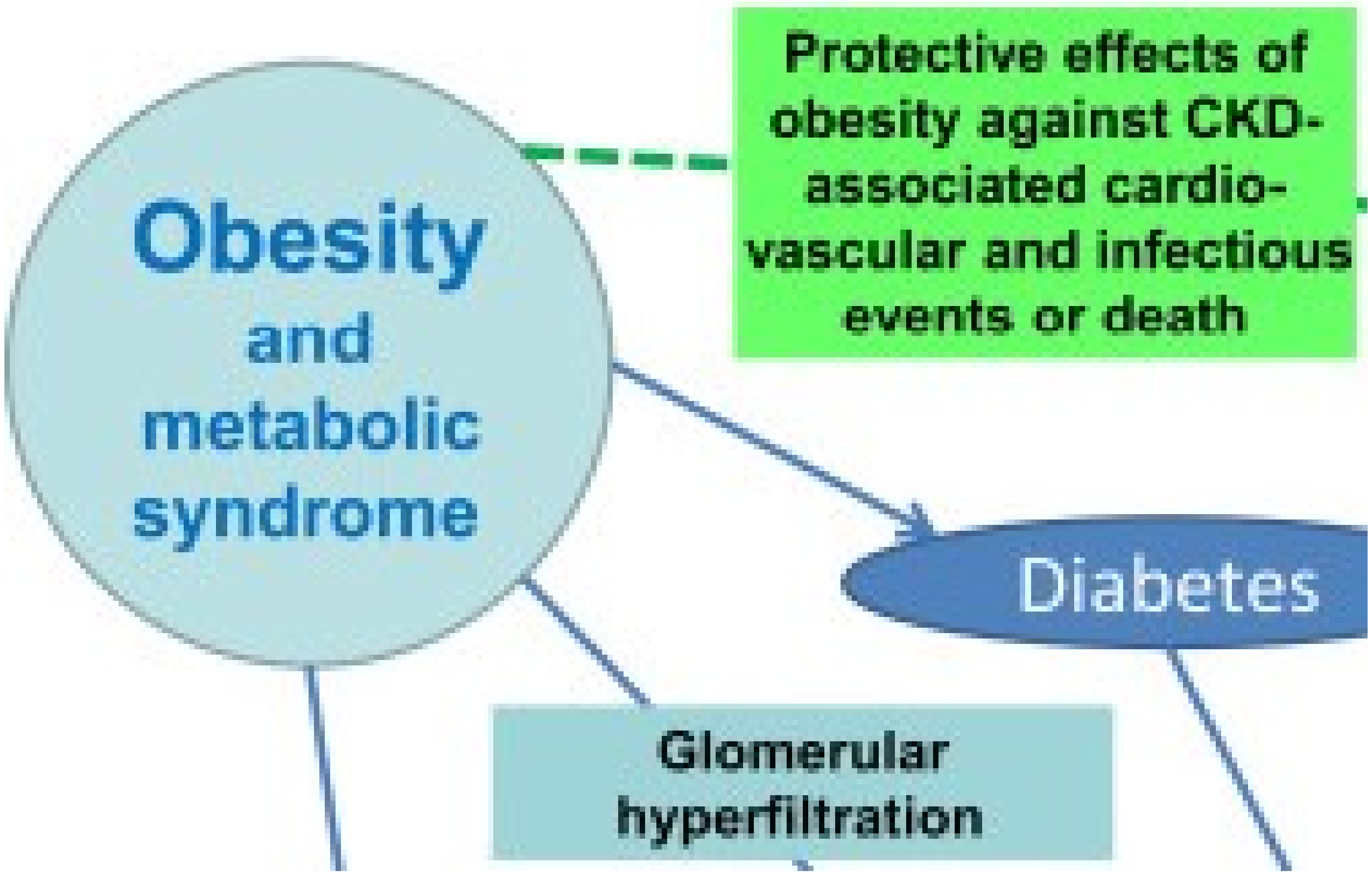
Johansen KL, Lee C. *Curr Opin Nephrol Hypertens* 2015; 24:268-75
Wong YV et al. *Int J Endocrinol* 2015; 2015: 570674

OBESITY AND KIDNEY DISEASE

Although visceral obesity is a major risk factor for the **development of cardiovascular disease**, some studies have shown that obesity is a **protective factor in individuals with end-stage CKD** (undergoing dialysis), **perhaps because malnutrition is associated with higher mortality when compared to obesity**.

Park J et al. *Prog Cardiovasc Dis* 2014;56:415-25

OBESITY AND KIDNEY DISEASE

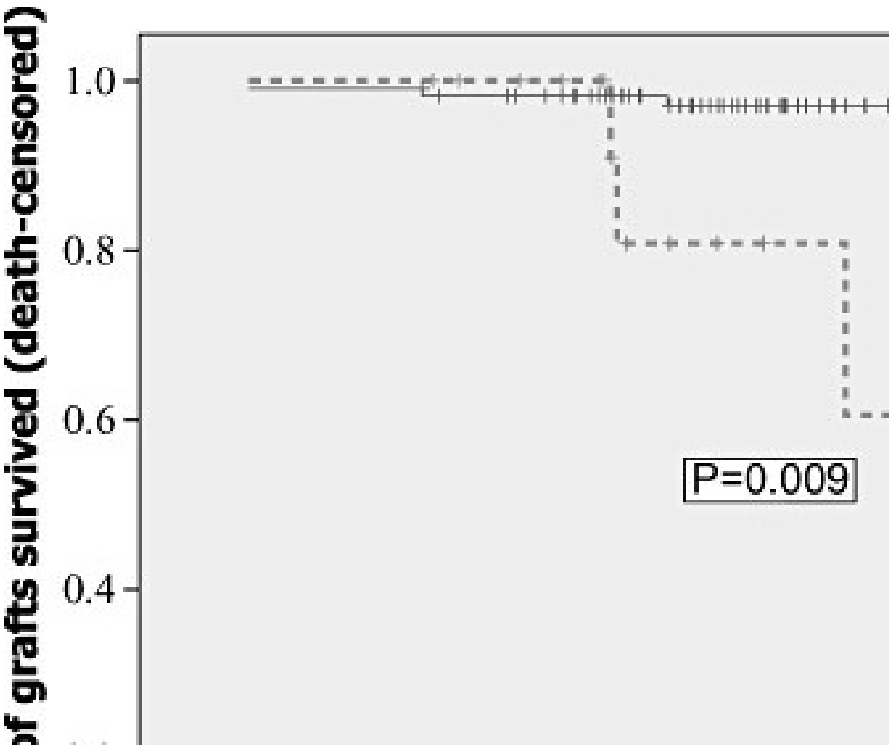


Chronic Kidney Disease. Prognosis Consortium, Matsushita K et al. *Lancet* 2010;375:2073-81
Gansevoort RT et al. *Lancet* 2013;382:339-52

OBESITY AND KIDNEY DISEASE

- Pretransplantation obesity and increased BMI after renal transplant have also **been associated with decreased renal allograft survival in pediatric patients**

Ku E et al. *J Am Soc Nephrol* 2016;27:551–558



OBESITY AND KIDNEY DISEASE

Children who are born small for gestational age or preterm (FETAL MALNUTRITION) have:

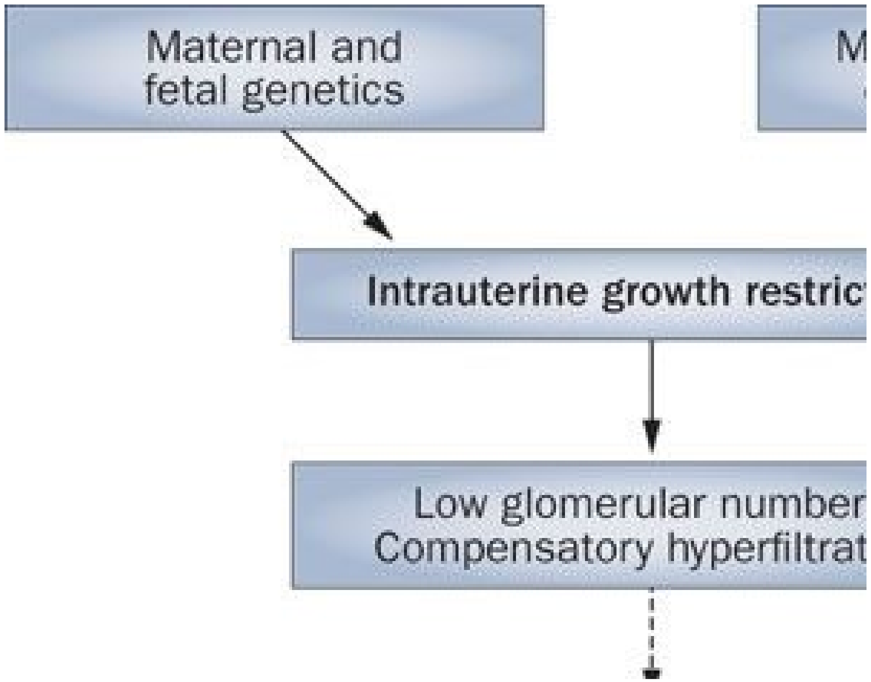
-reduced nephron mass

-permanent reduction of ß secretory cells of pancreas

-permanent reduction of muscle fibrils.

OBESITY AND KIDNEY DISEASE

Excessive weight gain will **increase the metabolic and hemodynamic load on each individual nephron**, whose number was fixed at birth.



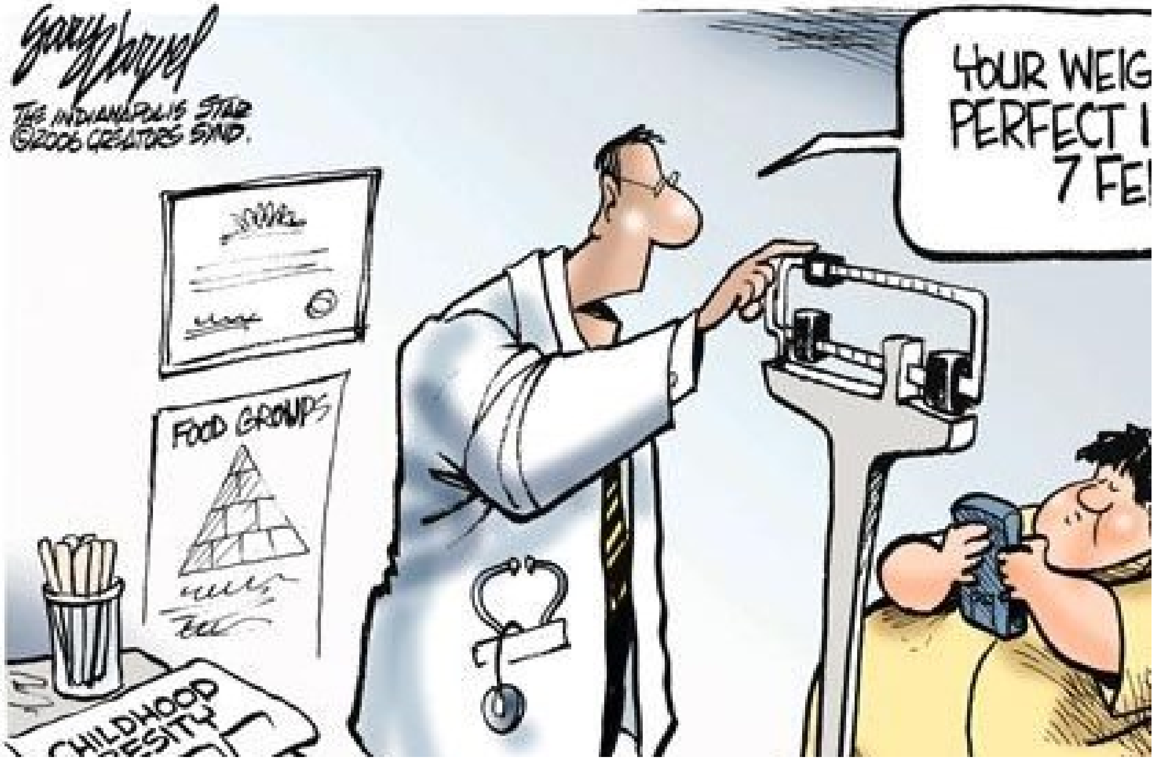
TREATMENT OF OBESITY

Treatment for obesity in children requires the motivation of the children and the physician, which is common frustrating for both.

It's basically a lifestyle change.

OBESITY AND KIDNEY DISEASE

- **Weight loss**, either by dieting or through bariatric surgery, leads to proteinuria reduction.



TREATMENT OF OBESITY

PHARMACOLOGICAL INTERVENTION

may slow down and prevent kidney damage.

ACE inhibitors and angiotensin blockers receptors (ARBs) are antihypertensives and renoprotective drugs.

TREATMENT OF OBESITY

Treatment with antiobesitic substances:

ORLISTAT prevents digestion and absorption fat in foods by **blocking activity of the lipase**.

SIBUTRAMINE causes a feeling of satiety with little food, that is, it **reduces appetite**.

CAUTION! the risk of side effects.

TREATMENT OF OBESITY

ACARBOSE (alpha glucosidase inhibitors)
it acts in the gut to slow it down digestion of carbohydrates,

METFORMIN - antidiabetic drug for type 2 diabetes.

TREATMENT OF OBESITY

THIAZOLIDINEDIONES are used in treatment type 2 of diabetes, reduce glomerulosclerosis, tubulointerstitial fibrosis and albuminuria. **They have anti-proliferative, anti-fibrotic and anti- inflammatory effects**.

Drugs which act to reduce levels of cholesterol in the blood - **statins**

PREVENTION OF OBESITY

Obesity prevention is an essential program.

It's a fight for the future.

It begins even before birth.

PREVENTION OF OBESITY

-**Continuous education** of the population about the importance of maintaining proper weight.

-**Exercise healthy eating habits and healthy lifestyle**.

-**Day physical activity** from half to one hour.

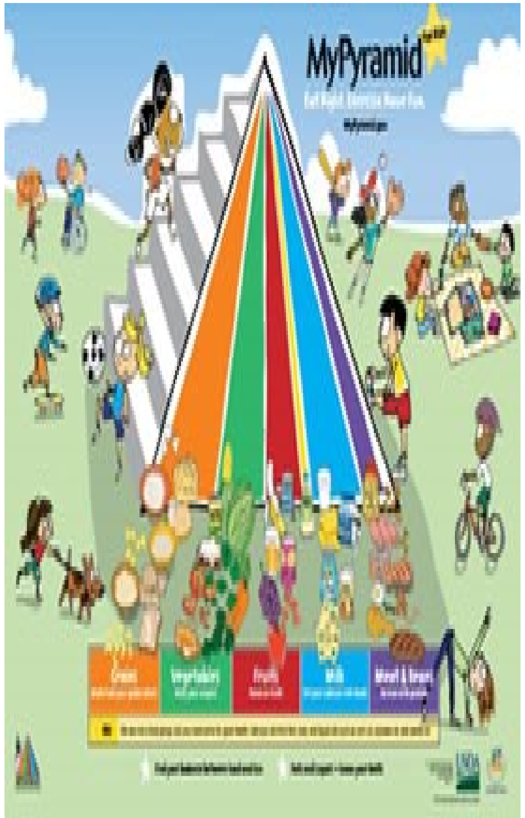
-**Removing TVs and computers from children's rooms.**

- **Regular main meals.**

-**Water as a basic drink**.

-**Consumption of fresh fruits and vegetables, fish, olive oil, integral bread.**

- **Importance of breastfeeding**.



PREVENTION OF OBESITY

-**The foundation is in the family** - where basic nutrition is formed habits and lifestyle

-Introduce "healthy menus" **in kindergartens and schools**

-**The importance of the local and wider community** in the prevention of obesity comes from co-financing healthy food in kindergartens and schools as well providing sufficient bicycle paths, gyms and playgrounds

-**Health professionals** need to identify children at risk for obesity and to be monitored and treated if necessary.

CONCLUSION

- The obesity has been increasing worldwide and is an **important risk factor for kidney disease**.

- The potential mechanisms between obesity and kidney disease need to be **further investigated**, **especially in children**.

CONCLUSION

- It is clear that **genetic** and **epigenetic factors** have influence on the events in our metabolism.

- **Each of us is programmed to maintain our weight**. This data explains why it is so difficult to lose weight in some persons.

CONCLUSION

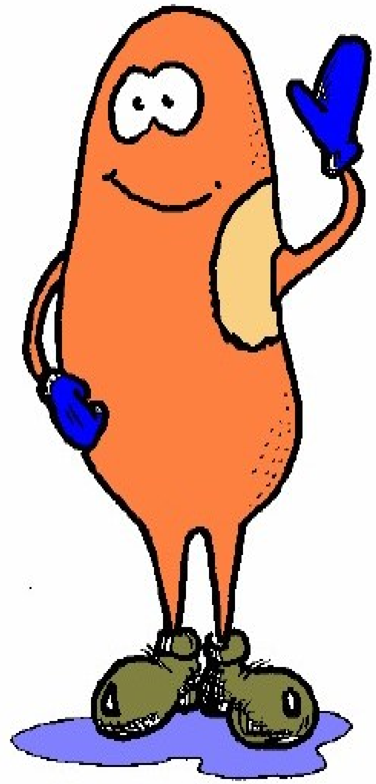
There is growing evidence that the **environment** is leading to an obesity epidemic. **Modern style life** increases the consumption of energy nutrients questionable quality and composition.

According to, modification of this epidemic is crucial for health and development kidney disease today and in the future.

CONCLUSION

- The implementation of prevention programs requires **coordination of the health and education systems at all levels with the support of the wider community and media**.

- **Don't forget in each obese child should look for proteinuria!**



THANK YOU FOR ATTENTION !

GOOD APPETITE!

DISTAL RENAL TUBULAR ACIDOSIS - AN UPDATE

PROFESSOR DANKO MILOSEVIC, MD, PHD

CROATIAN ACADEMY OF MEDICAL SCIENCES

Consultancy and honoraria by Advicenne

RENAL TUBULAR ACIDOSIS (RTA)

- group of tubular function disorders characterized by impaired bicarbonate absorption (HCO_3^-) or hydrogen ion secretion (H+)

- characterized by hyperchloremic metabolic acidosis with a normal level of non-measurable anions (anion gap) in serum, and a normal GFR

Pathophysiology and biochemical features

- hyperchloremic (Cl ↑)metabolic acidosis (pH < 7.35)
- normal anion gap in serum (hyperchloremia)
- low serum bicarbonate (< 21 mmol/L)
- Urine pH > 5.5 despite acidosis (except proximal RTA in serum HCO_3^- threshold)
- positive anion gap in urine
- hypokalemia (K ↓) (< 3.5 mmol/l)
- hypercalciuria (Ca↑)
- hypocitraturia (↓)
- nephrocalcinosis/urolithiasis
- hypoamoniuria
- rickets

Fixed acids are excreted in the form of sodium salts → serum Na↓

↓

Reabsorption of Na and Cl with K↓ ← Secondary hyperaldosteronism

Low serum HCO_3 → Plasma Cl↑ + acidosis

malacia,

kets ← Acidosis downregulates paracellular and transcellular calcium transport pathways + Bone buffers ($CaCO_3$) reduce

↑Ca is excreted in the urine

High urine pH + low excretion of citrate in the urine due to acidosis

Hypercalciuria + nephrocalcinosis + urolithiasis

erstitial damage interferes with the countercurrent multiplier + hypokalemia → Impaired ability to concentrate urine → polyuria

Clinical presentation

- symptoms of acidemia
- simptoms of hypokalemia
- rickets
- nephrocalcinosis/urolithiasis

Diagnosis

- primarily involves urinary measurement of indices of acid and HCO_3^- secretion in urine
- Low urine titratable acidity and NH_4^+ (or urine anion gap as a substitute)
- pCO_2 difference in blood and urine
- NH_4Cl loading test
- HCO_3^- loading test (no normal increase in pCO2 in the urine)
- furosemide/fludrocortisone test
- genetic analysis

Hypokalemia

- 63% of patients with dRTA have hypokalemia

- 25% of patients with dRTA during life experience an emergency metabolic situati (mainly due to hypokalemia) that can lead to muscle weakness, paralysis, arrhythmia, a breathing disorders (McSherry 1981.)

- Mortality has been described in as much as11% of pediatric patients with dRTA (Sharifian 2011.)

- Correction of acidosis is necessary before treatment of hypokalemia

OVERVIEW OF CURRENT THERAPEUTIC OPTIONS

Salts	Commercial names	Formullation	Dose	Alkali mmols	Alkali Equivalents
Sodium Citrate	Bicitra, Oracit, Cytra-2	Oral Solution	1ml	0.33 mmols of citrate	1 mEq of bicarbonate
Potassium Citrate	Cytra K	Tablets/ Solution	1100mg/5ml	3.3 mmols of citrate	10 mEq of bicarbonate
	Cytra K	Crystals	3300mg	10 mmols of citrate	30 mEq of bicarbonate
	Acalca/Urocit K	Tablets	1080mg	3.3 mmols of citrate	10 mEq of bicarbonate
	Uralyt Urate	Granules	2.5g	6.6 mmols of citrate	20 mEq of bicarbonate
	Urokit	Sachets	3g	10 mmols of citrate	30 mEq of bicarbonate
Sodium Citrate + Potassium Citrate	Polycitra LC Tricitrates Cytra-3	Oral Solution	5ml (550mg K-Citrate + 500mg Na-Citrate)	3.3 mmols of citrate	10 mEq of bicarbonate
	Uralyt-U	Granules	2.5g	9 mmols of citrate	27 mEq of bicarbonate
Potassium Bicarbonate + Sodium Citrate	Blemaren N	Effervescent tablets	1 tablet	10 mmols of bicarbonate + 3.3 mmols of citrate	20 mEq of bicarbonate
Potassium Citrate + Magnesium Citrate	Basica Vital	Sachets	5.5g	10 mmols of citrate	40 mEq of bicarbonate
Magnesium Citrate + Calcium Citrate	Cal-Mag Citrate	Effervescent powder	5.4 g (500mg Ca-Cit + 200mg Mg-Cit)	4.2 = 2.8 = 7 mmols of citrate	21 mEq of bicarbonate
Magnesium Citrate	Magnesium Diasporal 300mg	Sachets	5g	8.3 mmols of citrate	25 mEq of bicarbonate
Magnesium Citrate + Potassium Citrate	Lithoren	Sachets	1 sachet	10 mmols of citrate	30 mEq of bicarbonate
Sodium-Potassium-Calcium-Magnesium Citrate	Basica VItal	Powder	16g	5.5 mmols of citrate	16.5 mEq of bicarbonate
Sodium Bicarbonate	Nephrotrans	Tablets	500mg	6 mmol of bicarbonate	6 mEq of bicarbonate
Potassium Bicarbonate		tablets	1g	10 mmol of bicarbonate	10 meEq of bicarbonate

THE CURRENT STANDARD OF TREATMENT - DOSING SEVERAL TIMES A DAY

- Immediate-release drugs need to be taken several times during the day (on average 3 to 6 times a day, even at night) to establish optimal control of metabolic acidosis during 24 hours and ensure a positive effect on kidney function
- The latest results of studies have shown that the control of metabolic acidosis is not achieved in half of the patients, mainly in children suffering from chronic kidney disease.

1.Lopez Garcia SC; Emma F; Walsh SB; Fila M; Hooman N; Zaniew M et al. Treatment and long-term outcome in primary distal renal tubular acidosis. NDT 2019; 34: 981-989

GRANULES WITH PROLONGED ACTION

Fixed-dose combination of potassium citrate and potassium hydrogen carbonate as prolonged release granules

- Potassium Citrate (green) / Potassium bicarbonate (white)
- GI rezistent
- No taste
- Easy to swallow (suitable for children)

ADV7103-CK/BK granules

Ø= 2mm

ADV7103 sachets

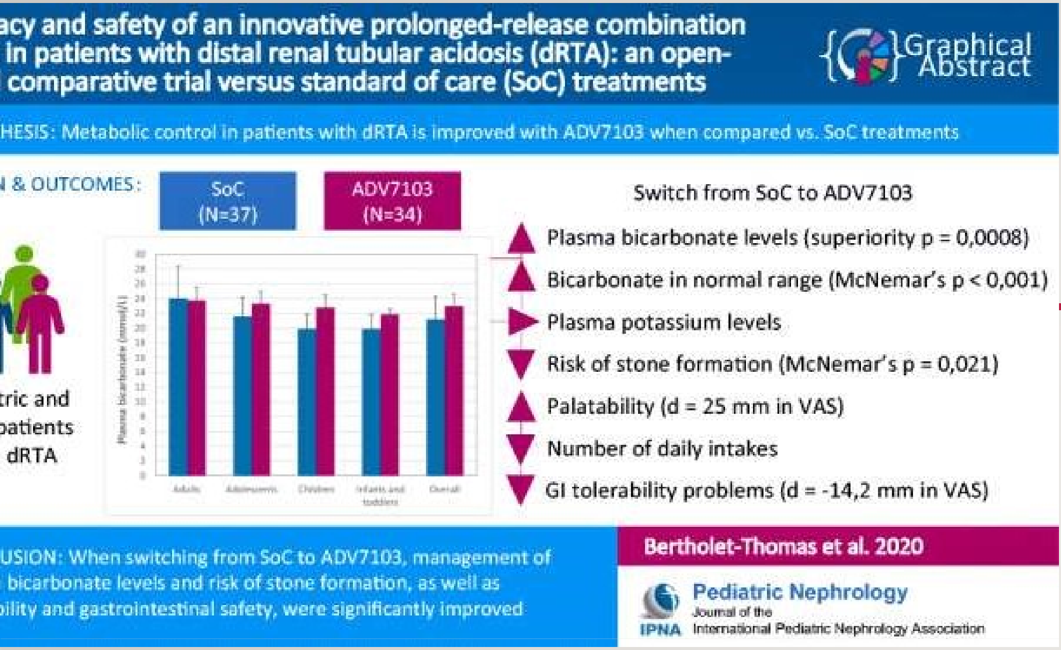
Long-acting formulation

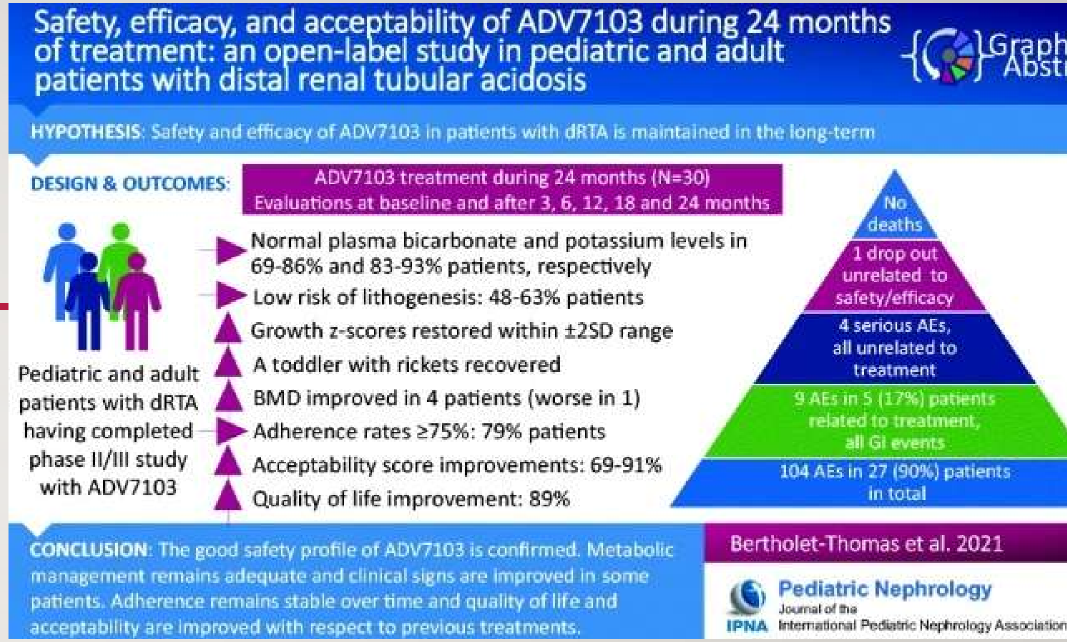
Dosing twice a day ensures metabolic control throughout 24 hours

- ~3h for Potassium Citrate
- ~12h for Potassium bicarbonate

Granules are registered for the treatment of distal renal tubular disease in adults, adolescents and children aged 1 year and older.

Guittet C, Roussel-Maupetit C, Manso-Silván MA, Guillaumin F, Vandenhende F, Gran
Innovative prolonged-release oral alkalising formulation allowing sustained urine pH in
with twice daily administration: randomised trial in healthy adults. Sci Rep. 2020 Aug
18;10(1):13960.





Bertholet-Thomas A, Guittet C, Manso-Silván MA, Joukoff S, Navas-Serrano V, Baudouin V, Cailliez M, Di Maio M, Gillion-Boyer O, Golubovic E, Harambat J, Knebelmann B, Nobili F, Novo R, Podracka L, Roussey-Kesler G, Granier LA. Safety, efficacy, and acceptability of ADV7103 during 24 months of treatment: an open-label study in pediatric and adult patients with distal renal tubular acidosis. Pediatr Nephrol. 2021 Jul;36(7):1765-1774.

The most common side effects with fixed-dose combination granules are abdominal pain and nausea (up to 1/10) at the start of therapy

The European Medicines Agency, therefore, decided that fixed-dose benefits are greater than its risks and it can be authorized for use in the EU.

In the Republic of Croatia, 6 patients are currently being treated with dRTA with success, and 1 patient with cystinuria

- There are no side effects
- It is well tolerated
- The patients report an improvement in taste compared to the previous therapy
- No mouth odor
- The control of acidosis is better
- It is more convenient to take than the previous therapy

Bertholet-Thomas A, Manso-Silván MA, Navas-Serrano V, Guittet C, Joukoff S, Bacch
Boyer O, Rodriguez Portillo M, Granier LA. Bone mineral density and growth changes
patients with distal renal tubular acidosis after two-years treatment with a new alkalizi
(ADV7103). Nefrologia (Engl Ed). 2022 Dec 16:S2013-2514(22)00171-7.

GREETINGS FROM CROATIA


IPNA
International Pediatric Nephrology Association
X SEPNWG MEETING AND TEACHING COURSE 2023
Course Director: Velibor Tasic (Skopje)
Scientific Committee: Constantinios J. Stefanidis (Athens), Danko Milosevic (Zagreb), Velibor Tasic (Skopje), Rezan Topaloglu (Ankara), Dimitar Roussinov (Sofia), Tanja Kerstnik Levart (Ljubljana), Brankica Spasojevic (Belgrade), Danka Pokrajac (Sarajevo), Diamant Schtiza (Tirana), Adrian Lungu (Bucharest), Valbona Nushi Stavilleci (Prishtina)
Organizing Committee: Velibor Tasic, Nora Abazi Emini, Aleksandra Jancevska, Ardiana Beqiri Jashari, Julija Gjorgjievska, Ivan Akimovski
1st to 3rd June, Skopje
Great care for little kidneys. Everywhere.
IPNA is a global, nonprofit charitable organisation that believes that all children deserve to be healthy and receive optimal treatment and care for kidney disease regardless of their economic level or political choice.
IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE
SUPPORTED BY:
Macedonian Society for Rare Diseases
LIFE with CHALLENGES
Life is a puzzle, collect it.
РЕТКО Е ДА СИ РЕДОК
RARE IS TO BE RARE
PEDIATRIC ASSOCIATION OF MACEDONIA
OUR CHILDREN'S SAFETY COMES FIRST

International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

NEW INSIGHTS INTO TREATMENT OF SYSTEMIC LUPUS ERYTHEMATODES – MONOCLONAL ANTIBODIES

DIMITAR ROUSSINOV
Sofia, Bulgaria

10 th SEPNWG MEETING AND TEACHING COURSE
Hotel Aleksandar Palace, Skopje, Republic of North Macedonia, 1-3 June 2023

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

DISCLOSURE

Dimitar Roussinov is a member of the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). Presented opinions are personal and do not engage both institutions with a positions or future decisions.

SLE PATHOPHYSIOLOGY

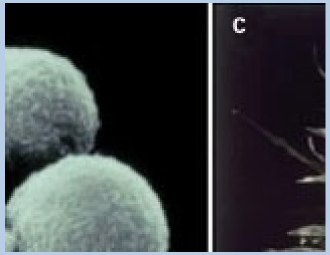
FACTORS

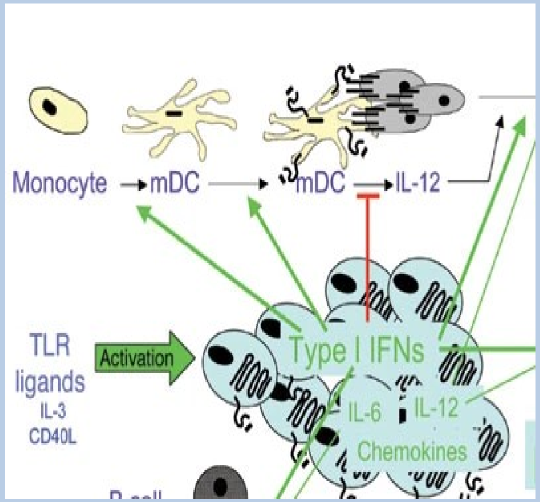
Genetic
Epigenetic
Environmental
Hormonal
Immunoregulatory
Viral

LOSS OF TOLERANCE AGAINST NUCLEAR AUTOANTIGENS

AUTOIMMUNIZATION

ENDOGENOUS DNA DIRECTLY ACTIVATE TOLL-LIKE RECEPTORS (TLR)7/9 ON pDCs OR BCs





IFNα DRIVEN IMMUNITY, ANTIGEN PRESENTATION, AND THE ACTIVATION OF AUTOREACTIVE Ly SUBSETS
pDC SECRETION OF IFNα AND IL-6 PROMOTE THE DIFFERENTIATION OF BCs INTO PLASMA CELLS AND LEAD TO AUTOANTIBODY PRODUCTION
AUTOANTIBODIES AND PROINFLAMMATORY CYTOKINE SIGNALING DRIVE THE INFLAMMATORY PROCESSES THAT CAN LEAD TO ORGAN INJURY AND SCARRING IN SLE

SLE TREATMENT

SLE

NEUROPSYCHIATRIC MANIFESTATIONS
GC±CYC, AZA

SKIN
- Mild – sunscreen high SPF UV-A and UV-B, HCQ, topical and/or systemic GC, CNIs, MTX
- Moderate – MMF, MTX, AZA, CyA
- Severe – MMF, AZA, CyA, RTX

PULMONARY MANIFESTATIONS
- GC
- Mild to moderate – AZA, MMF
- Severe – CYC, RTX

CONSTITUTIONAL SYMPTOMS
HCQ, low to moderate GC

HEMATOLOGIC MANIFESTATIONS
- GC+AZA, MMF or CyA
- If inadequate response CYC, RTX

LUPUS NEPHRITIS
- Induction – CYC or MMF
- Maintenance – MMF or AZA
- If severe NS – MMF+CNIs
- Nonresponding disease – RTX

MUSCULOSKELETAL
- Mild – HCQ
- Moderate to severe – MTX, AZA, MMF, RTX

CARDIAC MANIFESTATIONS
GC±CYC, AZA or MMF

Targeted Therapy for SLE-What Works, What Doesn't, What's Next
Veronica Venturelli [1], David Alan Isenberg [2]
J Clin Med . 2023 Apr 29;12(9):3198. doi: 10.3390/jcm1209319

MEDICAL NEEDS IN SLE

- The pathophysiology of SLE is generally well known
- Treatment options and guidelines exist, but some products are used off-label
- However, there is an unmet medical need still due to the complexity of the disease
- Increased knowledge in details of different pathophysiological mechanisms opens the door for new treatments

MONOCLONAL ANTIBODIES

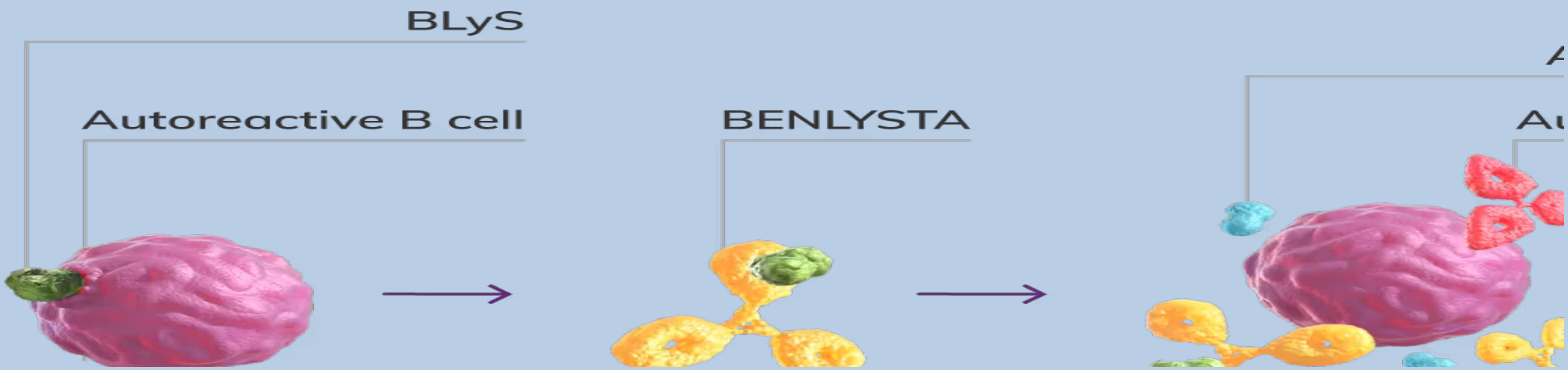
- **Monoclonal antibodies (MA) are a promising products for clinical studies in treatment of SLE**

- **They may target specific molecules and cell receptors participating in development of SLE**

- **Blocking single cytokine pathway may enhance treatment efficacy in autoimmunity without increasing systemic immunosuppression**

BLyS CYTOKINE

- The cytokine BLyS, also known as B-cell activating factor (BAFF) belongs to the tumor necrosis factor (TNF) superfamily and plays a central role in B-cell survival and function.
- BLyS expression is elevated in the glomeruli of patients with lupus nephritis
- Increased serum and intra-renal BLyS levels may promote renal inflammation and flares



Belimumab (Benlysta)

- Belimumab is a MA directed against the cytokine BLyS

- Benlysta is indicated for patients aged ≥ 5 years with active SLE or active lupus nephritis on top of standard of care (SOC) (s.c. injection)

- Benlysta is not recommended in patients with severe active central nervous system lupus.

- Belimumab is effective in most races and had greater efficacy in children.

- The possibility of combining B-cell depletion and anti-BLyS treatment might be more efficacious approach

The Role of Belimumab in Systemic Lupus Erythematosis: A Systematic Review
Ashna Joy [1], Abilash Muralidharan [2], Marwa Alfaraj [3], Darshan Shantharam [4], Akhila Sai Sree Cherukuri [3], Arun Muthukumar [5]
Cureus. 2022 Jun 13;14(6):e25887. doi: 10.7759/cureus.25887. eCollection 2022 Jun

INTERFERONES

- **Type-I and type-III interferons (INF) system, in particular INFα, plays an important role in the pathogenesis of SLE**
- **Dysregulation is suggested by the upregulation of INF-inducible genes observed in serial gene expression microarray studies**
- **In SLE, IFN-stimulated genes induced by IFN signaling contribute to a positive feedback loop of autoimmunity, resulting in perpetual autoimmune inflammation**

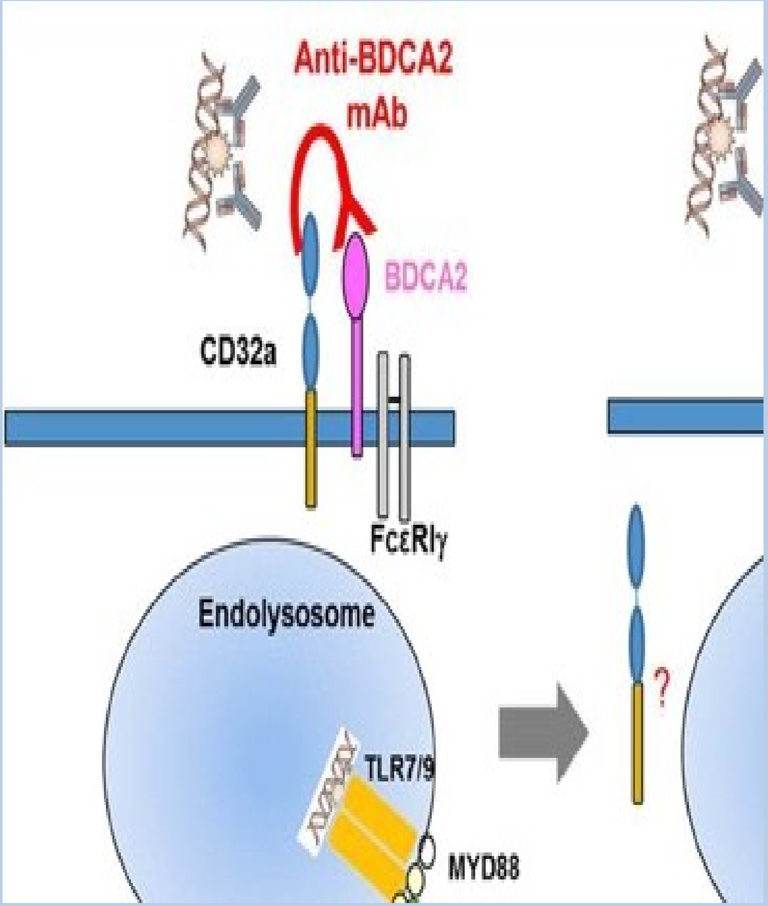
Anifrolumab (Saphnelo)

- Anifrolumab is a MA to type I interferon receptor subunit 1
- It blocks the action of type I IFN and reduces the inflammation and organ damage that occur in SLE
- Authorised for patients aged ≥ 18 years with moderate to severe, active SLE on top of SOC (i.v. infusion)
- Use in pediatric population is under evaluation (ClinicalTrials.gov.)

BDCA2

- Blood Dendritic Cell Antigen (BDCA2) is a receptor that is specifically expressed on pDCs that inhibits TLR7 and TLR9-mediated type I IFN

- pDCs derived type I IFN is thought to play an important role in the pathogenicity of SLE



Anti-BDCA2 monoclonal antibody inhibits plasmacytoid dendritic cell activation through Fc-dependent and Fc-independent mechanisms
Alex PellerinKarel OteroJulie M CzerkowiczHannah M KernsRenée I ShapiroAnn M RangerKevin L OtipobyFrederick R TaylorThomas O CameronJoanne L VineyDania Rabah
EMBO Mol Med (2015)7:464-476

BIIB059 (litifilimab)

- BIIB059 (litifilimab) is a MA against BDCA2, a pDC specific antigen (s.c. injection)
- Administration leads to BDCA2 internalization in vivo and dampens TLR9-mediated type I IFN without depleting pDCs
- It inhibits type I IFN from immune complex-stimulated pDCs through BDCA2 ligation as well as Fc-dependent down-modulation of CD32a
- Not authorised yet
- Clinical trial Phase 3 in SLE is running and recruiting (ClinicalTrials.gov.)

Obinutuzumab (Gazyvaro)

- Obinutuzumab is a next generation anti-CD20 MA targeting pre-B and B cells, not pro-B cells
- Licensed for haematological malignancies (i.v. infusion)
- It might be effective in renal and nonrenal SLE patients
- Clinical trial currently running (ClinicalTrials.gov.)

IL-17A AND Th17

- IL-17A is a proinflammatory cytokine produced by activated T cells
- It regulates the activities of NF-kappaB and mitogen-activated protein kinases
- It can stimulate the expression of IL-6 and COX-2, as well as enhance the production of nitric oxide
- IL-17A is the central cytokine in multiple autoimmune and inflammatory processes
- IL-17-producing T helper type 17 (Th17) cells, drive inflammation and contribute to renal immunopathology.
- Both play significant role in LN

The gene expression of type 17 T-helper cell-related cytokines in the urinary sediment of patients with systemic lupus erythematosus
Kwan B. C-H. , L-S. Tam, K-B. Lai, F. M-M. Lai, E. K-M. Li, G. Wang, K-M. Chow, P. K-T. Li, C-C. Szeto
Rheumatology, Volume 48, Issue 12, December 2009, Pages 1491–1497

IL-17 and IL-23 in lupus nephritis - association to histopathology and response to treatment
Zickert A., P. Amoudruz, Y. Sundström, J. Rönnelid, V. Malmström, I. Gunnarsson
BMC Immunology **volume 16**, Article number: 7 (2015)

Secukinumab (Cosentyx)

- **Secukinumab is a MA targeting IL-17A (s.c. injection)**
- **Authorised indication(s): moderate to severe plaque psoriasis, active psoriatic arthritis, active ankylosing spondylitis, Enthesitis-Related Arthritis and Juvenile Psoriatic Arthritis in patients aged ≥ 6 years**
- **Clinical trial Phase 3 in SLE and lupus nephritis is running and recruiting (ClinicalTrials.gov.)**

IL-21

- IL-21 is an autocrine cytokine predominantly produced by follicular helper T (Tfh) and Th17 cells

- It has been proven to play an important role in the immune system by promoting proliferation and development of Tfh and Th17 cells, balancing helper T cell subsets, inducing B cell generation and differentiation into plasma cells, and enhancing the production of immunoglobulin

- IL-21 has been linked to autoimmune diseases

- IL-21 levels are increased in the peripheral blood and tissues of patients with SLE

Clinical significance and immunobiology of IL-21 in autoimmunity
Long D, Chen Y, Wu H, Zhao M, Lu Q. (2019)
J Autoimmun, 99: 1-14. [PMID:30773373]

Avizakimab

- **Avizakimab is a MA targeting IL-21 (s.c. injection)**
- **It is expected blockade of IL-21 to be beneficial for patients with autoimmune diseases, including SLE**
- **Not authorised yet**
- **Clinical trial Phase 2 in SLE as add-on therapy on top of SOC is completed (ClinicalTrials.gov.)**

CD40 AND ITS LIGAND CD40L

- The cluster of differentiation 40 ligand (CD40L) is expressed on several types of cells, including activated T cells
- Through interactions with its receptor, cluster of differentiation 40 (CD40), CD40L plays an important role in regulating interactions between T cells and other immune cells, notably B cells and antigen-presenting cells
- It mediates important functional events involved in autoimmune disease and inflammation
- In addition to its role in "classical" inflammatory pathways, CD40L appears to be involved in mechanisms that may also be critical in SLE, such as atherosclerosis, platelet activation potentially leading to pathological thromboembolic events, T cell trafficking, capillary leakage, and generation of fibrosis

CD40 in coronary artery disease: a matter of macrophages?
Jansen MF, Hollander MR, van Royen N, Horrevoets AJ, Lutgens E.
Basic Res Cardiol. 2016;111:38

Dapirolizumab pegol

- Dapirolizumab pegol (DZP) is a MA, which binds to CD40L and inhibits interaction with its receptor, CD40 (i.v. infusion)

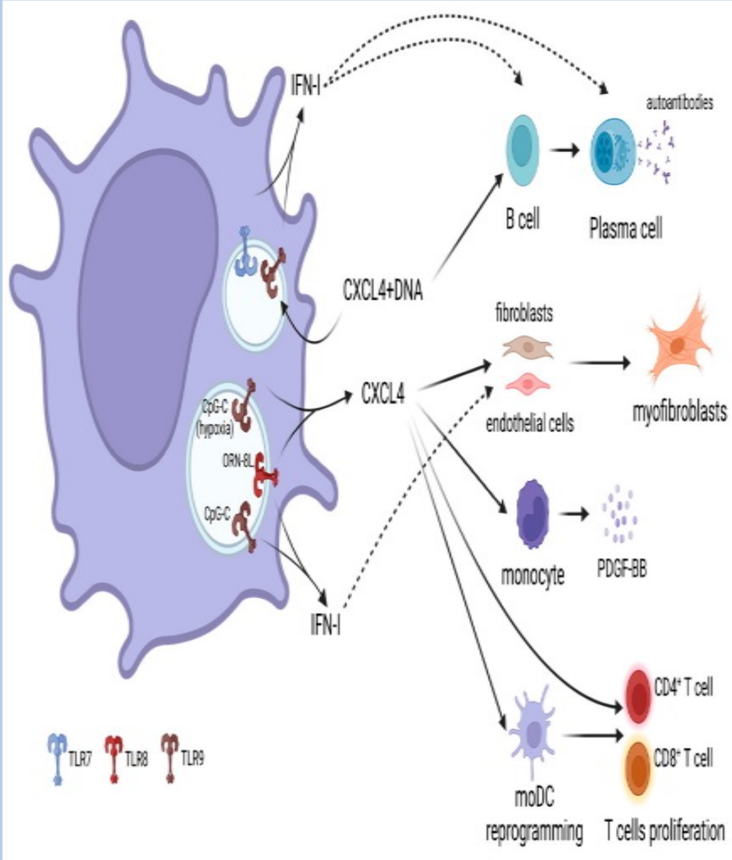
- Through blockade of the CD40-CD40L interaction, DZP is expected to inhibit several different pathways of the autoimmune response

- Not authorised yet

- Clinical trial Phase 3 in SLE as add-on therapy on top of SOC is running and recruiting (ClinicalTrials.gov.)

ILT7

- Endogenous nucleic acids directly activate TLRs on pDCs or B cells, which drives IFNα-related immunity, antigen presentation, and the activation of autoreactive lymphocyte subsets
- Human immunoglobulin-like transcript 7 (ILT7) is a surface molecule selectively expressed by pDCs
- ILT7 cross-linking suppresses pDC activation and IFN-I secretion following TLR7/9 engagement



Daxdilimab

- Daxdilimab is MA directed against human ILT7 on the surface of pDCs (s.c. injection)

- Binding to ILT7 on the surface of pDCs leads to recruitment of macrophages and natural killer cells, thus inducing cytolysis, depletion and removal of pDCs from circulation for a period of time

- Not authorised yet

- Clinical trial Phase 2 in SLE and lupus nephritis is running and recruiting (ClinicalTrials.gov.)

MA FAILURE IN SLE

- Ustekinumab – anti IL-12 and IL-23
- Epratuzumab – anti CD22
- Tabalumab – anti-B-cell activating factor (BAFF)

- They failed to meet the primary endpoints in randomized clinical trials (RCT)in SLE
- Pharmacodynamic effect is not enough and B/R ratio should be evaluated in RCT with clinically significant end points

Not all that glitters is gold

CONCLUSIONS

- For many years, the failure of randomized controlled trials has prevented patients with SLE from benefiting from biological drugs
- Only two biologics are approved for SLE (1 below 18 years) and they can only be administered to a restricted proportion of patients
- Recently, several new biologics have been evaluated for efficacy and safety in extra-renal SLE and lupus nephritis
- Some trials have reported encouraging results, with an improvement in multiple clinical and serological outcome measures. However, the final assessment of B/R ratio is pending.

THANK YOU FOR YOUR ATENTION

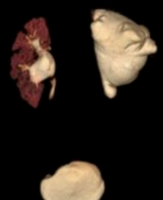
10th SEPNWG MEETING AND TEACHING COURSE

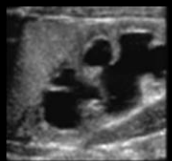
International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS, EVERYWHERE

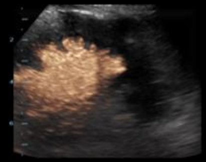
Imaging in pediatric Nephro - Urology

Goran Roić

Children's Hospital Zagreb







Introduction

Today's tendency in Pediatric radiology:

- *NO radiation or reduced radiation exposure*
- *Provide morphology & function*
- ➢ *Enable "one-stop-shop" imaging !*

State-of-the-Art Renal Imaging in Children
Viteri B, Juan S Calle-Toro, Furth S, Darge K, A Hartung EA, Otero H
2020 Feb;145(2):e20190829. doi: 10.1542/peds.2019-0829. Epub 2020 Jan 8.

Pediatric Nephro - Urology imaging

Imaging modalities:

- **Conventional radiography**
  - *- Intravenous urography /IVU/*
  - *- Voiding cystourethrography (VCUG)*
- **Computed tomography (CT)**
  - *- CT urography /CTU/*
- **Ultrasonography (US)**
  - *- Focused Renal Sonography /FRS/*
  - *- Contrast-enhanced Ultrasonography /CEUS/*
  - *- "Contrast-enhanced Voiding Ultrasonography /ceVUS/*
- **Magnetic resonance imaging (MRI)**
  - *- MR urography /MRU/*
  - *- functional MRU /fMRU/*

Great Impact




Intravenous urography (IVU)

➢ *The use of paediatric **IVU** decreased dramatically with <u>only few</u> potential indications:*

- Rare cases of pre- or post-operative imaging (*MRI anavailable !)*
- Suspected renal and ureteral trauma (*CT anavailable !*),
- Urolithiasis, if US is insufficient for therapy decision
- Rare pelvicalyceal or ureteral pathology
  (e.g., calyceal diverticula, medullary sponge kidney, ureteral valves)

Pediatr Radiol (2010) 40:1315–1320. ESPR uroradiology task force and ESUR paediatric working group: imaging and procedural recommendations in paediatric uroradiology: intravenous urography, uro-CT and MR-urography in childhood Michael Riccabona & Fred E. Avni & Jean-Nicholas Dacher & Maria Beatrice Damasio & Kassa Darge & M. Luisa Lobo & Lil-Sofie Ording-Müller & Frederika Papadopolou & Ulrich Willi

Current role of uro-CT ?

As a rule:

- one should try to **avoid CT** in children whenever possible

  /rarely a first-line technique/

However,

- there are paediatric conditions that justify and require **uro-CT**
  - ⇒ ***adapted*** *CT technique to children*
  - ⇒ ***avoid*** *multiphase scans !*

Before going to CT:

- *Previous **high-level** dedicated paediatric US*
- *Consider **MRI** as alternative*
- *Clinical queries, therapeutic impact ?*

IPNA

Paediatric “uro-CT” - Indications

Current role of **CT** in pediatric uroradiology:

- **Severe renal/abdominal (*poly*) trauma**
- Complicated stone disease (*urolithiasis*)
  - *- if US + radiography not sufficient; if impacts therapy*
- Complicated infection
  - *- if US inconclusive, MRI not available*
- Tumor & D.D.
  - *- if MRI not available*
- Reno-vascular disease
  - *- if intervention therapy planned*

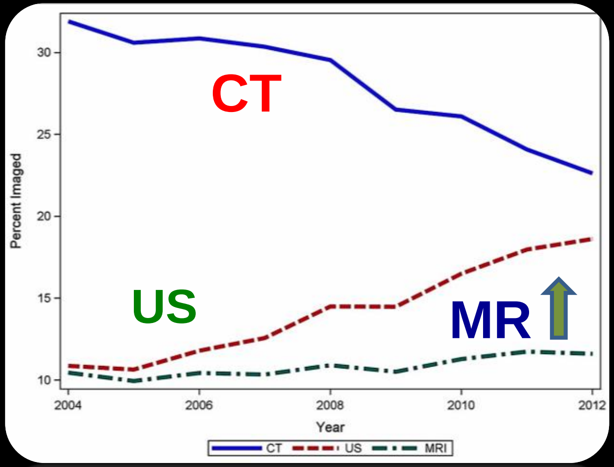
Relatively **high radiation** dose !

- *main disadvantage in paediatrics*

Paediatric Uroradiology

- Inatravenous urography (IVU)
- Paediatric "uro-CT"

Trends in *Pediatric Radiology*



NOT
routine imaging methods
in children

State-of-the-Art Renal Imaging in Children
Viteri B, Juan S Calle-Toro, Furth S, Darge K, A Hartung EA, Otero H
2020 Feb;145(2):e20190829. doi: 10.1542/peds.2019-0829. Epub 2020 Jan 8.

Ultrasonography (US)

- **B-mod US** - mainstay of paediatric nephro-uroradiology
- Answers to most queries and clinically relevant question
- D.D.
- helps to tailor additional imaging *(MRU-fMRU, CEUS, ceVUS ?)*
- ideal for initial information + follow-up

➢ particularly in light of "Image gently" campaign !!

- is **US** sufficient !?
  - *not always, even if performed adequately*

Focused Renal Sonography

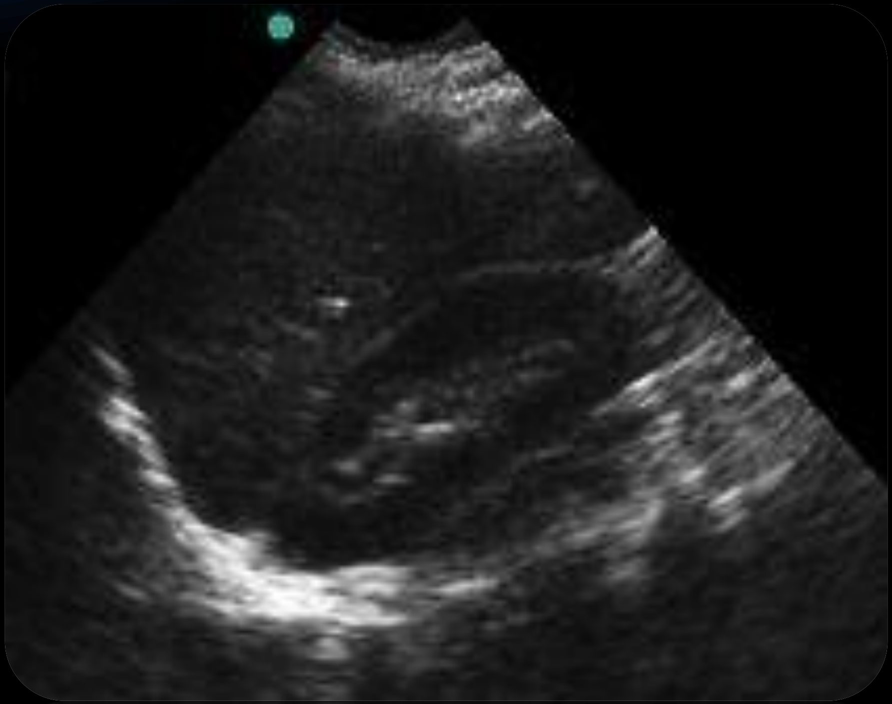
Radiographics. **2010** Sep;30(5):1287-307.

Renal Pyramids: *Focused Sonography of Normal and Pathologic Processes*

Daneman AI, *Navarro OM, Somers GR, Mohanta A, Jarrin JR, Traubici J.*

- Linear transduser
- High mega-hertz range *(up to **17** MHz)*
- One or two pyramids and surrounding cortex
- Focal zone at level of region of most interest

Focused Renal Sonography ?



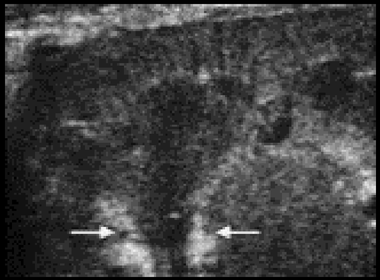
!?

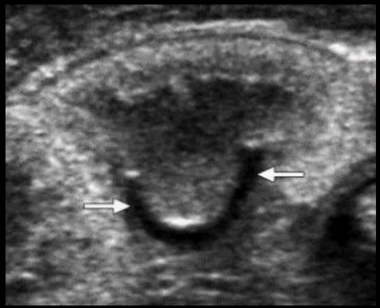
We need :

- *detailed images of renal parenchyma*
- *helpful in understanding underlying disease*
- *may help establishing an accurate diagnosis*

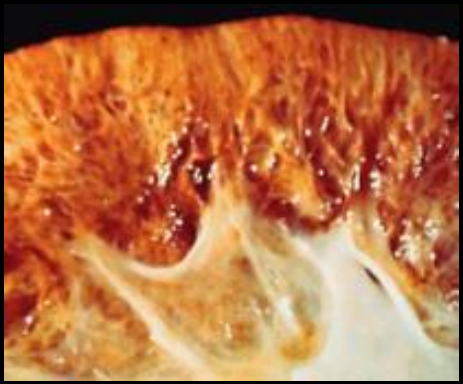
Focused Renal Sonography

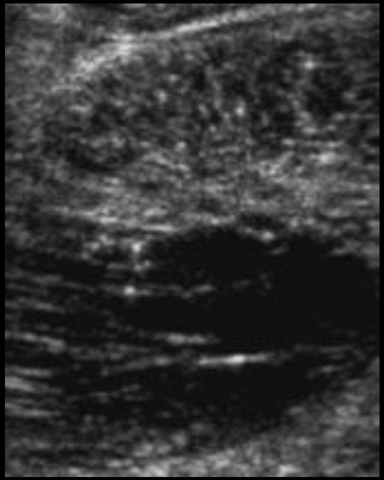
Normal *US appearance of renal pyramids in infants*



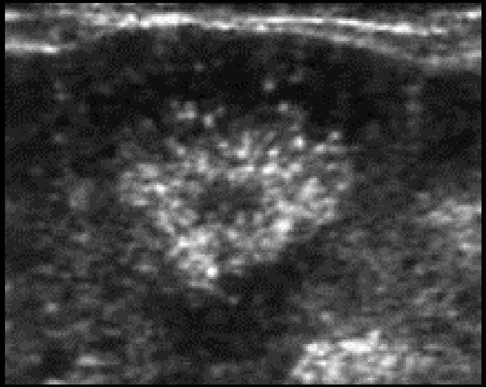


ARPKD in a neonate



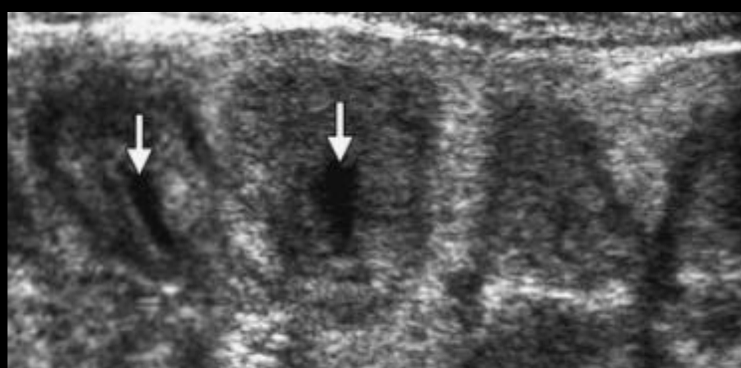


Medulary nefrocalcinosis

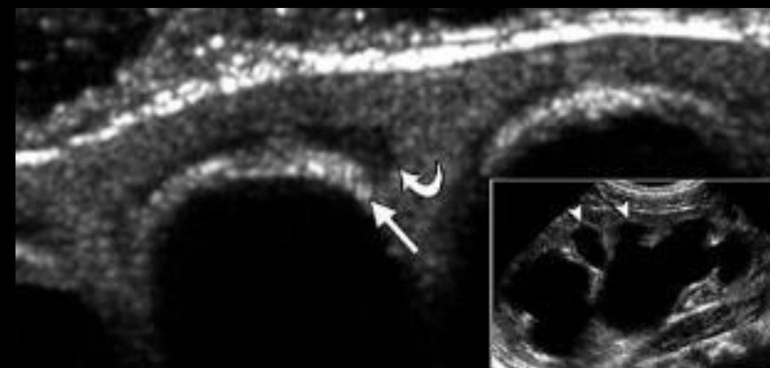


Focused Renal Sonography

Medullary ischemia in a neonate /perinatal asphyxia/



Opstructive hydronephrosis



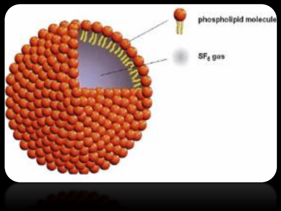
CEUS

"Contrast-Enhanced UltraSonography"

Contrast specific US techniques

+

Second-generation USCA



“Contrast-Enhanced UltraSonography”

CEUS

Intravenous CEUS

- Liver
- Spleen
- Pancreas
- Kidney + urinary sys.
- Gallbladder
- Bowel
- Aorta
- Testis

Endocavitray CEUS

- Intravesical
- Intraoperative
- Percutaneous
- Oral

- ceVUS

Ultrasound INTERNATIONAL OPEN | Thieme

Ultrasound Int Open. 2017 Feb; 3(1): E2–E7. PMCID: PMC5331928
doi: 10.1055/s-0042-124502 PMID: 28255580

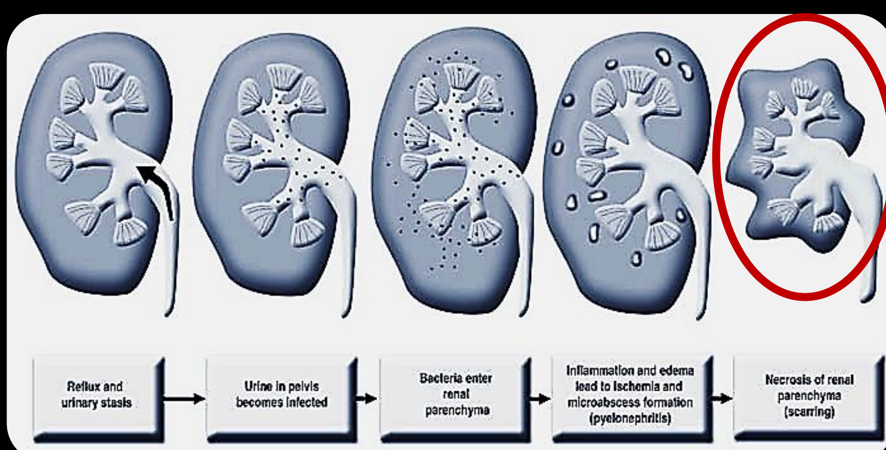
Clinical Applications of Contrast-Enhanced Ultrasound in the Pediatric Work-Up of Focal Liver Lesions and Blunt Abdominal Trauma: A Systematic Review

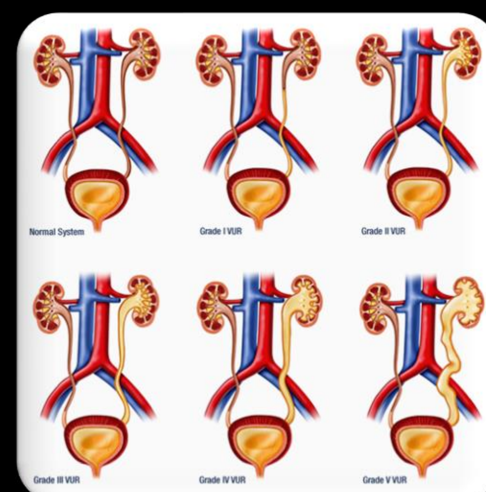
Nicolaj Grønbæk Laugesen,[1] Christian Pallson Nolsoe,[2] and Jacob Rosenberg[3]

IPNA

Contrast enhanced voiding US (ceVUS)

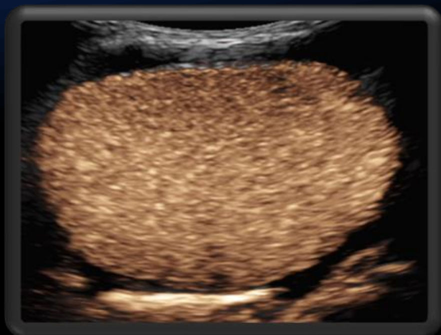
- today most common diagnostic procedure for VUR diagnosis ***/"gold standard"/***
- contrast-specific US techniques
- safe & reliable
- higher VUR incidence than conventional **VCUG**
- **NO** radiation issues
- **Aim of imaging** prevent development of small kidney with scars as end stage of reflux nephropathy

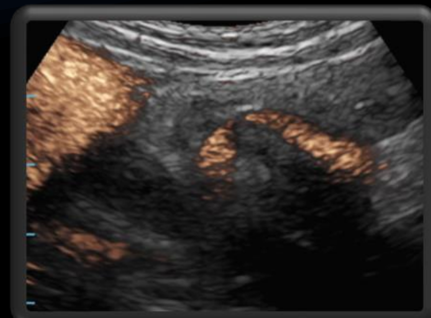


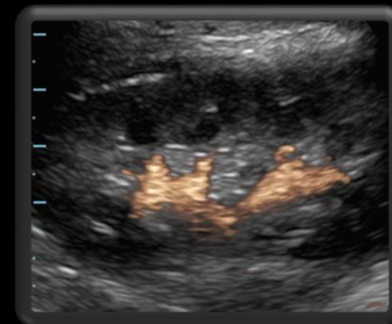


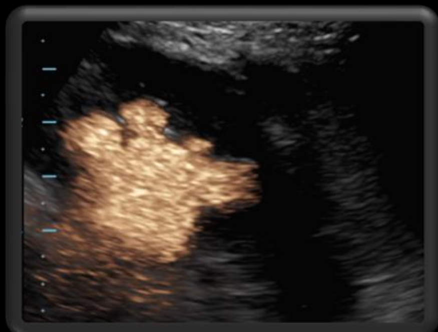
Contrast enhanced voiding urosonography

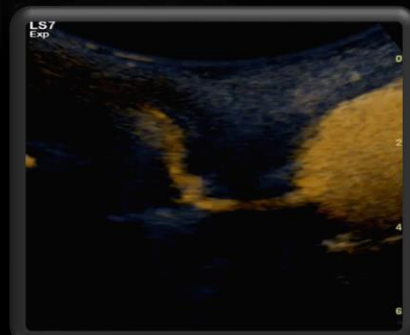
(ceVUS)



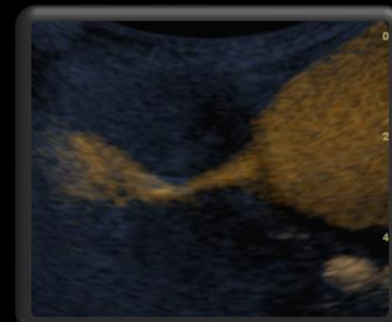




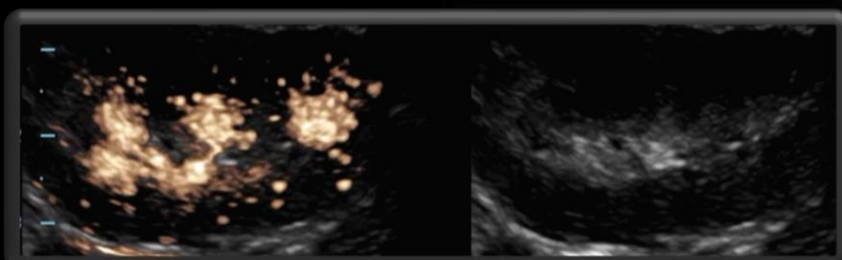




M urethra



F urethra



Intrarenal reflux (IRR)

Comparison of different modalities

	Kateter	Zračenje	Sens.	Spec.	Anat. detalji
MCUG	+	+++	++	+++	++
DRNC	+	 +	+++	+	+
ceVUS	+	 0	+++	+++	+++

Contrast enhanced voiding urosonography (ceVUS)

ceVUS - well recognizedis recognised as practical, safe and radiation-free modality with high sensitivity

- European Federation of Societies for Ultrasound in Medicine & Biology
- European Society of Pediatric Radiology (ESPR) &
- European Society of Urogenital Radiology (ESUR)"

added it in their guideline and current imaging pathway recommendations

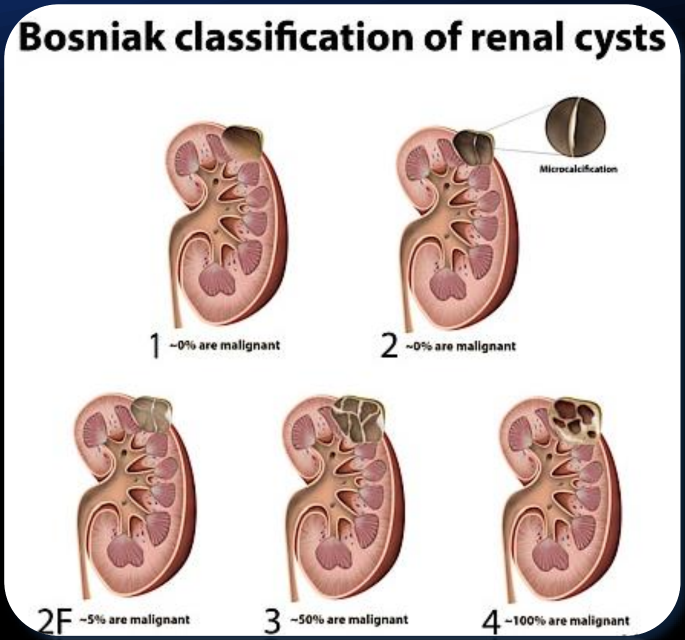
Kidney **CEUS**

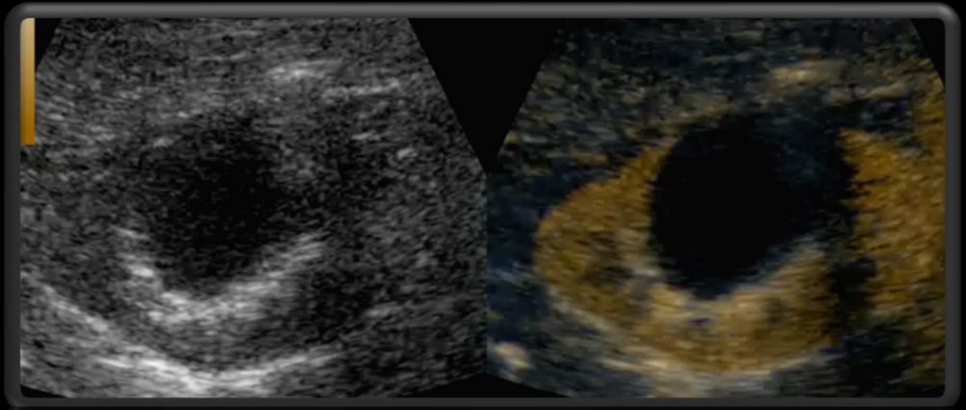
Most common indications:

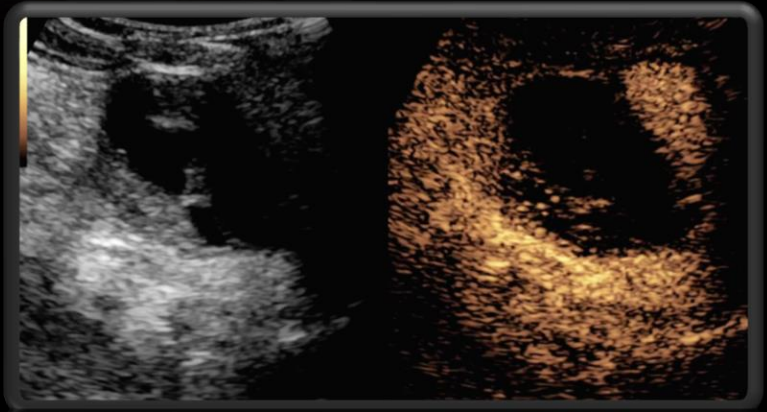
- Evaluation of renal *“pseudo-tumors”*
- Detection of solid lesions
- Differential diagnosis between solid and cystic lesions
- Characteristion of complex cystic masses
- Identification of clinically suspected renal abscesses in patients with complicated urinary tract infection

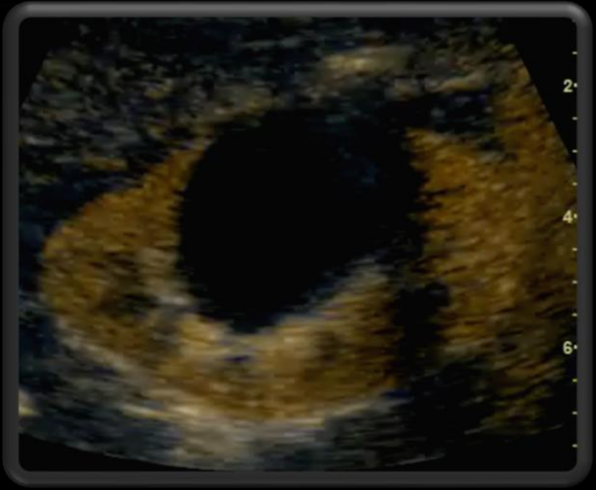
➢ **Renal trauma** - CEUS !

Renal Cyst


Bosniak classification of renal cysts
Microcalcification
1 ~0% are malignant
2 ~0% are malignant
2F ~5% are malignant
3 ~50% are malignant
4 ~100% are malignant

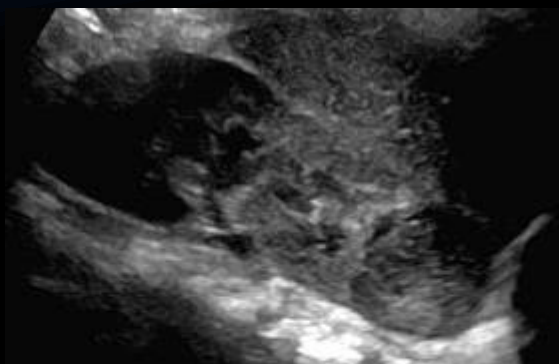


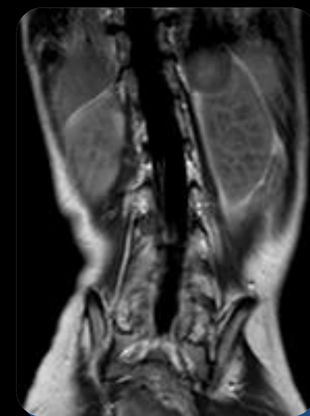


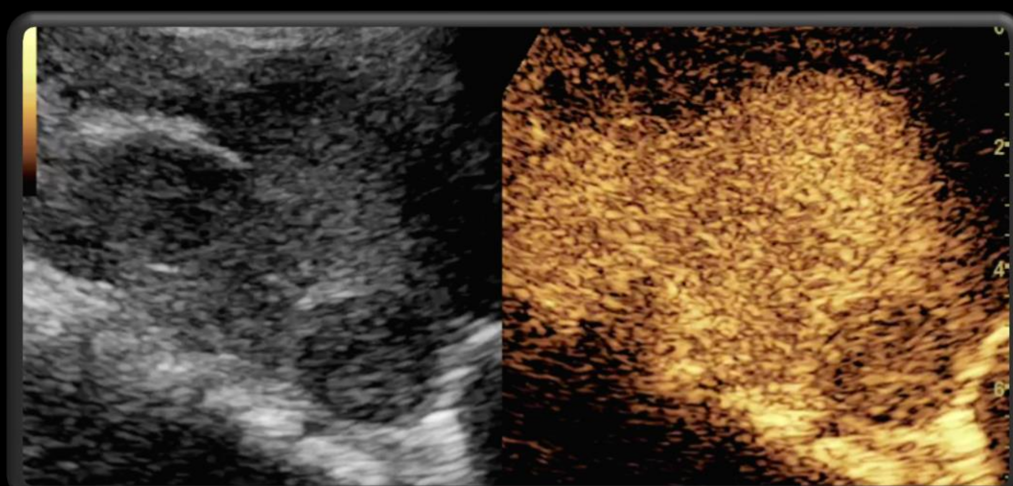


Cyst ?   Solid lesion ?

Problem solving







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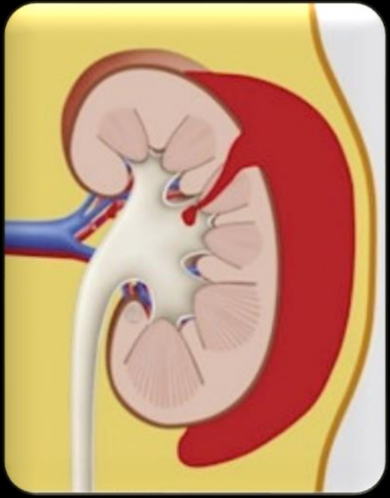
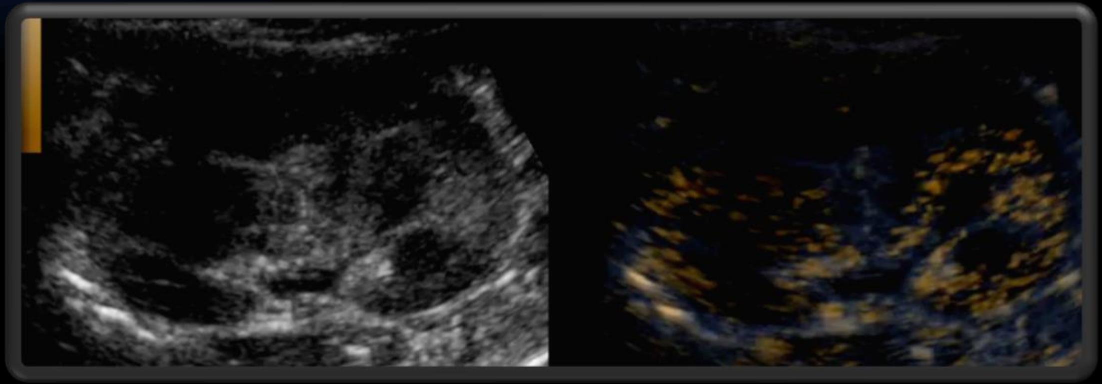
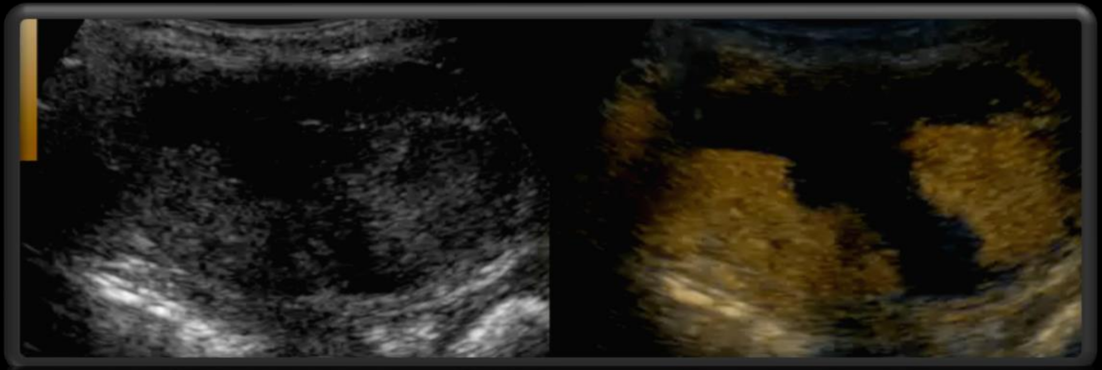
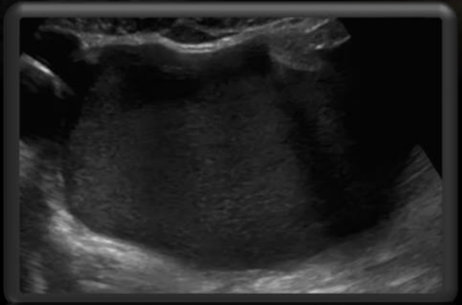
Renal trauma - *CEUS !*

Grade IV





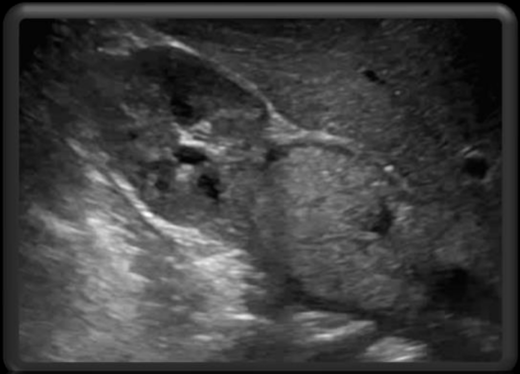


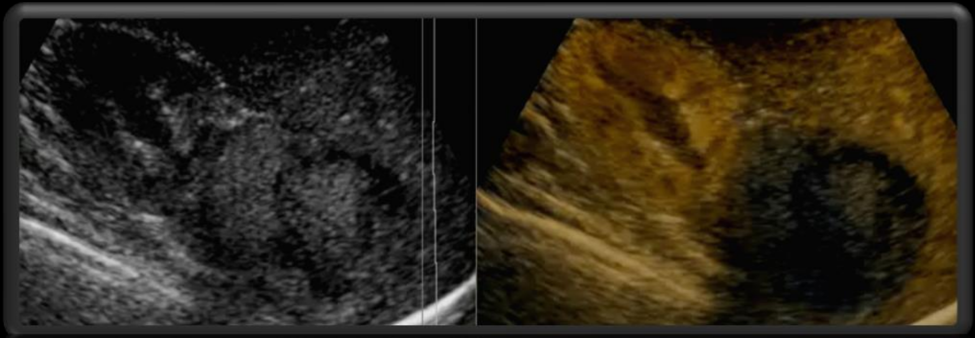


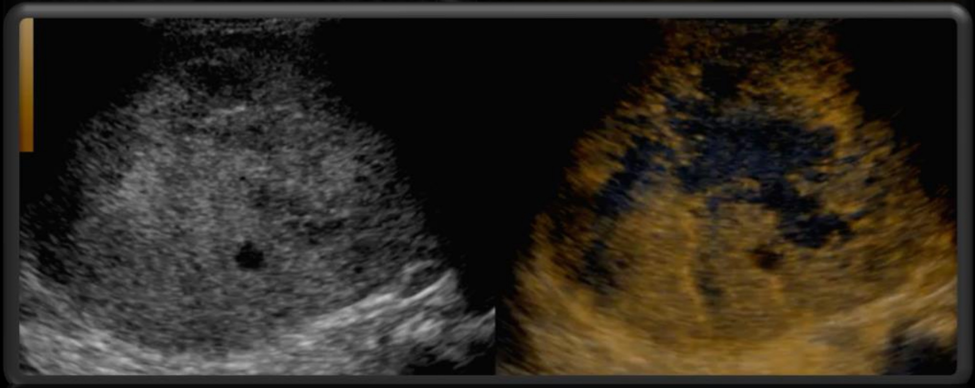
Evaluation of chemotherapy response

CEUS - evaluate/monitor reaction of tm to chemotherapy

/proportion of vital tm tissue in relation to necrotic part of tm/

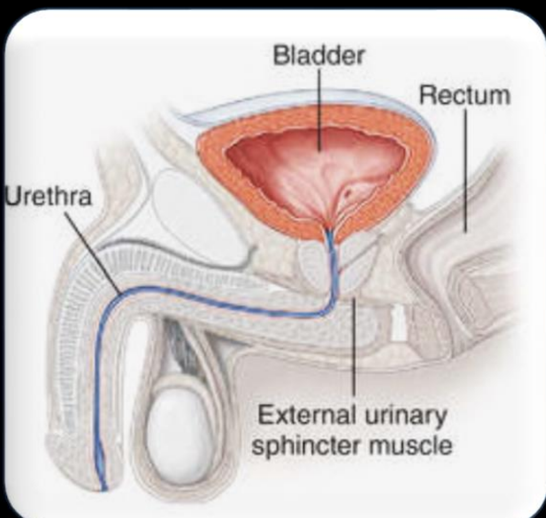


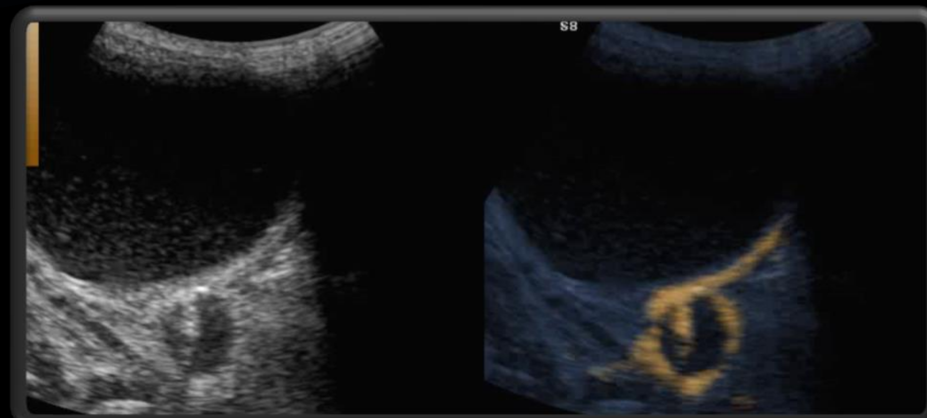




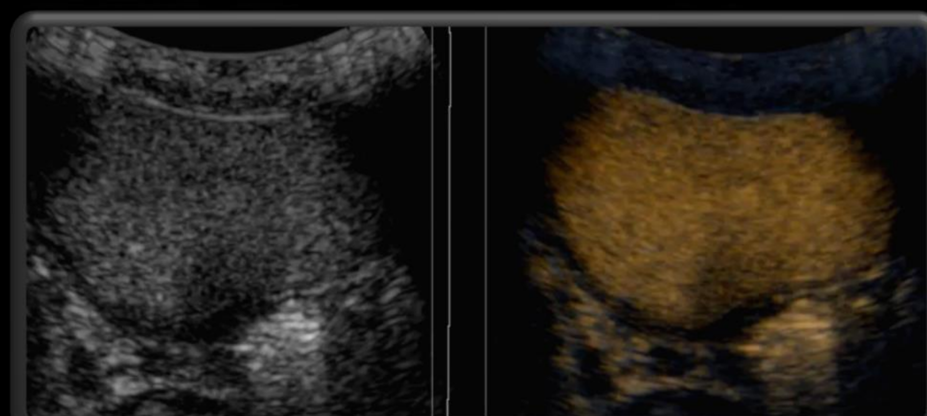
Urethral perforation

Problem solving





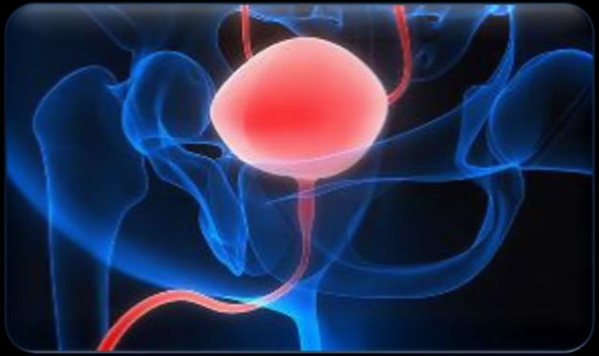
○ *after bladder surgery*

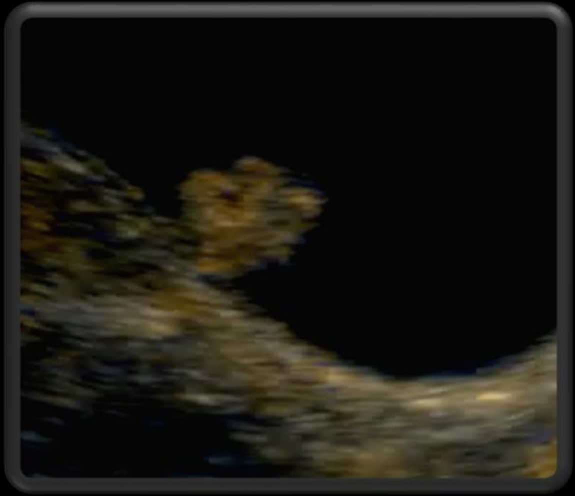


➢ *after intervention*

Fibroepithelial polyp - bladder

Problem solving

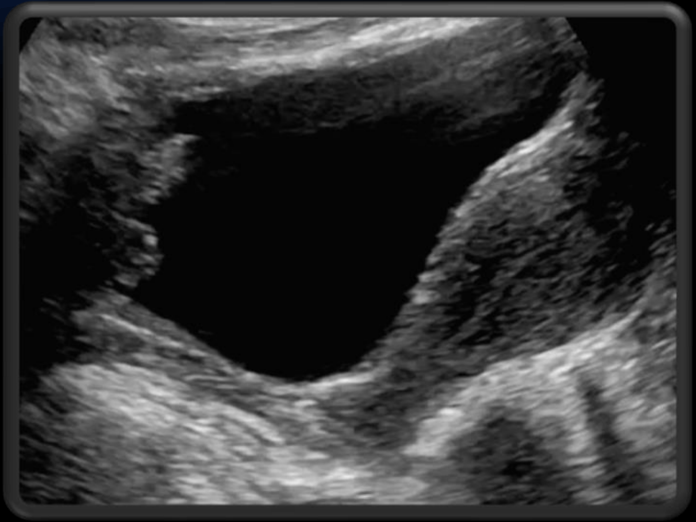


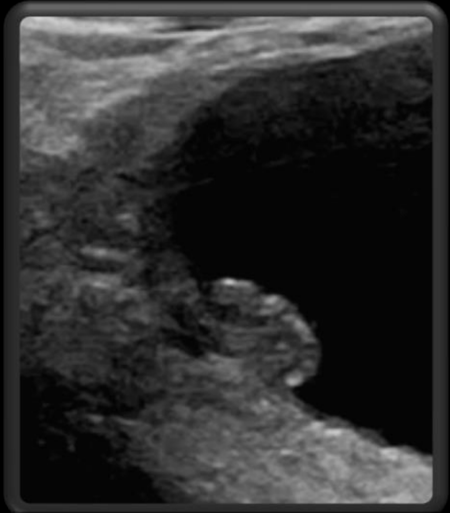


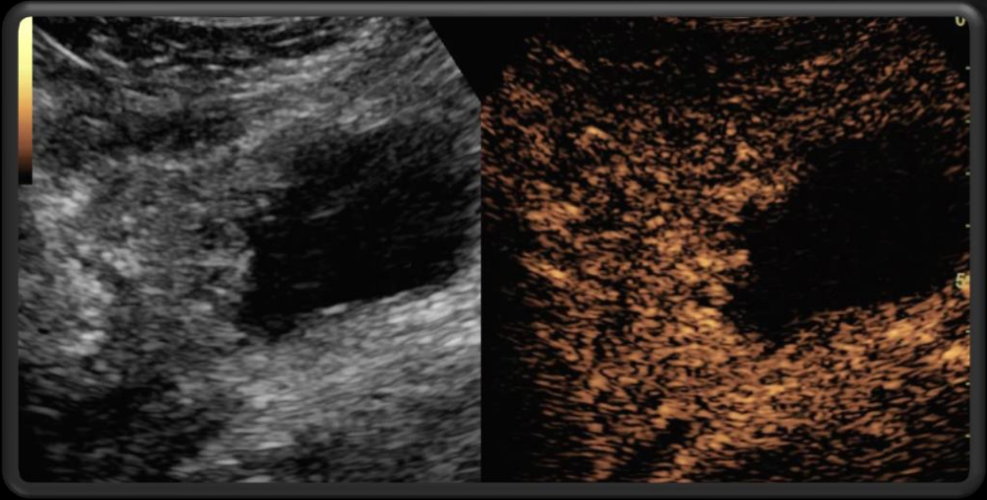
10th SEPNWG MEETING & TEACHING COURSE

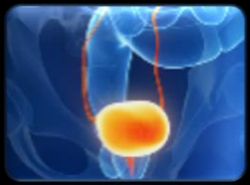
Residua - ? *(**RMS** - ur. bladder)*

Problem solving



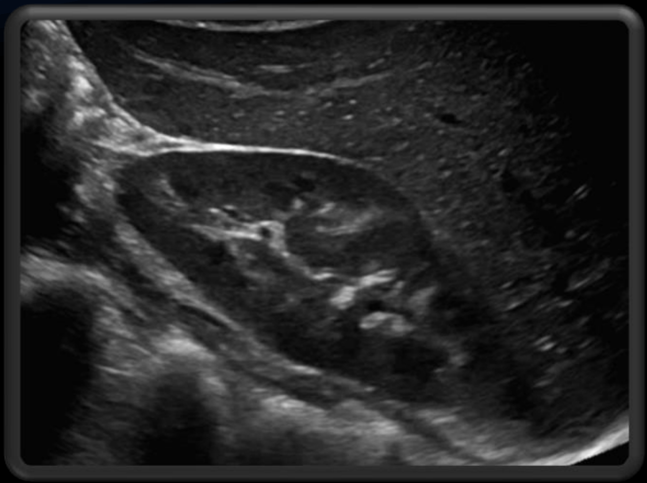


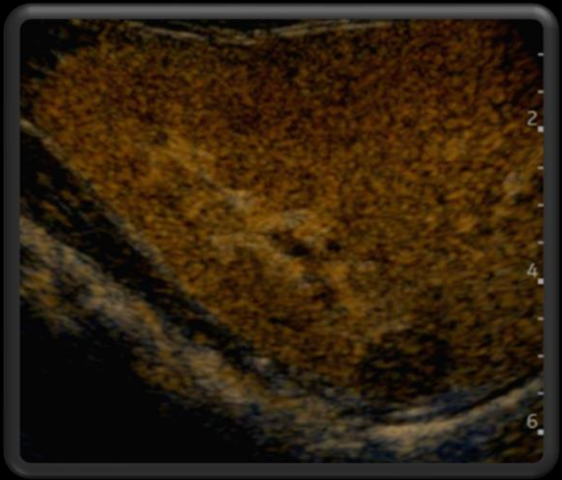




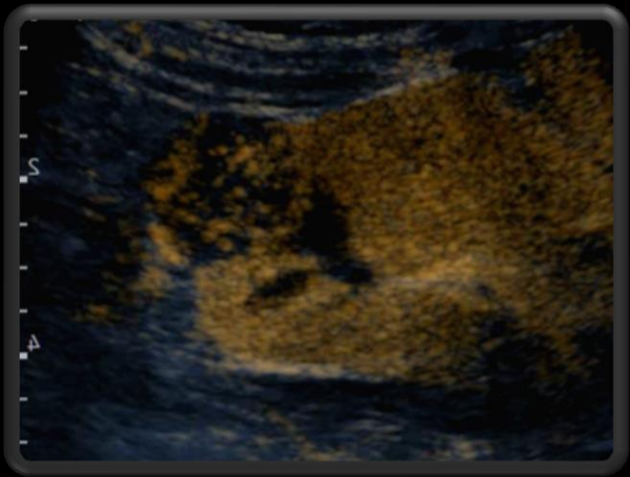
Solid lesion ?

Dex.





Sin.



MR Urography - (MRU)

- MRI exam optimized for urinary tract assessment
  - *Anatomy* vs. *function* vs. *both*
- Reduces need for multiple imaging studies
  - Information provided = *US + retrograde pyelography + excretory urography + renal scintigraphy + CT combined*
- Does not require **ionizing radiation**
- *However*, may require sedation (5y.)

Technique:

- **MR hydrography -** T2-weighted imaging of water (*urine*)
  - Excellently depicts dilated/obstructed urinary tract
- **Postcontrast MRU -** T1-weighted imaging of urinary tract + IV contrast
  - Excellently depicts non-dilated/non-obstructed urinary tract - **fMRU**

MR urography - Indications

Most common indications for pediatric MRU include:

1. Evaluation of complex/unusual urinary tract anatomy that cannot be defined with US & ceVUS/VCUG
   - *e.g., duplex system, ectopic ureter, complex pelvic congenital malformations*
2. Characterize location & degree of obstructive nephropathy/uropathy
3. Assess renal parenchyma, including:
   - *Qualitative appearance*
   - *Differential renal function & estimated GFR*

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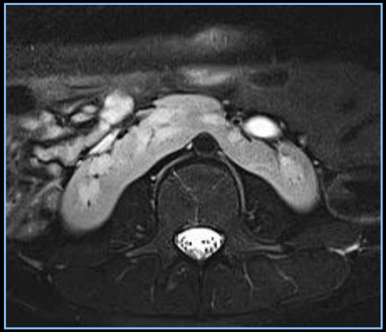
MRU … A Basic standardized approach to reviewing urinary tract anatomy

1. Kidneys
   - Number, size, location, fusion?, parenchyma
2. Upper urinary tract
   - Single vs. multiple, narrowing/dilatation, course, ureteric insertion
3. Urinary bladder
   - Capacity, wall, filling defects/masses, contours

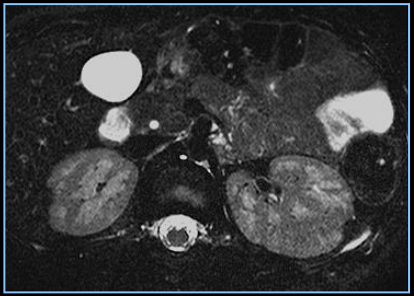
Cross-Fused Ect.

Solitary Kidney

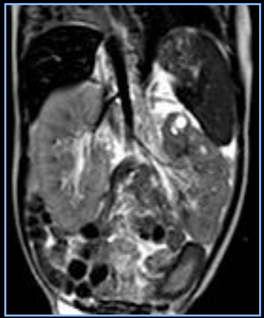


Horseshoe Kidney

Renal Atrophy



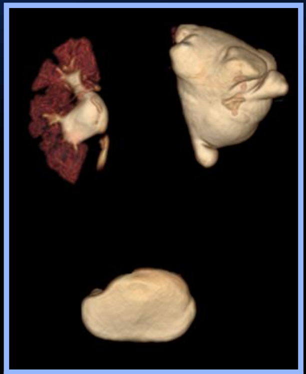
Renal Scarring



Renal Dysplasia

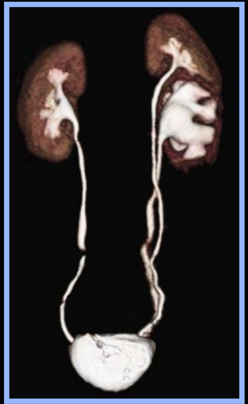
MRU ... A Basic Anatomy

1. Kidneys
   - Number, location, size, fusion?, parenchyma
2. Upper urinary tract
   - Single vs. multiple, narrowing/dilatation, course, ureteric insertion
3. Urinary bladder
   - Capacity, wall, filling defects/masses, contours



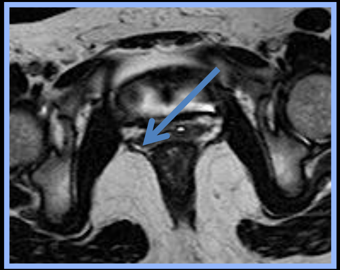
UPJ Obstruction

"Y" Duplication



Complete Duplic.

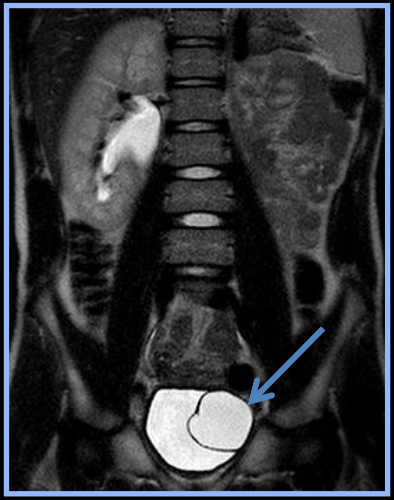
Cong. Megaureter



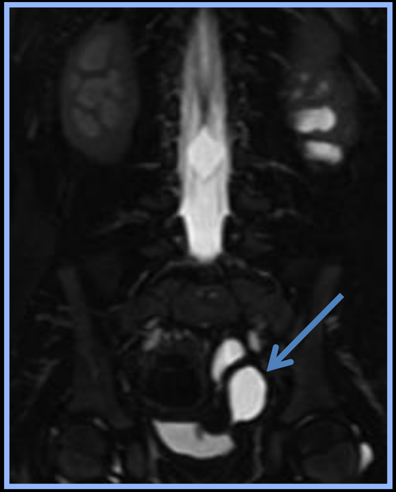
Ectopic Ureter

MRU ... A Basic Anatomy

1. Kidneys
   - Number, location, size, fusion?, parenchyma
2. Upper urinary tract
   - Single vs. multiple, narrowing/dilatation, course, ureteric insertion
3. Urinary bladder
   - Capacity, wall, filling defects/masses, contours



Ureterocele



Diverticulum

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Volume-Rendering Technique */3D volume rendering/*

- **VRT** *(Volume Rendering Technique)* is used to provide **3D** presentation
- provide excellent overview of urinary tract anatomy

3D VRT - MRU could make a difference !!

Hydroureteronephrosis

UPJ Obstruction

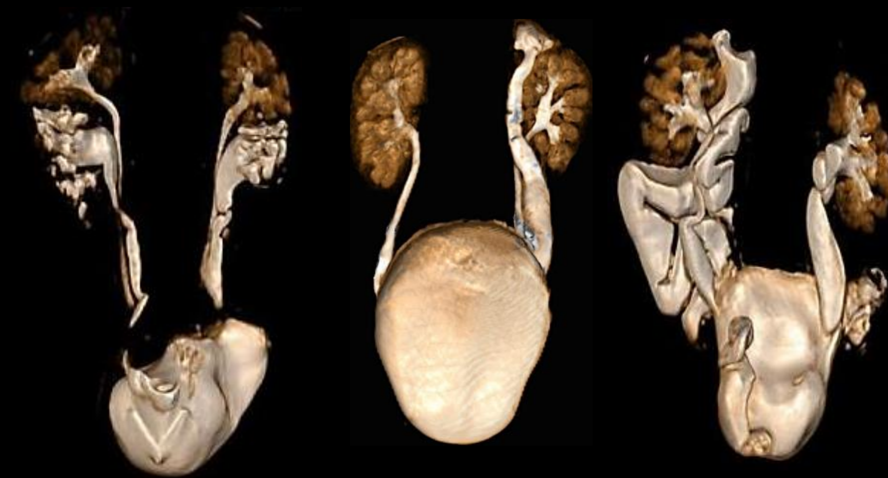
Renal duplication, “Y” ureter

“*Blind ending*” ureter

3D VR

Megaureter

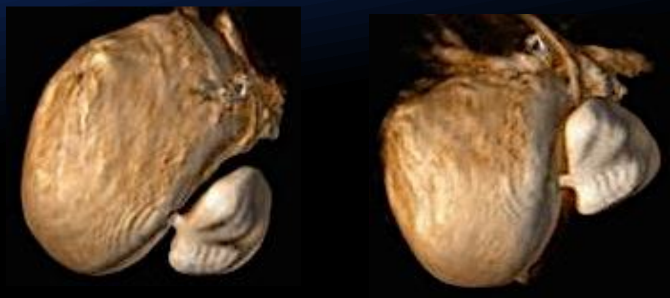
Complex Kidney Duplication



Ectopic Ureter

3D VR

Bladder Diverticulum



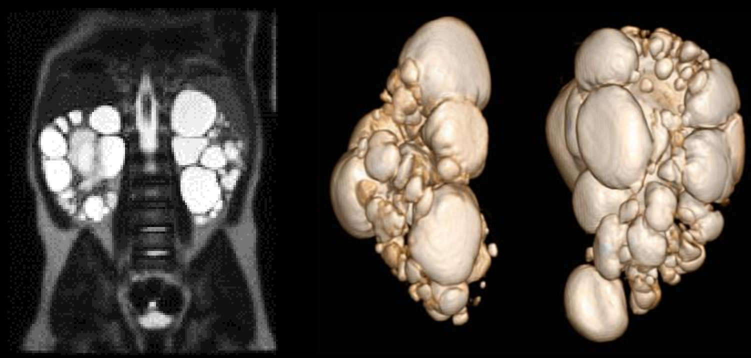
Renal cyst

Neurogenic Bladder

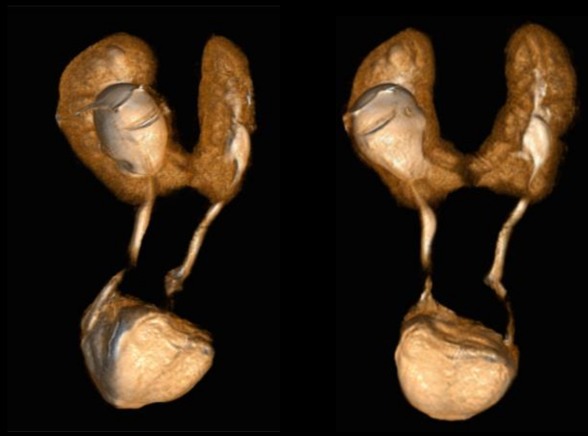
Multicystic Dysplastic Kidney

3D VR

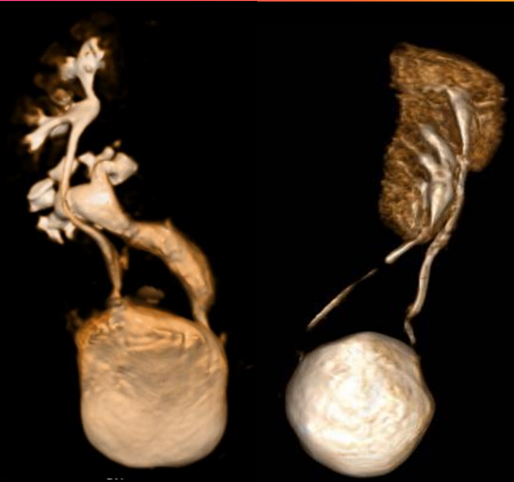
Tuberous sclerosis (ADPKD)



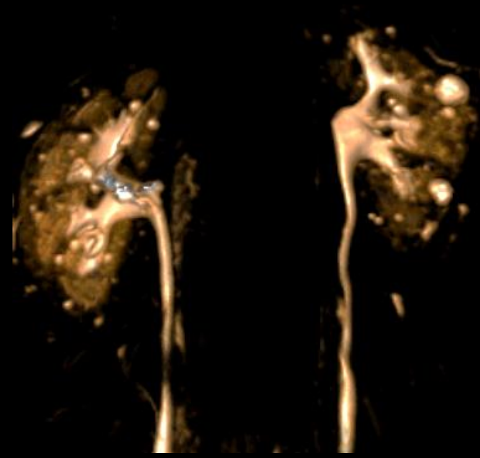
Ren arcuatus



Crossed ectopia



ADPKD

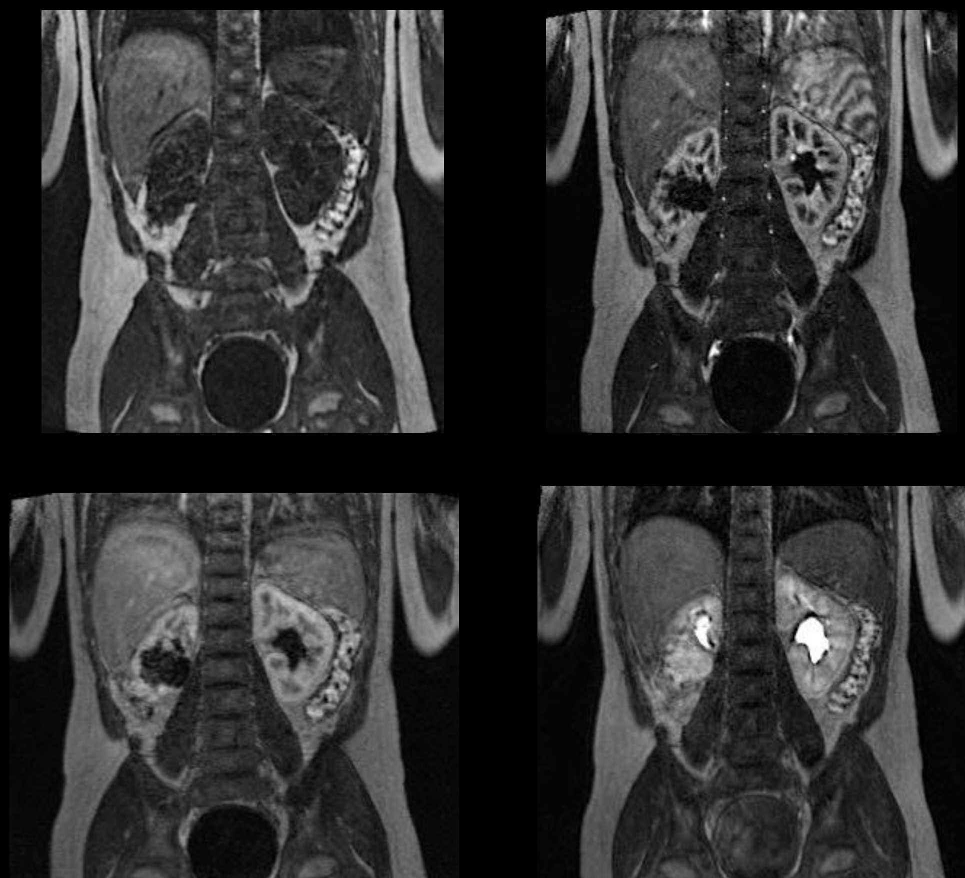


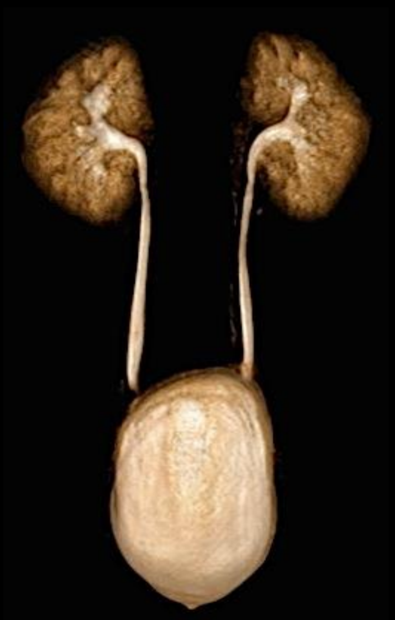
Postcontrast MRU

Postcontrast "Dynamic" imaging allows assessment of renal perfusion, quality of parenchymal enhancement;

- *These images are used for <u>formal functional analysis (fMRU)</u>*

Function !?





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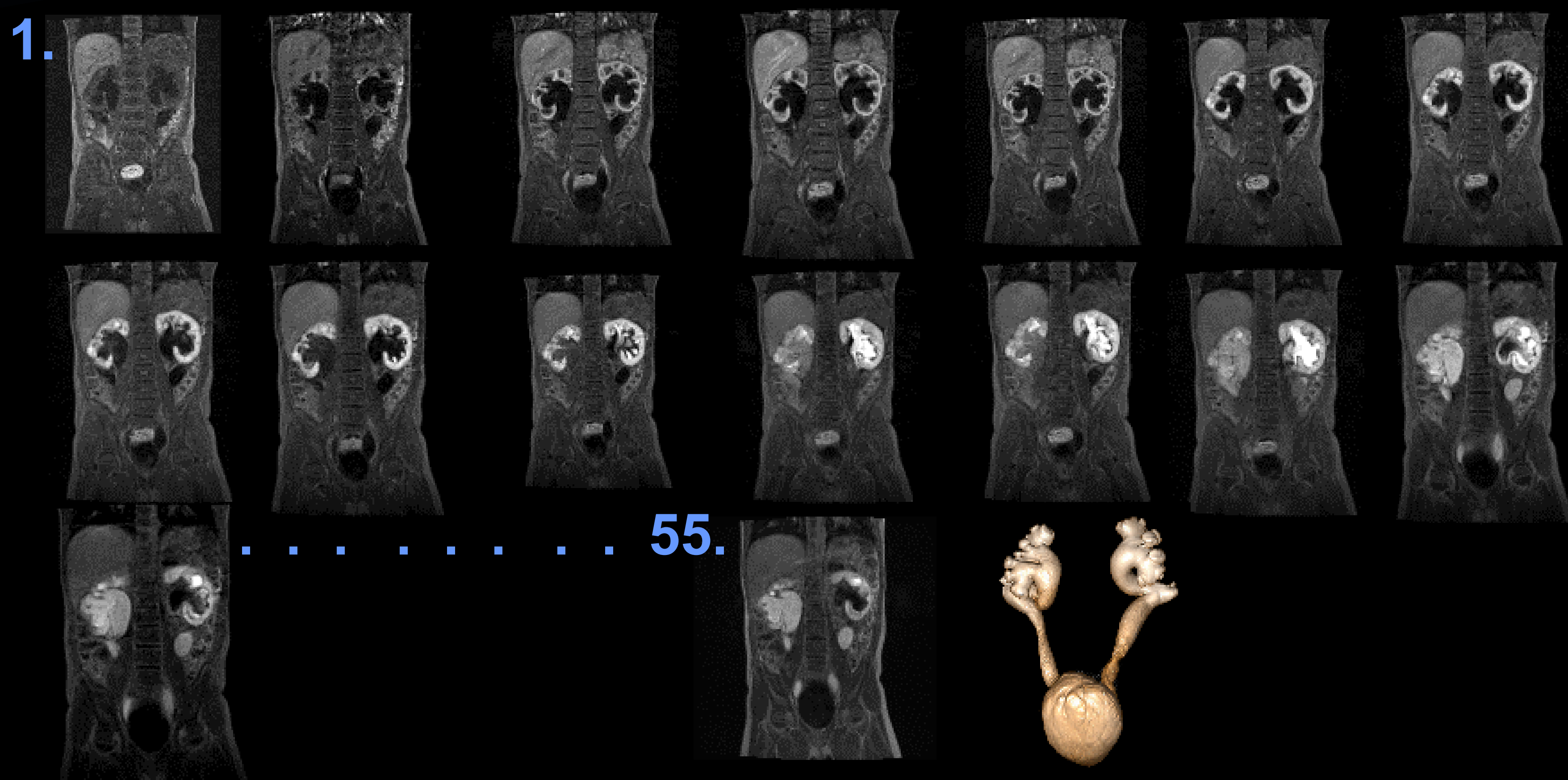
fMRU (functional MRU)

Post-contrast dynamic imaging:

- **Based on** acquisition of **55 3D** gradient-recalled echo (GRE) imaging volumes through kidneys & urinary tract



Coronal 3-D T1 GRE sequence with fat saturation [VIBE], dynamic,
(55 repetitions) (TR/TE 3.63/1.23, 2 mm, matrix 256 ×168)

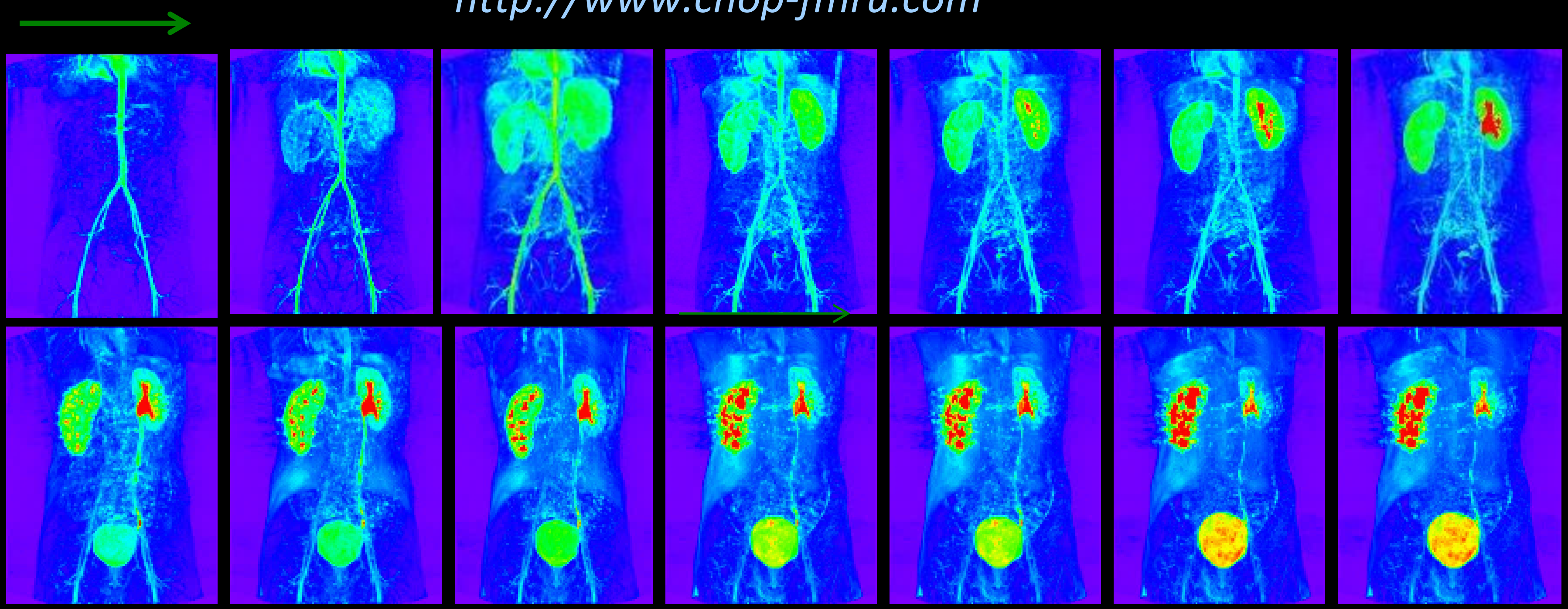
fMRU (functional MRU)

Post-contrast dynamic imaging:

Automated functional analysis

CHOP-fMRU

http://www.chop-fmru.com



Khrichenko D, Darge K. Functional analysis in MR urography - made simple. Pediatr Radiol 2010;40(2):182–199.

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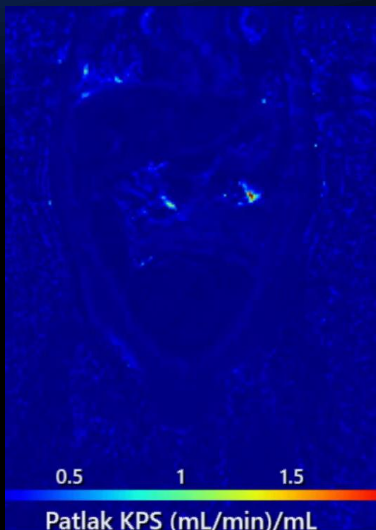
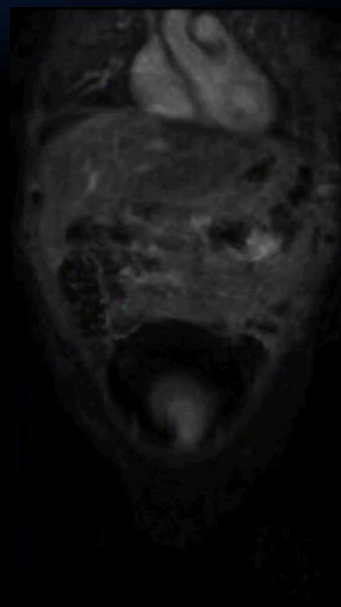
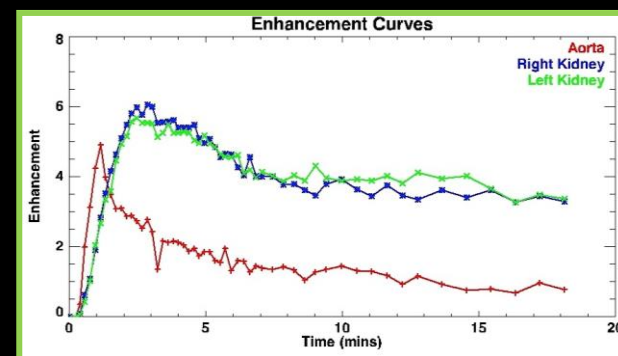
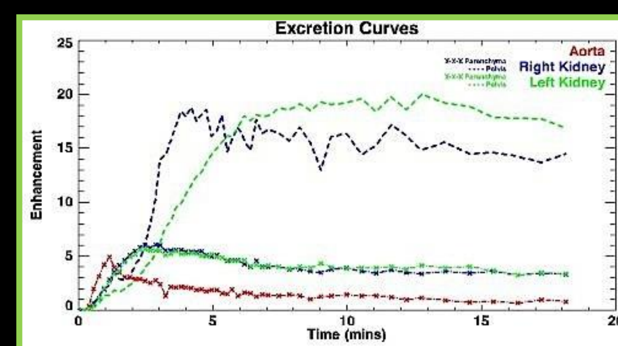
Automated functional analysis

CHOP-fMRU









	Right Lower Pole	Right Upper Pole	Total Right	Left Kidney
CTT [min, sec]	3m 31s	3m 31s		3m 5s
RTT [min, sec]	4m 37s	5m 30s		5m 3s
TTP [min, sec]	6m 9s	5m 16s		4m 50s
Volume [mL]	26,31	20,59	46,90	37,70
vDRF [%]	31,10	24,34	55,44	44,56
pDRF [%]	31,23	32,87		35,90
vpDRF [%]	28,81	23,74	52,55	47,45
Patlak [(mL/min)/mL]	0,30646	0,32257		0,35222

goran.roic@kdb.hr

Hydroureteronephrosis

fMRU

	Right Kidney	Left Kidney
1. CTT	2min(s) 33sec(s)	2min(s) 46sec(s)
2. RTT	5min(s) 20sec(s)	10min(s) 28sec(s)
3. TTP	2min(s) 5sec(s)	3min(s) 0sec(s)
4. Whole Volume(mL)	52.40mL	63.07mL
5. Parenchymal Vol(mL)	21.35mL	7.328mL
6a. vDRF	74.45%	25.54%
6b. pDRF	56.98%	43.01%
6c. vpDRF	79.42%	20.57%
7. Difference vDRF pDRF	17.46%	17.46%
8. Patlak(mL/min)/mL	0.57203	0.43184
9. BSA Patlak(mL/min)/mL	1.77359	1.33895

Conclusions

Take home

- IVU & MSCT - NOT routine in childhood

- **ceVUS** - highly reliable in diagnosis of VUR
- **Focused r. sonogr.:** echomorphology of r.parenchyma
- **CEUS**:
  - *focal lesions of kidney parenchyma*
  - *kidney trauma*
  - *assessment of chemotherapy response*
  - *problem solving*
- **MRU - fMRU** one-stop morphologic & functional imaging modality of urinary tract in children

ONE STOP SHOP

♥ Absence of ionizing radiation !

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

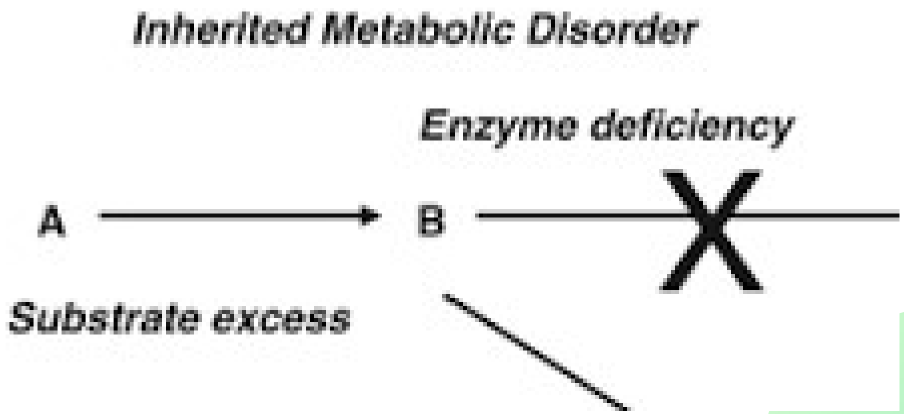
PEDIATRIC NEPHROLOGIST AND INHERITED METABOLIC DISEASES

Jovana Putnik

Why are they so difficu

- Inborn Errors of Metabolism (IEM) include a group of rare genetically transmitted disorders in which a block in a metabolic pathway, result either in

  - product deficiency or
  - accumulation of substrate or toxic metabolites

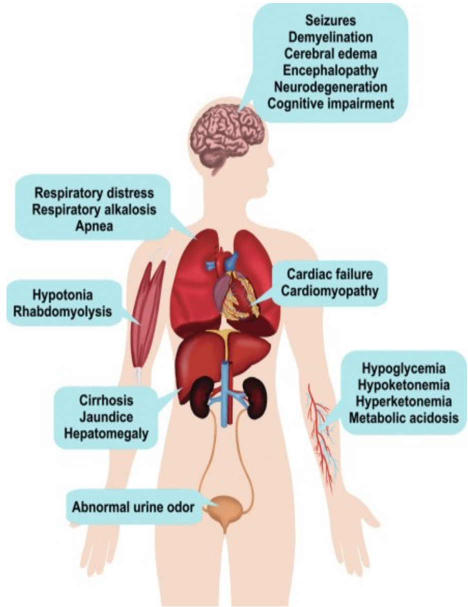


- Usually involve multiple organ systems
- Clinical manifestations can appear at any age group,
  but the most of these disorders are recognized in pediatric age
- Some of these patients never rich the adult age
  and never meet the adult nephrologist

Why are they so difficu

- Inborn Errors of Metabolism (IEM) are characterized by a significant heterogeneity in pathophysiological mechanisms and non specific clinical manifestations

- vomiting
- failure to thrive
- seizures
- encephalopathy
- hypotonia
- mental retardation
- organomegaly
- jaundice
- cardiomyopathy
- hearing loss
- ocular disturbance



- metabolic acidosis
- hyperlactatemia
- hypoglycaemia
- electrolyte disturbances
- hyperammonaemia
- ketonuria

Urine color

red	Porphyria
blue green	Hartnup disease
black	Alkaptonuria

Urine odor

marple syrup	MSUD
sweaty feet	Isovaleric academia

ROLES OF THE NEPHROLOGIST

- The nephrologist's role in the diagnosis and treatment of the metabolic disorders varies and depends of the underlying disease

- **One and only**
  - when kidney is only affected organ (cystinuria)

- **The first-line doctor**
  - kidney manifestations are first recognisable (primary hyperoxaluria)

- **Equal among equals** - kidney involvement is part of the phenotype (MMA, Glycogenosis, Cystinosis, Zellweger syndrome, OXPHOS)

ROLES OF THE NEPHROLOGIST

- **Ready to help** - Diseases in which kidney is intact, but the urgent help of the nephrologist in the evacuation of the toxic supstrate or metabolite is occasionaly necessary (hyperammonemia in urea cycle disorders, branched-chain amino acids accumulation in MSUD)

These metabolic disturbances are ussually recognised at the time of the diagnosis or during the episodes of the acute metabolic decompensations due to infectiones or when the nutritional restrictions were not followed

Why are they so difficu

- The kidney is a target organ in several inherited metabolic diseases:

  - organic acidemias
  - aminoacidemias
  - carbohydrate disorders
  - lysosomal
  - purine and pyrimidine
  - mitochondrial disorders

- The most frequent associated specific kidney disorders are:

  - Fanconi syndrome
  - nephrolithiasis/nephrocalcinosis
  - tubulointerstitial disorders
  - glomerular disorders
  - renal cysts
  - CAKUT
  - CKD

FANCONI SYNDROME

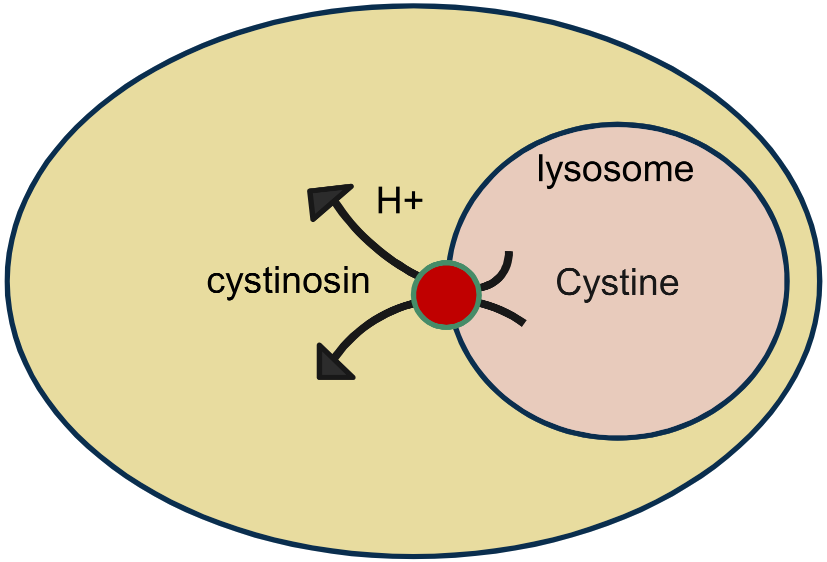
ONSET	DIAGNOSIS	INHERITANCE	ASSOCIATED FEATURES
Neonatal	Galactosemia	AR	Jaundice, sepsis, encephalopathy, cataract
	Tyrosinemia	AR	Poor growth, hepatic enlargement and dysfunction
	Mitochondrial disorders	MI, AR, XL	Multisystem dysfunction (brain, muscle, heart, liver)
Infancy	Cystinosis	AR	Poor growth, blond hair, rickets, corneal cystine crystals
	Fructose intolerance	AR	Vomiting, hypoglycemia, hepatomegaly
	Lowe syndrome	XLR	Cataract, hypotonia, developmental delay
	Glycogen storage disease type I	AR	Poor growth, hypoglycemia, hepatomegaly, lactic acidosis, neutropenia + nephrocalcinosis
Childhood	Wilson's disease	AR	Hepatic and neurological disease, Kayser-Fleisher rings

CYSTINOSIS

Autosomal recessive disorder

CTNS gene 17p13 – cystinosin which mediates cystine transport out of lysosome

Defective transport leads to increased lysosomal cystine accumulation



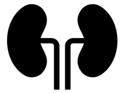
INFANTILE NEPHROPATHIC CYSTINOSIS

Normal at birth

Median age of onset -10 months

Vomiting
Excessive thirst
Polyuria
Poor weight gain or weight loss

Blond hair
Severe short stature
Rickets (frontal bossing, rosary)


Fanconi syndrome


Hypothyroidism, DM
Hypogonadism


in 2nd -3rd decade

Why are they so difficu

CYSTINOSIS- diagnosis

Corneal crystals - slit lamp
(photophobia, visual impairment)

Cystine crystals
bone marrow, lymph nodes, kidney

Biochemical diagnosis
cystine level measurement (WBC, fibroblasts)

Molecular diagnosis
+ genetical counselling

CYSTEAMINE

- approved 30 years ago

- reduces the intra-lysosomal cystine concentration
- very efficiently clears the cystine from the cells

Changed natural history by delaying clinical manifestations

- It is not a cure
- doesn't prevent the Fanconi syndrome even if started very early in life

NEPHROLITHIASIS/NEPHROCALCINOSIS

ONSET	DISEASE	INHERITANCE	ASSOCIATED FEATURES
Infancy	Hyperoxaluria type 1 Hereditary orotic aciduria	AR AR	Rethinopathy, pathological fractures, heart block Megaloblastic anemia, immunodeficiency, failure to thrive
Childhood	Hyperoxaluria type 1, 2, 3 Cystinuria Lesh Nyhan syndrome Xanthinuria	AR AR XLR AR	As above or less Only stones Developmental delay, self mutilation, spasticity, choreo-athetoid movements Myopathy, arthropathy
Adulthood	Alkaptonuria Hereditary renal hypouricemia	AR AR	

LESH NYHAN SYNDROME

Rare inborn error of purine metabolism

X-linked recessive disease

Caused by the absence or a deficient activity of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT)

Hyperuricemia/hyperuricosuria

kidney stones
impaired kidney function

acute gouty arthritis

neurological impairment
self-mutilating behaviour
lip and finger biting
head banging

involuntary movements
muscle spasticity

TREATMENT

- Alopurinol
  - prevention of urolithiasis and gouthy artritis
  - doesn't prevent neurological manifestationes
- Self injury prevention
  - protective devices (splint, mouthguard)
  - tooth extraction
  - immobilization
- Antispasmodic agents (baclofen)

OUR PATIENTS

2 months - “orange sand” in the diapers

up to 3rd months - normal psychomotor development

5 months- Cerebral palsy, Spastic quadriparesis with extrapyramidal signs

3 years-Bit his lower lip

6 years- haematuria and vomiting
AKI, nephrolithiasis
hyperuricemia
(1500 $\mu mol/L$)

Genetic test
boy and mother
HPRT1 mutation (c.135-1G>A)

Younger brother healthy

New pregnancy after 3 years
Family refused prenatal genetic diagnosis

Newborn boy
Hyperuricemia and hyperuricosuria

Compete neurological symptomatology despite early allopurinol introduction

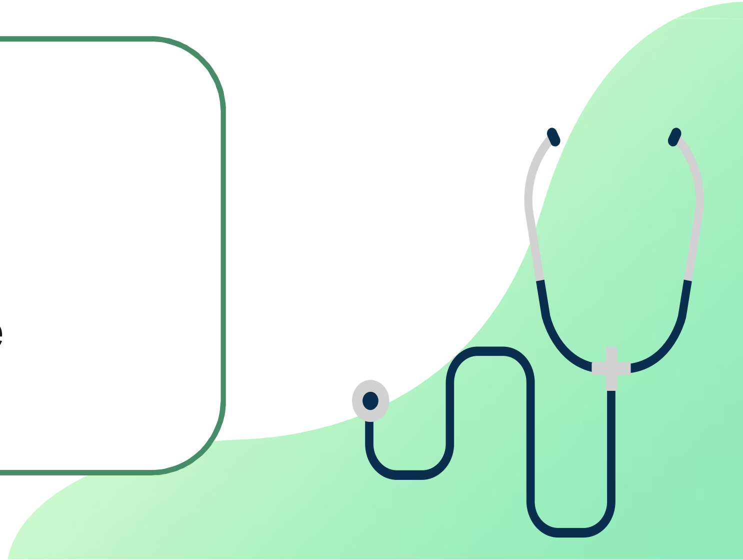
TUBULOINTERSTITIAL DISORDERS

ONSET	DIAGNOSIS	INHERITANCE	ASSOCIATED FEATURES
Infancy	Methylmalonic acidemia	AR	Vomiting, failure to thrive, recurrent metabolic acidosis, hypotonia, lethargy, hyperuricemia, CKD
	Propionic acidemia	AR	Vomiting, hypotonia, failure to thrive, hyperammonemic coma, encephalopathy, CKD
	Lysinuric protein intolerance	AR	Vomiting, failure to thrive, hepatosplenomegaly, immune dysfunction, encephalopathy

METHYLMALONIC ACIDURIA

- Rare and severe autosomal recessive disorder characterized by metabolic instability, multisystemic complications and high mortality

- Caused by deficiency of the
  - enzyme methylmalonyl-CoA mutase,
  - its cofactor (adenosyl-cobalamin)
  - enzyme methylmalonyl-CoA epimerase



MMA – CLINICAL MANIFESTATIONES

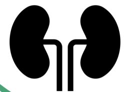
- Neonatal period
  - vomiting
  - lethargy
  - poor feeding
  - failure to trive
  - recurent metabolic acidosis
  - hyperuricaemia


intellectual deficiency
neurological impairment


optic neuropathy


chronic pancreatitis


osteopenia


CKD

MMA- KIDNEY DISEASE

- Accumulation of methylmalonate interfere with mitochondrial function
- HP: tubulointerstitial nephritis
- Renal tubular dysfunction during the episods of metabolic decompensation (triggered by infectiones)

- Progression into chronic tubulointerstitial nephritis and ESKD at young age
- Isolated kidney Tx may provide partial enzyme replacement and have safer outcome compared to liver Tx
- Combined liver kidney transplantation

GLOMERULAR DISORDERS

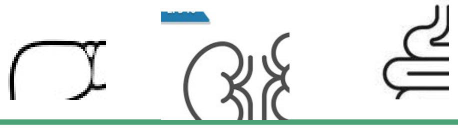
ONSET	DIAGNOSIS	INHERITANCE	ASSOCIATED FEATURES
Neonatal	Glycogen storage disease type IB	AR	Poor growth, hypoglycemia, neutropenia, hepatomegaly, lactic acidosis, IBD
Infancy	Mitochondrial disorders	MI AR XLR	Hypoptonia, hyperlactatemia, myocardiopathy, myopathy, deafness, macular dystrophy
Childhood	CoQ10 deficiency	AR	Myopathy, cardiomyopathy, liver failure, encepalopathy
	Hurler syndrome	AR	Coarse face, visceromegaly, developmental delay
Aduthood	Gaucher’s disease	AR	Hepatosplenomegaly, hypersplenism
	Fabry disease	XLR	Recurrent painful crisis, angiokeratoma, abdominal pain, cardiomyopathy

GLYCOGEN STORAGE DISEASE type 1b

Autosomal recessive inheritance

Defect in glucose-6-posphatase complex

Accumulation of glycogen in



Clinical manifestations and laboratory findings

Poor tolerance to fasting	**Hypoglycemia**
Hepatomegaly	Lactic acidosis
Growth retardation	Hyperuricemia
Recurrent infections	**Neutropenia**
IBD	

KIDNEY MANIFESTATIONS in GSD

Glomerular dysfunction

Hyperfiltration
Albuminuria
Proteinuria
Hypertension
CKD

Tubular dysfunction

Subclinical
Fanconi syndrome is rare
Nephrolithiasis due to hypercalciuria and hyperuricosuria
Gitelman-like syndrome

Ultrasound: kindney enlargement secondary to glycogen deposition

HP-focal and global GS, glycogen deposits in proximal tubules, glomerular enlargement

TREATMENT of GSD

Antiproteinuric and
Lipid lowering agents

Liver Tx prevents malignant changes in hepatic adenomas

Combined liver-kidney transplantation has been successful

Empagliflozin
- an inhibitor of the renal glucose transporter SGLT2

Beneficial effects

- on neutrophil dysfunction and its clinical consequences
- on reducing the cardiovascular risk and progression of kidney disease

RENAL CYSTS

ONSET	DIAGNOSIS	INHERITENC E	ASSOCIATED FEATURES
Neonatal	Glutaric aciduria type I	AR	Prematurity, hepatomegaly, hypotonia, odor, metabolic acidosis, hypoglicemia
Infancy	Zellweger syndrome	AR	Facial dysmorphism, hypotonia, severe developmental delay, hepatomegaly

Why are they so difficu

ZELLWEGER SYNDROME

Autosomal recessive disorder caused by mutations in PEX genes that cause peroxisomal dysfunction leading to the accumulation of VLCFA in the cells

neonatal hypotonia/seizures
feeding difficulties

sensorineuronal hearing loss

blindness

hepatomegaly

polycystic kidneys
nephrolithiasis (hyperoxaluria)

Craniofacial abnormalities:

- high forehead
- large fontanel
- midface hypoplasia
- hypoplastic supraorbital bridges
- epicanthal folds

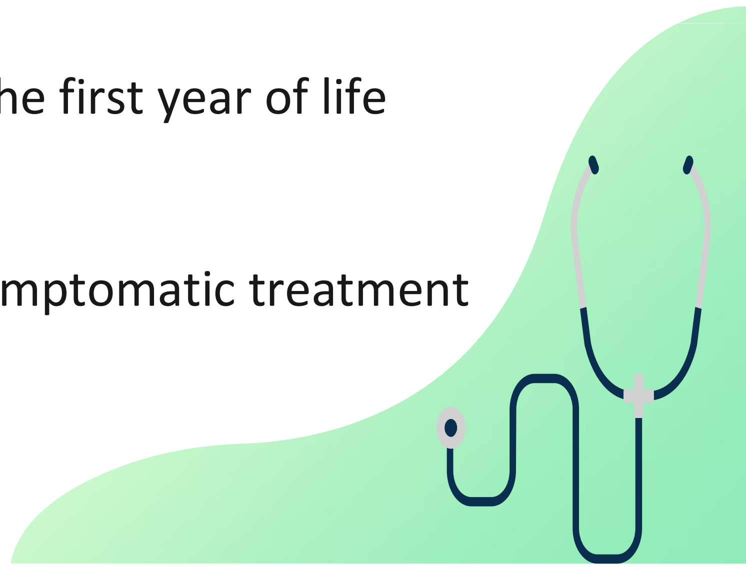
ZELLWEGER SYNDROME

- Diagnosis
  - increased levels of very long-chain fatty acids in the blood
  - genetic molecular testing

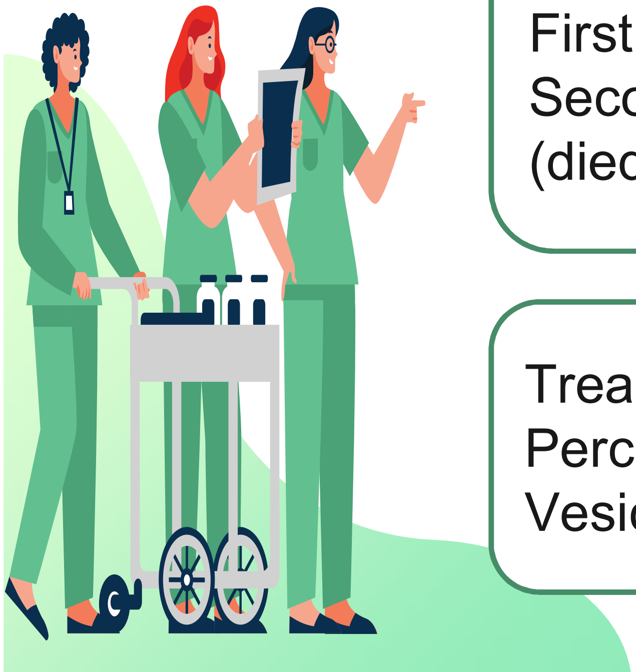
- Prognosis
  - poor prognosis, most infants expiring within the first year of life

- Treatment
  - currently no cure, only supportive care and symptomatic treatment

- Monitoring for hyperoxaluria



OUR PATIENT



10 years old boy
First child in family
Second child was born before proband's diagnosis
(died at the age of 3 years)

Treacheostoma - home mechanical ventilation
Percutaneous Endoscopic Gastrostomy - feeding
Vesicostomy - bladder catheterisation

CAKUT

ONSET	DIAGNOSIS	INHERITENCE	ASSOCIATED FEATURES
Infancy	Menke's disease	XLR	Kinky hair, mental regression, seizures, skin laxity
	Smith-Lemli-Opitz	AR	Facial dysmorphism, hypotonia, cataract, mental retardation, limbs abnormalities
	CHILD sydrome	XLR	**C**ongenital **H**emidysplasia**, I**chthyosiform erythroderma **L**imb **D**efects

RENAL TUBULAR ACIDOSIS

ONSET	DIAGNOSIS	INHERITENCE	ASSOCIATED FEATURES
Infancy	Carnitine palmitoyl transferase deficiency 1	AR	Fasting-induced hypoketotic hypoglycemia, liver failure. seizures, encephalopathy,
	Metachromatic leukodystrophy	AR	Neurologic and intellectual regression, ataxia, spasticity, optic atrophy

HUS

ONSET	DIAGNOSIS	INHERITENCE	ASSOCIATED FEATURES
Infancy	Cobalamine deficiencies	AR	Developmental delay, hydrocephalus, microcephaly, megalobalstic anemia, pancythopenia
	Methyl Tetrahidrofolate (MTHF deficiency)	AR	megalobalstic anemia, combined immune deficiency

MITOCHONDRIAL DISORDERS

Large group of diseases with heterogenous clinical features

Defects in the respiratory chain enzymes in mitochondria result in disturbed energy production

Myopathy, encephalopathy, seizures, ophthalmoplegia, retinopathy, cardiomyopathy, endocrinopathies, liver disease

Kidney manifestations

Proximal tubular cells have high energy consumption and are very rich in mitochondria

Fanconi syndrome
Isolated RTA
Low molecular weight proteinuria
Barter like syndrome

Primary glomerular disease

CONCLUSION

- Inborn errors of metabolism are rare, mostly severe and progressive.
- Nephrologist should consider a possibility of a metabolic disorder in every child with kidney disease and additional extrarenal symptoms. The recognition of specific patterns of kidney involvement must raise suspicion for an underlying inborn error of metabolism.
- Searching for kidney manifestations should be a necessary part of the routine follow-up of children with metabolic diseases. Due to mostly reduced muscle mass, serum creatinine is usually misleading marker of renal function. Other markers, such as cystatin C may be more reflective of GFR
- Early recognition and adequate treatment of inborn metabolic disorders could delay progression of the disease or even preserve the function of affected organs


THANK YOU !

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GREAT CARE FOR LITTLE KIDNEYS.

MEMBRANOUS GLOMERULONEPHRITIS IN BULGARIAN CHILDREN

Assoc. Prof. Maria Gaydarova, M.D., Ph.D

Department of Pediatric nephrology and dialysis,
Specialized Children's Hospital „Prof. Dr. Ivan Mitev“,
Sofia, Bulgaria

Faculty of Medicine, Medical University Sofia, Bulgaria

Disclosure:

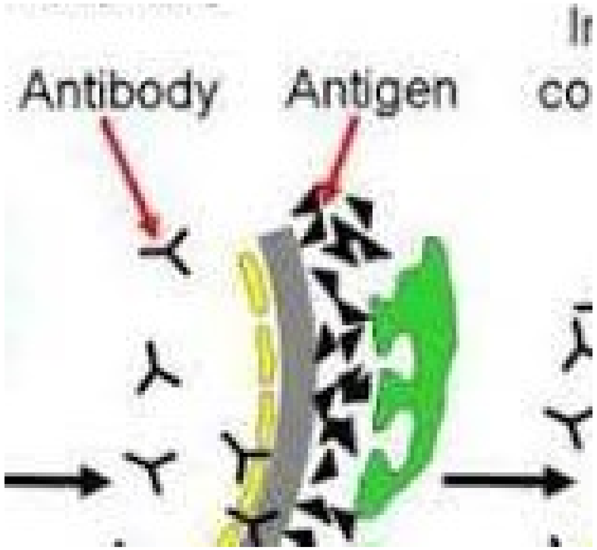
- Assoc. Prof. Gaydarova , M.D., Ph.D. reports:

- I have no financial disclosure or conflicts of interest with the presented material in this presentation.

- Advisory board, advisory committee, consultancy: no

- Research/investigator grants: no

Membranous nephropathy



- Glomerular disease that mainly affects adults
- In children, it is a rare disease, and its diagnosis is currently made on a biopsy indicated because the atypical clinical presentation and/or outcome under steroid therapy.
- Characterized by the accumulation of immune deposits on the subepithelial (outside) aspect of the glomerular capillary wall, which causes a membrane-like thickening with the formation of spikes.
- The immune deposits consist of immunoglobulin (Ig) G, of antigens that have long eluded identification, and of the membrane attack complex of complement.

Safar-Boueri L, Piya A, Beck LH Jr, et al. Membranous nephropathy:diagnosis, treatment, and monitoring in the post-PLA2R era. Pediatr Nephrol.

International Pediatric Nephrology Associati
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Incidence and prevalence

Historically, while in adults its incidence was found to be 1.2/100.000/year, in children it was 0.1/100.000/year.

The incidence of MN is rising steadily in the last 10–15 years.

Its frequency as the underlying cause of NS steadily increases with age from about

- 1–2% at ages 1–5 years of age
- 5% at 10 years of age
- 10% at 15 years of age
- 18–22% at 18–20 years of age.

Because many pediatric patients with steroid-sensitive nephrotic syndrome are never biopsied, the relative prevalence of MN versus MCD and FSGS is unclear.

In terms of gender, while in adults primary MN is more frequent in males compared to females, in children, the frequency is very similar between genders.

Safar-Boueri L, Piya A, Beck LH Jr, et al. Membranous nephropathy:diagnosis, treatment, and monitoring in the post-PLA2R era. Pediatr Nephrol. 2019
Liu A, Wu H, Su Y, et al. Idiopathic membranous nephropathy in children in China. Fetal Pediatr Pathol. 2015;34:185–9.

CLINICAL EPIDEMIOLOGY www.jasn.org

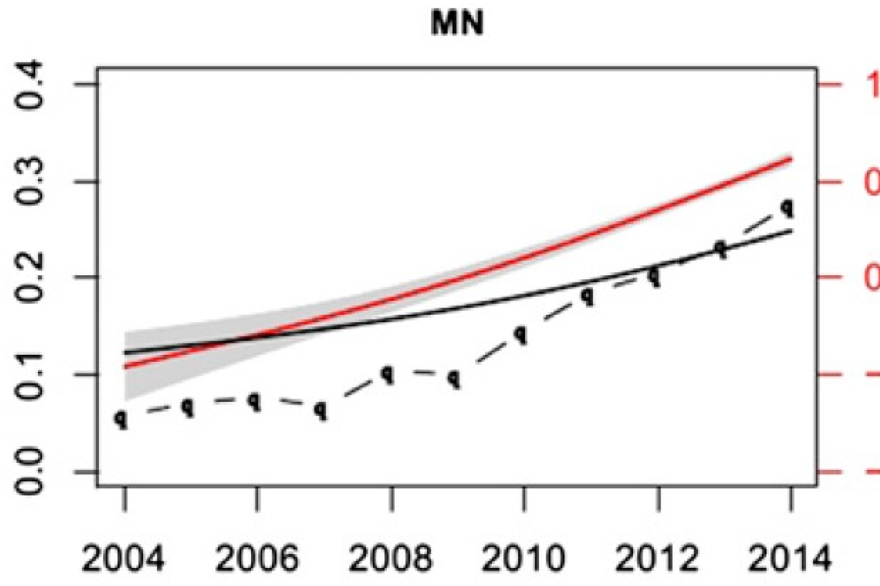
IPNA International Pediatric Nephrology
GREAT CARE FOR LITTLE KIDNEYS. E

Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China

Xin Xu,* Guobao Wang,* Nan Chen,† Tao Lu,* Sheng Nie,* Gang Xu,‡ Ping Zhang,§ Yang Luo,‖ Yongping Wang,* Xiaobin Wang,¶ Joel Schwartz,** Jian Geng,††‡‡ and Fan Fan Hou*

The adjusted odds for MN in adults rose 13% annually over the 11-year period, and that long-term exposure to high levels of pollution, quantified as fine particulate matter <2.5 µ, increased the risk of MN.

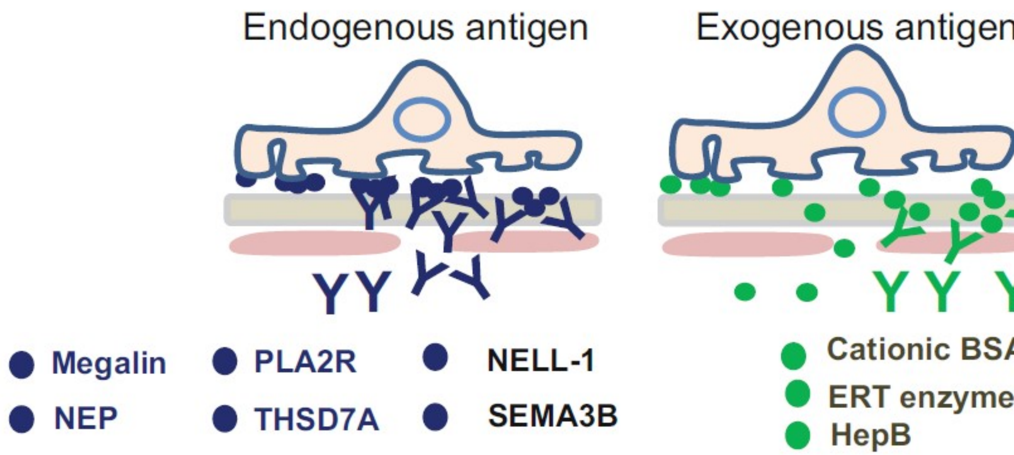
Within the same study population, a subsequent study focused on children showed a rise in prevalence of MN from 3% of pediatric glomerular diseases in 2004 to 7% in 2014.



X. Xu et al., “Long-term exposure to air pollution and increased risk of membranous nephropathy in China,” J. Am. Soc. Nephrol., vol. 27, no. 12, pp. 3739–3746, 201

Pathophysiology

Intrinsic and Extrinsic Podocyte Antigens



- The discovery of target antigens has introduced an additional layer of heterogeneity as membranous nephropathy can now be defined molecularly by serological studies of antibody or by biopsy staining of antigen.
- This has major implications for the care of patients with membranous nephropathy as they drive the etiolog investigations and provide invaluable markers for treatment monitoring.
- These antigens are age-dependent, i.e., each antigen has a specific prevalence according to age.
- Identification of these antigens has reduced the number of “idiopathic” cases of MN and elucidated the link between certain diseases (cancer, SLE) and MN.

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GREAT CARE FOR LITTLE KIDNEYS. E

1959

1982

Production of Nephrotic Syndrome in Rats by Freund's Adjuvants and Rat Kidney Suspensions.* (24736)

WALTER HEYMANN, DONALD B. HACKEL, SARGENT HARWOOD, SYDNEY G. F. WILSON AND JANET L. P. HUNTER
Babies and Children's Hospital, and Cleveland Metropolitan General Hospital, Western Reserve University School of Medicine, Cleveland, O.

The pathogenic antigen of Heymann nephritis is a membrane glycoprotein of the renal proximal tubule brush border

(experimental glomerulonephritis/nephritogenic antigen/immunocytochemistry)

DONTSCHO KERJASCHKI AND MARILYN GIST FARQUHAR
Section of Cell Biology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510

Communicated by George E. Palade, May 27, 1982

It has been shown that renal disease produced in rats by intravenous injection of anti-rat kidney serum obtained from rabbits simulates the nephrotic syndrome as observed in infants and children(1). This observation has stimulated the view that the disease in man may be due to an antigen-antibody reaction. The following suggestive evidence supports this hypothesis: 1) It has been noted that in nephrotic patients complement activity in blood serum is decreased(2,3), and 2) Increased deposition of globulins has been noted in the glomerular structures of nephrotic kidneys(4). Even though heteronephrotoxic antibodies have been shown to induce the ne-

* Supported by grant from Nat. Inst. of Health, U. S. P. H. S.

antigenic component is released from intact microvilli by trypsi
By immunoperoxidase staining it was localized to the luminal sid
of the brush border membranes. These results indicate that
gp330 is the pathogenic antigen of HN; (*ii*) the antigen is a gl
coprotein of the brush border membrane; and (*iii*) it is dispose
with its pathogenic domain(s) facing the tubule lumen.

Heymann W, Hackel DB, Harwood S, et al. Production of nephrotic syndrome in rats by Freund's adjuvants and rat kidney suspensions. Proc Soc Exp Biol Med. 1959;100:660–
Kerjaschki D, Farquhar MG. The pathogenic antigen of Heymann nephritis is a membrane glycoprotein of the renal proximal tubule brush border. Proc Natl Acad Sci U S A. 198

2002

ANTENATAL MEMBRANOUS GLOMERULONEPHRITIS DUE TO ANTI–NEUTRAL ENDOPEPTIDASE ANTIBODIES

HANNA DEBIEC, PH.D., VINCENT GUIGONIS, M.D., BÉATRICE MOUGENOT, M.D., FABRICE DECOBERT, M.D., JEAN-PHILIPPE HAYMANN, M.D., ALBERT BENSMAN, M.D., GEORGES DESCHÊNES, M.D., PH.D., AND PIERRE M. RONCO, M.D., PH.D.

two proteins are expressed on the human podocyte.[5,6]

In this article, we report that anti–neutral endopeptidase antibodies produced by a pregnant woman were transferred to her fetus, in which a severe form of membranous glomerulonephritis developed prenatally. The mother had a deficiency of neutral endopeptidase and probably had become immunized against the antigen at the time of or after an earlier miscarriage.

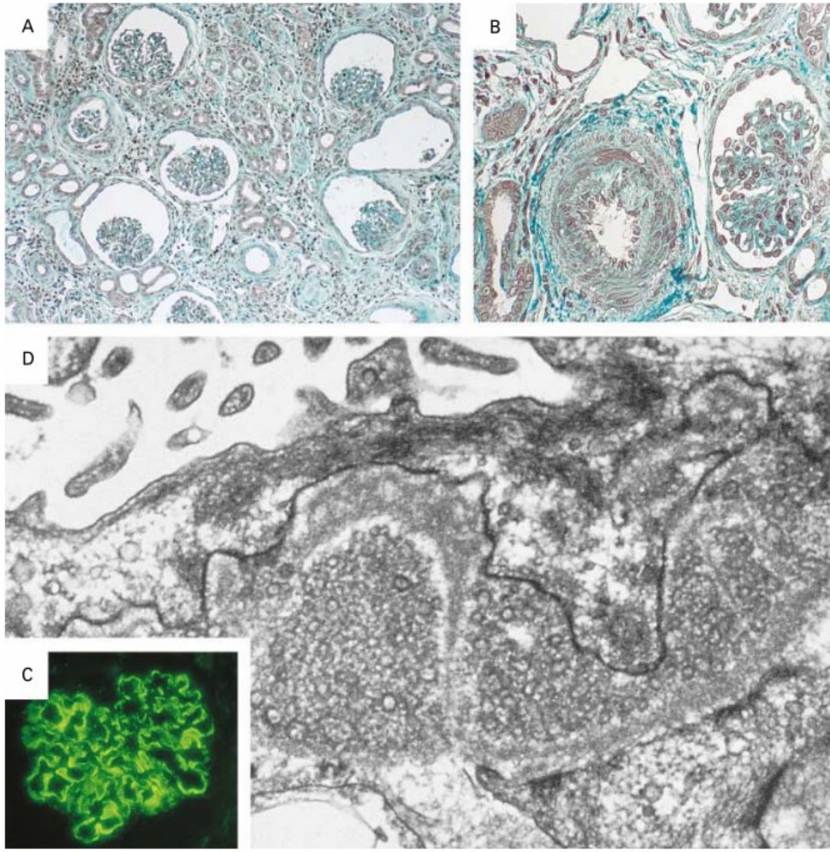

Figure 1. Renal-Biopsy Specimen Obtained from the Infant at Four Weeks.

Debiec H, Guigonis V, Mougenot B, et al. Antenatal membranous glomerulonephritis due to anti neutral endopeptidase antibodies. N Engl J Med. 2002;346(26):2053–60.

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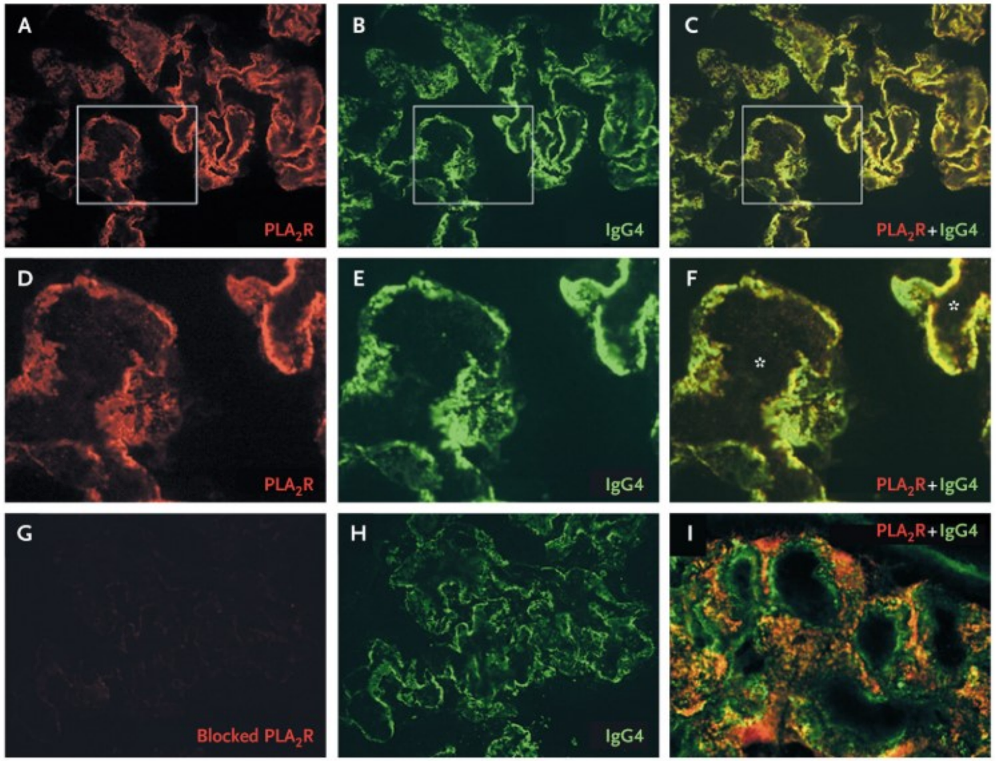
2009

ORIGINAL ARTICLE

M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.



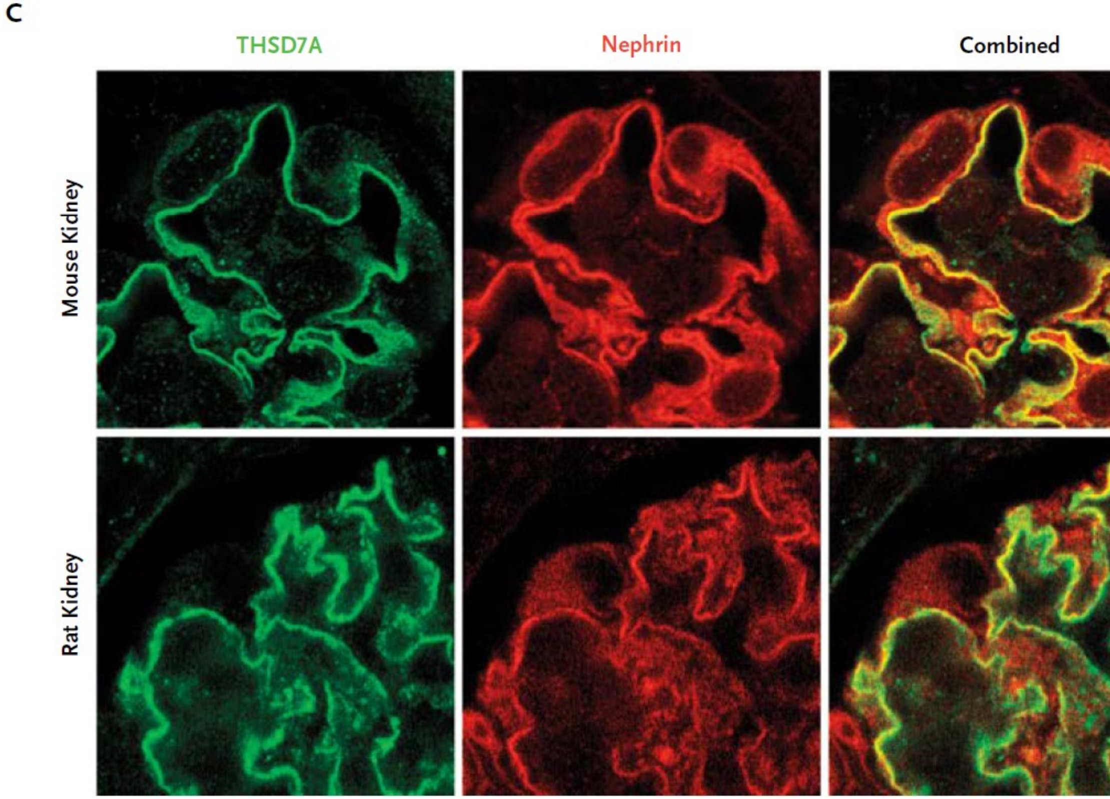
Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):11–21.

2014

ORIGINAL ARTICLE

Thrombospondin Type-1 Domain-Containing 7A in Idiopathic Memb Nephropathy

Nicola M. Tomas, M.D., Laurence H. Beck, Jr., M.D., Ph.D., Catherine Meyer-Schwesinger, M.D., Barbara Seitz-Polski, M.D., Hong Ma, Zahner, Ph.D., Guillaume Dolla, M.S., Elion Hoxha, M.D., Udo Helmchen, M.D., Anne-Sophie Dabert-Gay, Ph.D., Delphine Debayle, P Merchant, Ph.D., et al.

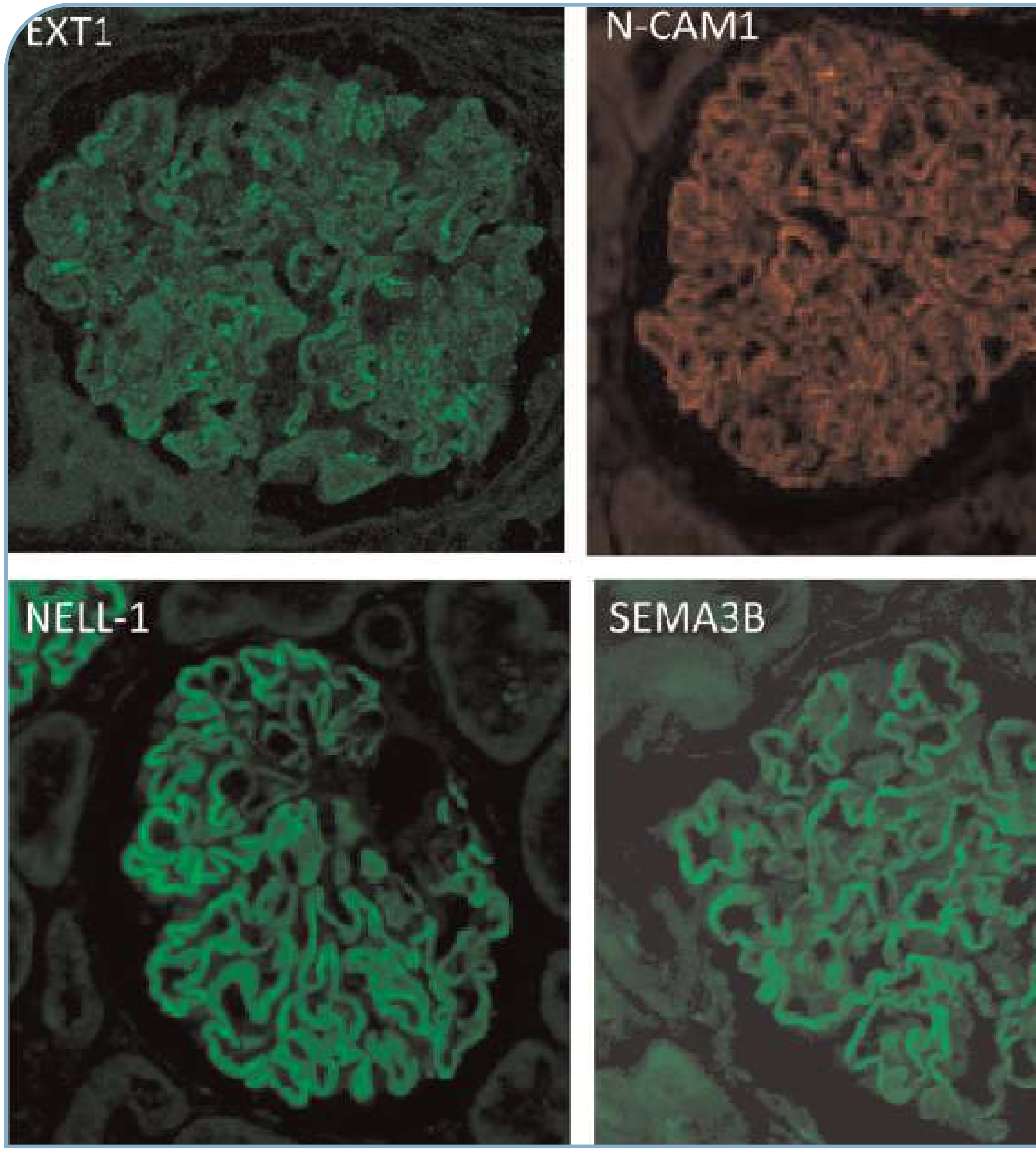


Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopa membranous nephropathy. N Engl J Med. 2014;371(24):2277–87.

2019: ANOTHER TURN IN THE DISCOVERY OF MEMBRANOUS NEPHROPATHY

LASER MICRODISSECTION OF GLOMERULI AND MASS SPECTROMETRY

New antigens, which were localized by immunohistochemistry - **exostosins 1 and 2 (EXT1/2), neural epidermal growth factor-like 1 protein (NELL-1), semaphorin 3B (Sema3B), and neural cell adhesion molecule 1 (NCAM1)**



Sethi S, Madden BJ, Debiec H, et al. Exostosin 1/Exostosin2-associated membranous nephropathy. J AmSoc Nephrol. 2019;30(6):1123–36.
P. Ronco and H. Debiec, "Membranous nephropathy: Current understanding of various causes in light of new target antigens," *Curr. Opin. Nephrol. Hypertens.*, vol. 30, no. 3, pp. 287–293, 202

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ORIGINAL ARTICLE

Early-Childhood Membranous Nephropathy Due to Cationic Bovine Serum Albumin

Hanna Debiec, Ph.D., Florence Lefe

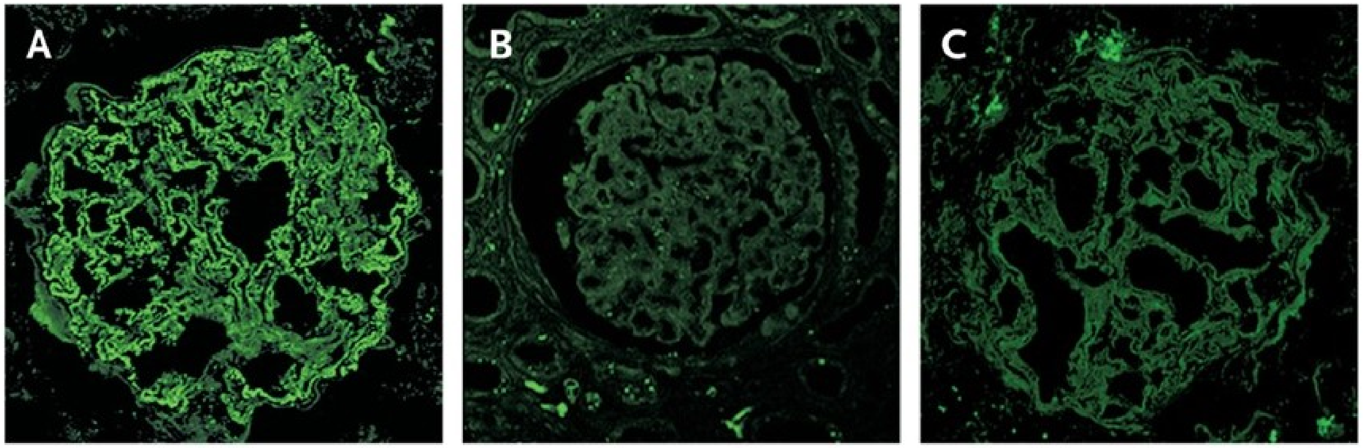
Nephrotic syndrome complicating alpha-glucosida replacement therapy for Pompe disease

Tracy E Hunley [1], Deyanira Corzo, Martha Dudek, Priya Kishnani, Andrea Amalfitano, Yuan-Tsong Chen, Susan M Richards, John A Phillips 3rd, Agnes B Fogo, George E Tiller

With cBSA and Anti-BSA

Without cBSA, and with or without Native BSA, and Anti-BSA

BSA



Debiec H, Lefeu F, Kemper MJ, et al. Early-childhood membranous nephro cationic bovine serum albumin. N Engl J Med. 2011;364(22):2101–10.
Hunley TE, Corzo D, Dudek M, et al. Nephrotic syndrome complicating alp glucosidase replacement therapy for Pompe disease. Pediatrics. 2004;114

Secondary forms

In children > 2 and below the age of 10–12 years, MN tends to be more frequently secondary

Infections	Autoimmune	Medications	Neoplasia	Other
Hepatitis B	SLE	Gold	Ovarian tumor	Sickle cell hemoglobinopathies (SS and SA)
Hepatitis C	Sjogren's	Penicillamine	Neuroblastoma	De novo; post-renal transplant
Streptococcal infections	Primary biliary cirrhosis	NSAIDS	Angiomatoid fibrous histiocytoma	Mercury
Tuberculosis	Autoimmune hepatitis	Captopril		
Syphilis	Sarcoidosis	Infliximab		
CMV		Etanercept		
EBV		Tiopronin		
Malaria				

PRIMARY VERSUS SECONDARY MEMBRANOUS NEPHROPATHY: SHIFTING FROM ETIOLOGICA SEROLOGICAL CLASSIFICATION

	PLA2R1	THSD7A	EXT1/EXT2	NCAM1	NELL-1	Sema3B
UniProt ID	Q13018	Q9UPZ6	Q16394, Q93063	P13591 (120 kDa isoform)	Q92832	Q13214
Size (in amino acids)	1463	1657	746, 718	858	810	749
Compartment	Transmembrane glycoprotein	Transmembrane glycoprotein	Glycosyltransferase in Golgi and secreted	Transmembrane glycoprotein	Secreted	Secreted
Evidence for expression by podocyte	Strong	Strong	**Moderate (EXT2 > EXT1)**	**Weak if any**	**Weak**	Strong Sema3A **??? Sema3B**
Presence in subepithelial deposits	Yes	Yes	Yes	Yes	Yes, **often segmental**	Yes
Circulating Ab	Yes	Yes	**No**	Yes	Yes	Yes, **reduced Ag**
Predominant subclass in deposits	IgG4	IgG4	**IgG1**	**IgG1 +/− other subclasses**	**IgG1**	**IgG1 / not IgG4**
Distinctive associations	Prototype for primary MN	Malignancy in a minority of cases	**Lupus (#30%) or other systemic autoimmune disease**	**Lupus (#7%)**	**Association with malignancy (NELL-1 in tumor cells)**	**Pediatric MN; early onset**

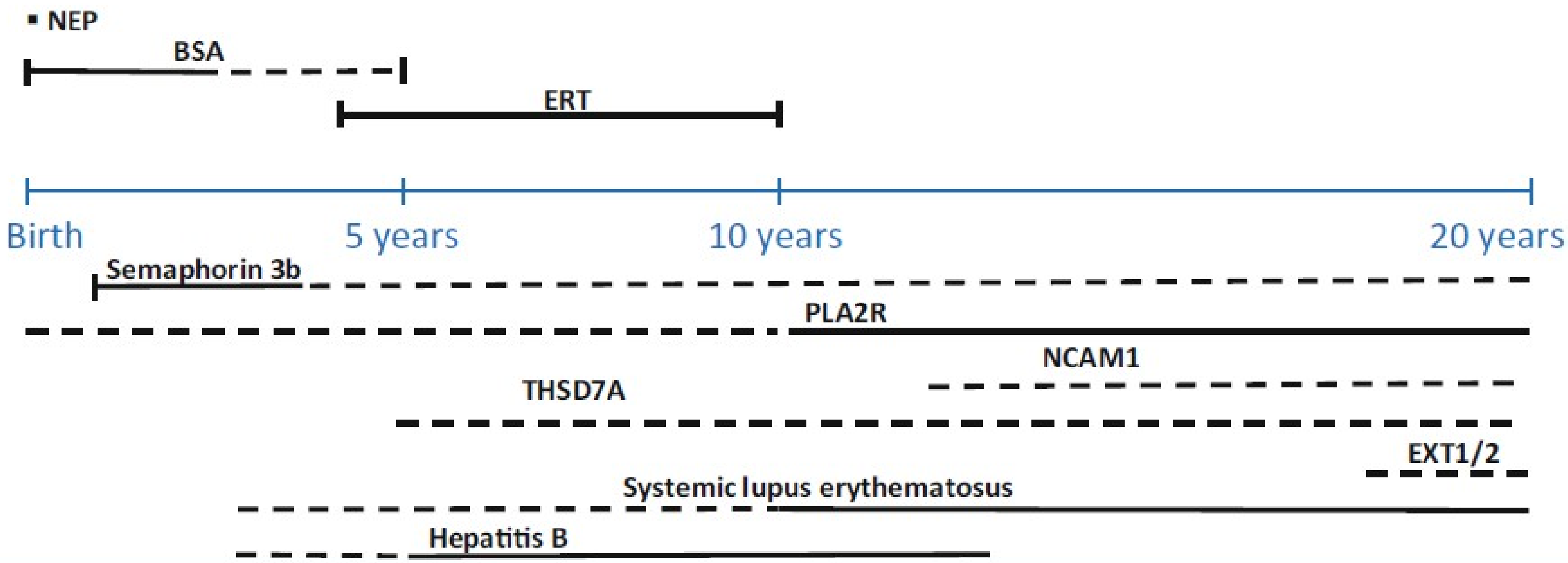
P. Ronco and H. Debiec, "Membranous nephropathy: Current understanding of various causes in light of new target antigens," *Curr. Opin. Nephrol. Hypertens.*, vol. 30, no. 3, pp. 287

Primary MN- when the disease is associated serologically with antibodies to a known podocyte antigen.

Iopathic MN is referred to cases in which the target antigen is yet unknown and serum antibodies are not recognizable and the disease does not appear to be secondary.

Secondary MN is identif
when the histologic lesio
MN can be associated w
other systemic illness o
exposures and the
management relies prima
on treatment of the underl
cause of disease.

Upon diagnosis of MN: consider the age of the patient to formulate an appropriate search for likely causes



HBV, SLE, other systemic disease, drugs, cancer: manage specifically based on etiology

Safar-Boueri L, Piya A, Beck LH Jr, et al. Membranous nephropathy:diagnosis, treatment, and monitoring in the post-PLA2R era. Pediatr Nephrol. 20

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Gene Polymorphisms and Risk of Primary MN

ORIGINAL ARTICLE

Risk HLA-DQA1 and PLA_2R1 Alleles in Idiopathic Membranous Nephropathy

Horia C. Stanescu, M.D., Mauricio Arcos-Burgos, M.D., Ph.D., Alan Medlar, M.Sc., Detlef Bockenhauer, M.D., Ph.D., Anna Kottgen, M.D., M.P.H., Liviu Dragomirescu, Ph.D., Catalin Voinescu, B.Sc., Naina Patel, B.Sc., Kerra Pearce, M.Sc., Mike Hubank, Ph.D., Henry A.F. Stephens, Ph.D., Valerie Laundy, F.I.M.L.S., Sandosh Padmanabhan, M.D., Ph.D., Anna Zawadzka, Julia M. Hofstra, M.D., Marieke J.H. Coenen, Ph.D., Martin den Heijer, M.D., Ph.D., Lambertus A.L.M. Kiemeney, Ph.D., Delphine Bacq-Daian, M.Sc., Benedicte Stengel, M.D., Ph.D., Stephen H. Powis, Ph.D., F.R.C.P., Paul Brenchley, Ph.D.,

Interaction between PLA2R1 and HLA-DQA1 Variants Associates with Anti-PLA2R Antibodies and Membranous Nephropathy

Jicheng Lv, Wanyin Hou, Xujie Zhou, Gang Liu, Fude Zhou, Na Zhao, Ping Hou, Minghui Zhao, and Hong Zhang

Renal Division, Department of Medicine, Peking University First Hospital; Peking University Institute of Nephrology; Key Laboratory of Renal Disease, Ministry of Health of China; and Key Laboratory of Chronic Kidney Disease Prevention and Treatment, Peking University, Ministry of Education, Beijing, China

- The authors concluded that patients with both risk alleles confer >11 times the risk o developing MN.

- They also correlated the presence of risl alleles to PLA2R antibodies.

J. Lv *et al.*, “Interaction between PLA2R1 and HLA-DQA1 variants associates with anti-PLA2R antibodies and membranous n *J. Am. Soc. Nephrol.*, vol. 24, no. 8, pp. 1323–1329, 2013.

H. C. Stanescu *et al.*, “ Risk HLA-DQA1 and PLA 2 R1 Alleles in Idiopathic Membranous Nephropathy ,” *N. Engl. J. Med.*, vol. 3 pp. 616–626, 2011.

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Clinical features

Variable degree of proteinuria, which can be asymptomatic or more intense and quite frequently 25–100% of cases in different reports in the nephrotic range, leading to NS.

Asymptomatic nephrotic-range proteinuria has been reported in 16–38% of cases.

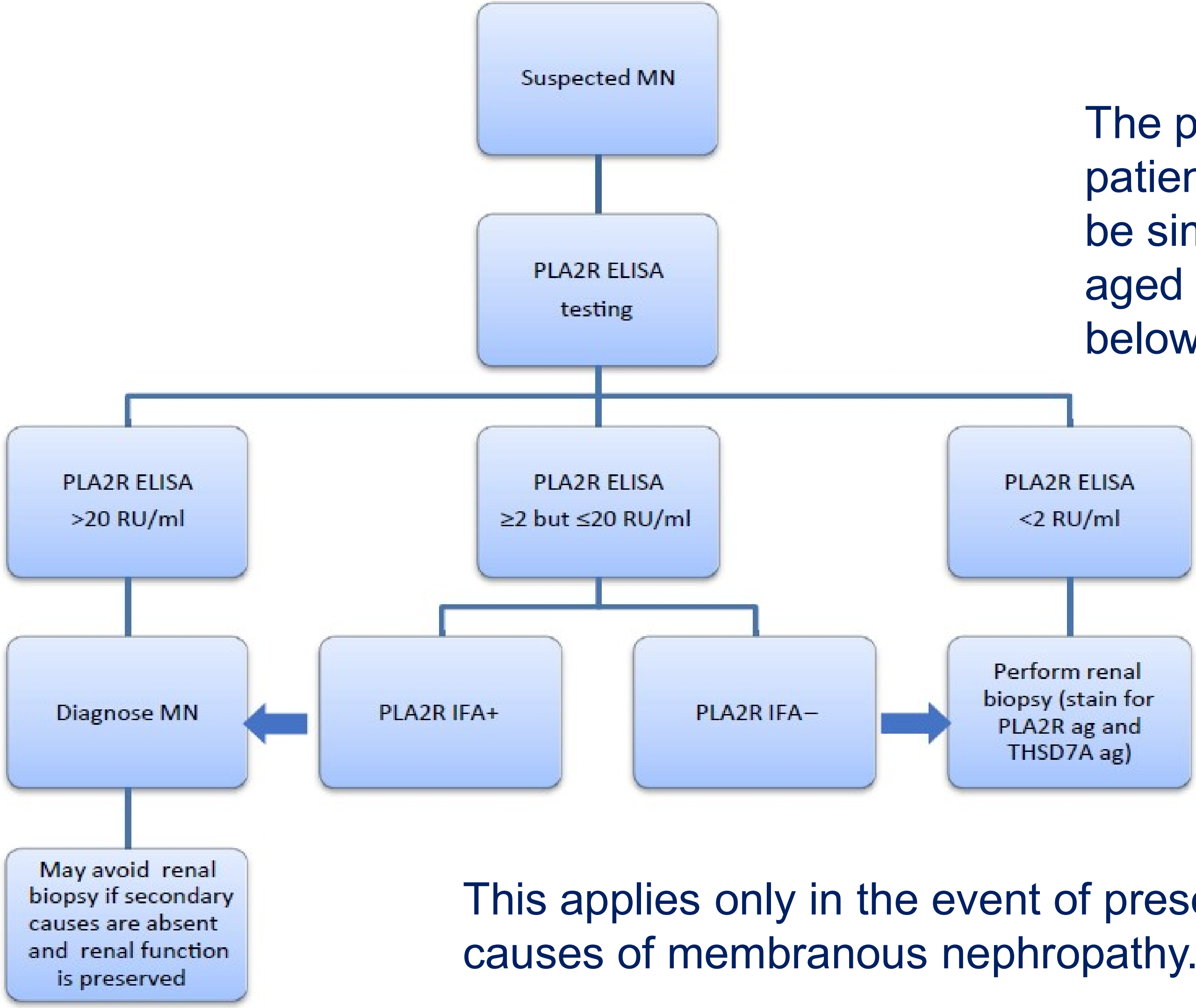
Microscopic hematuria is frequently present 70-90 %, while gross hematuria is reported in up to 40% of patients

Renal function is usually preserved

Hypertension is uncommon, but may be present in up to 36% of children at onset

Chen A, Frank R, Vento S, et al. Idiopathic membranous nephropathy in pediatric patients: presentation, response to therapy, and long-term outcome. BMC Nephrol. 2007;6:8
Tsukahara H, Takahashi Y,Yoshimoto M, et al. Clinical course and outcome of idiopathic membranous nephropathy in Japanese children. Pediatr Nephrol. 1993;7(4):387–91.
Wang R, Wang M, Xia Z, et al. Long-term renal survival and related risk factors for primary membranous nephropathy in Chinese children: a retrospective analysis of 217 case
2020.

Algorithm for centers preferentially performing enzyme-linked immunosorbent assays (ELIS



The prevalence of anti-PLA2R in adolescent patients with primary MN has been suggested to be similar to adult patients (81.1% in 11 children aged 13–17 years), while it is rare in children below 10 years of age

It is reasonable to suggest performing an anti- PLA2R ELISA before a kidney biopsy in an adolescent with atypical presentation or steroid-resistant proteinuria

This applies only in the event of preserved renal function and absence of seconda causes of membranous nephropathy.

Bobart SA, De Vriese AS, Pawar AS, et al. Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. Kidney Int. 2019;95:429–38.
Zhang D, Wu Y, Zhang C, et al. Compared staining of the phospholipase A2 receptor in the glomeruli of Chinese adults and children with idiopathic membranous nephropathy. Pathol Re

Treatment

- In adults the rate of spontaneous remission is reported to be between 30% and 40%

- Current guidelines suggest to employ antiproteinuric therapy in all MN patients, and to “wait and see” without adding immunosuppression for 6 months

- In adult MN, rituximab is now head-to-head with cyclophosphamide as first line of treatment in patients with MN and persisting NS

Chen Y, Schieppati A, Chen X, et al. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Cochrane Database Syst Rev. 2014;2014(10):CD0042

Treatment

- About 20% of pediatric cases reach **end-stage renal disease**
- In children, there is little evidence for the use of steroid monotherapy. In some small case series 50% do not respond **to steroids.**
- More favorable safety profile of **calcineurin inhibitors (CNI)** compared to alkylating agents have led to their use being relatively frequent in children with MN. However, evidence of their effectiveness is tempered by the repeated finding of about 50% relapse of proteinuria following their discontinuation in children with MN.
- Based on the extensive experience acquired in the use of anti-CD20 monoclonal antibodies, especially in children with nephrotic syndrome, the use of **rituximab** appears reasonable as a first-line immunosuppressive agent, when available. Evidence of its efficacy in childhood forms of MN is very scarce and limited to case reports

Valentini RP, Mattoo TK, Kapur G, et al. Membranous glomerulonephritis: treatment response and outcome in children. Pediatr Nephrol. 2009;24(2):301–8.
Ravani P, Magnasco A, Edefonti A, et al. Short-term effects of rituximab in children with steroid- and calcineurin- dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephro

СБАЛ по детс
"Проф. Иван

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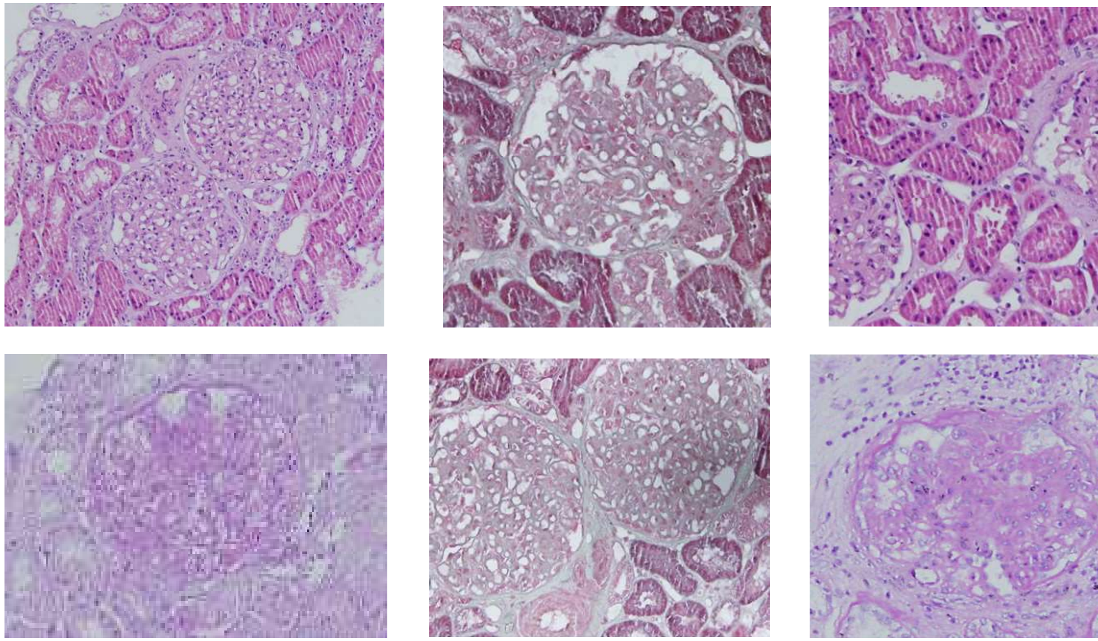
Retrospective study of 12 patients with biopsy-prov Membranous nephropathy (MN) seen from 2009 to 2023 in Department of nephrology and dialysis in University pediatric hospital in Sofia



- For 14 years period from 264 kidney biopsy only 12 children with MN were diagnosed (4.5%).
- 6 patients (50%) were referred to as “idiopathic,”
- 6 patients (50%) were classified as “secondary” and involved conditions such as systemic lupus erythematosus, Hepatitis B infection, immune diseases.

All children with membranous nephropathy

- The mean age of the MN patients was 10.6 years old
- There were 5 males and 7 females

- 9 children (75%) had **nephrotic syndrome**
- **Asymptomatic proteinuria** had 3 children (25%)
- 11 children (91%) had **microscopic hematuria**
- All of the children (100%) were with **normal kidney function**
- 5 children (41%) had **hypertension** at the time of renal biopsy

Treatment

- All of them (100%) were treated with glucocorticoids
- 9 children (75%) were treated with cyclosporin A
  and 5 children (41%) with other immunosuppression drugs (MMF, cyclophosphamide, levamisole)
- 2 children were tested for AntiPla2R antibodies – **negative results**

Follow up

- 9 children (75%) have full remission
- 3 children (25%) have persistent low-grade proteinuria

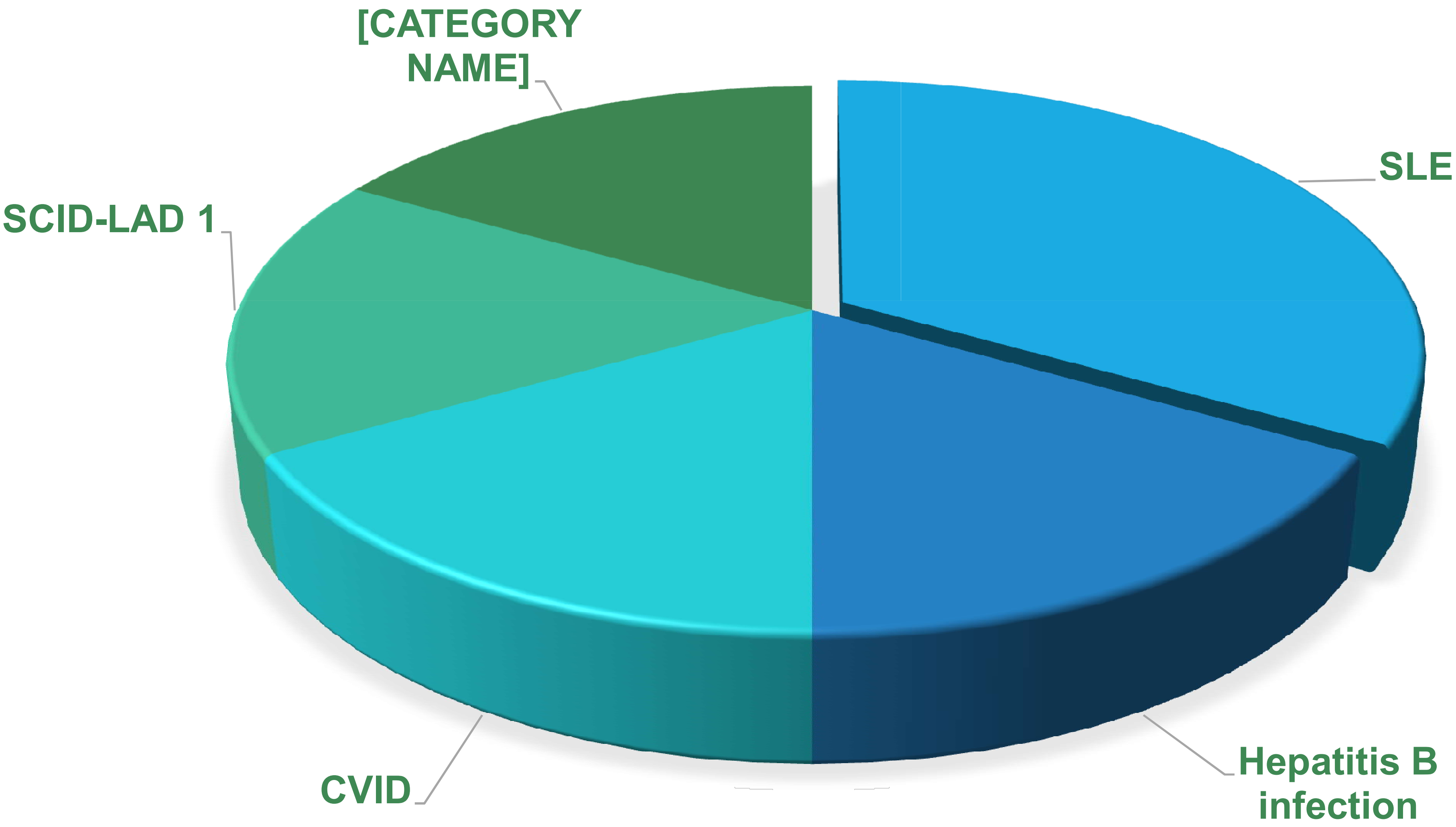
Primary/Idiopatic MN – 6 children

Clinical features	Nephrotic syndrome	Asymptomatic proteinuria	Hematuria	Hypertention	Normalю kidneyю function
Children	6 (100%)	0	5 (83%)	3 (50%)	6 (100%)

Treatment	Glucocorticoids	Cyclosporin A	Cyclophosph amide	MMF	Levamisole
Children	6 (100%)	6 (100%)	2 (33%)	1 (16%)	1 (16%)

Follow up	Full remission	Low - grade proteinuria	Normal kidney function	Hypertention
Children	4 (66%)	2 (33%)	6 (100%)	3 (50%)

Secondary MN

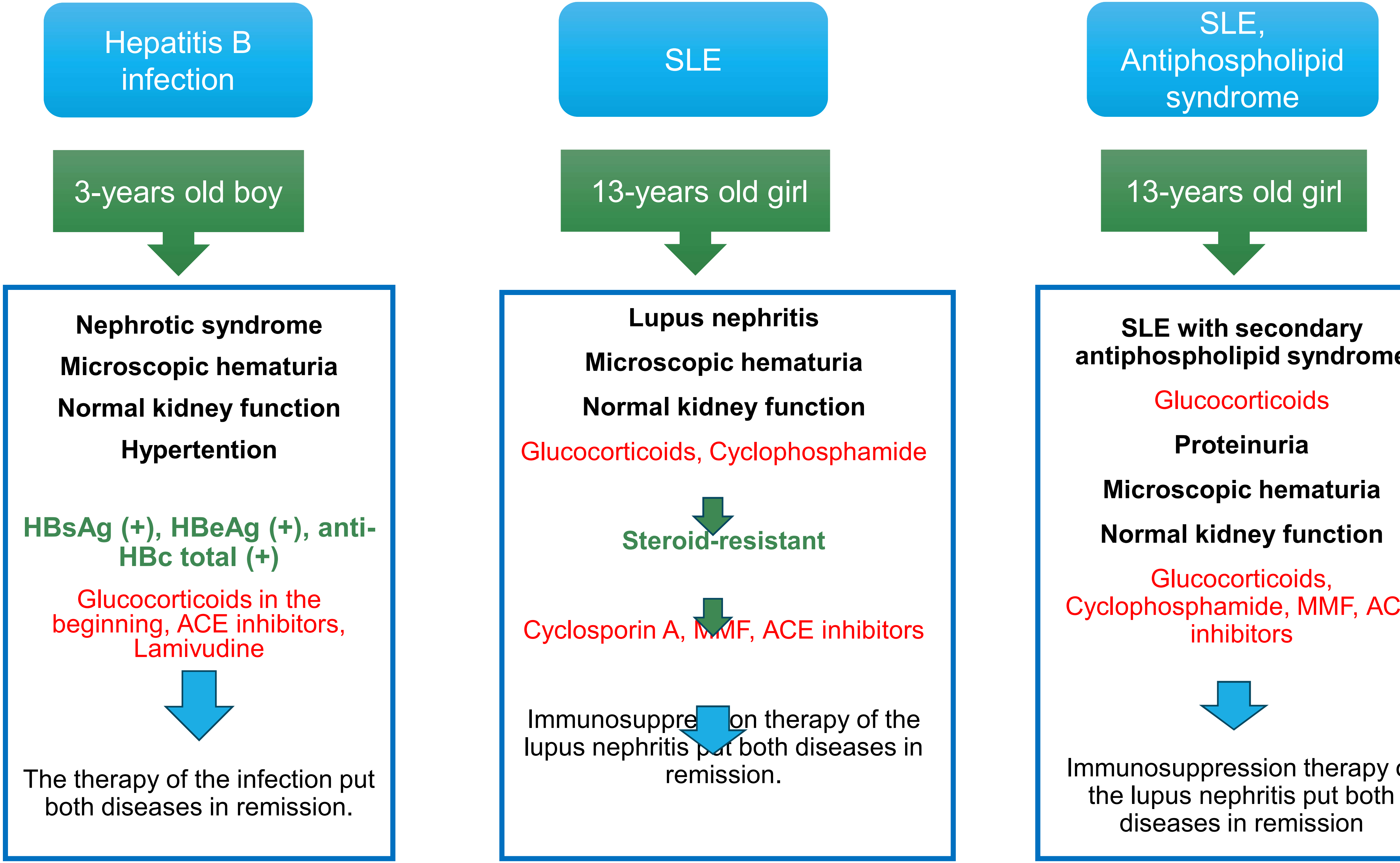


Secondary MN – 6 children

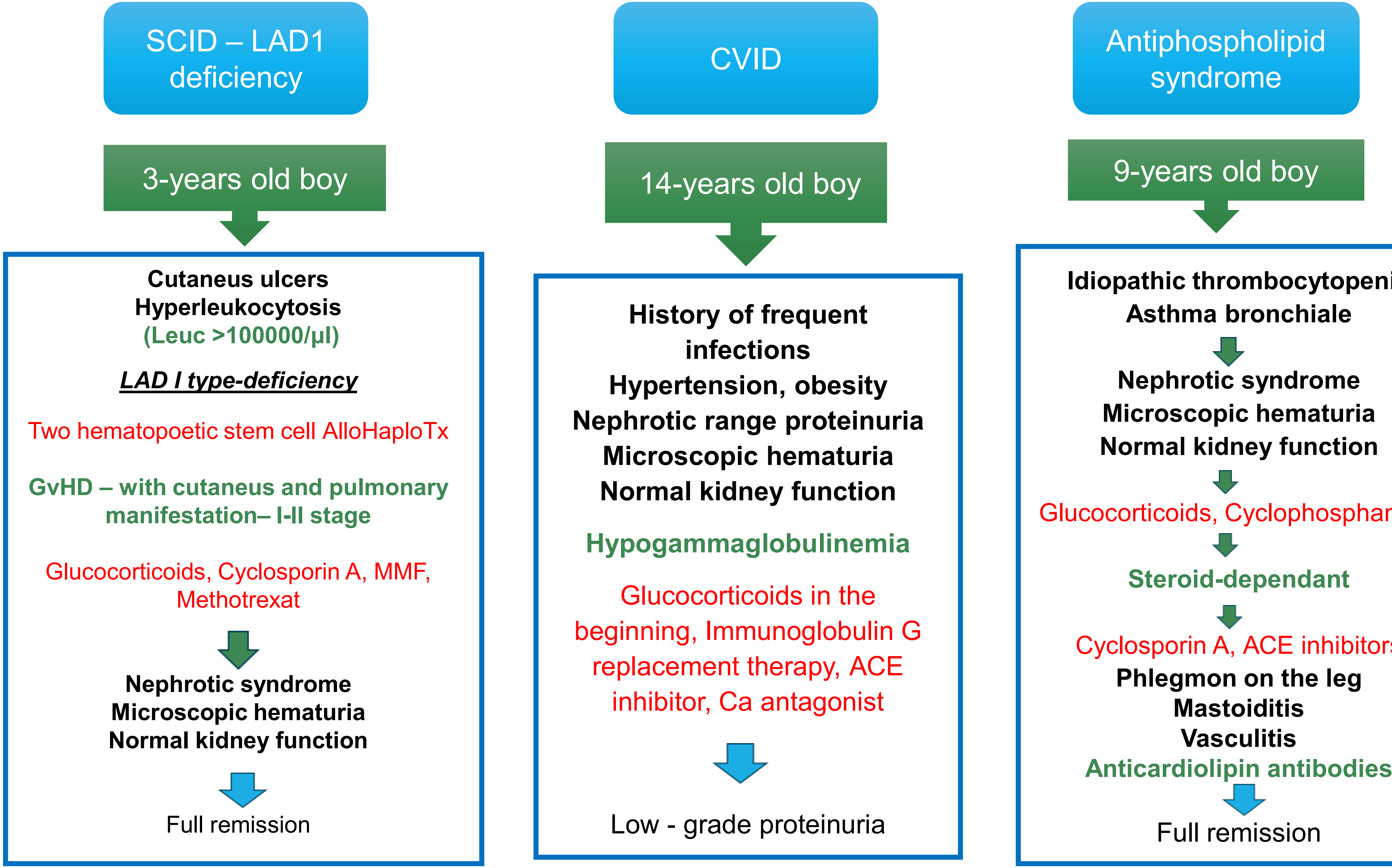
Clinical features	Nephrotic syndrome	Asymptomatic proteinuria	Hematuria	Hypertention	Normalю kidney function
Children	3 (50%)	3 (50%)	6 (100%)	2 (33%)	6 (100%)

Treatment	Glucocorticoids	Cyclosporin A	Cyclophosph amide	MMF	Levamisole
Children	6 (100%)	3 (50%)	3 (50%)	3 (50%)	0

Follow up	Full remission	Low - grade proteinuria	Normal kidney function	Hypertention
Children	5 (83%)	1 (16%)	6 (100%)	2 (33%)



Hepatitis B infection
3-years old boy
Nephrotic syndrome
Microscopic hematuria
Normal kidney function
Hypertention
HBsAg (+), HBeAg (+), anti-HBc total (+)
Glucocorticoids in the beginning, ACE inhibitors, Lamivudine
The therapy of the infection put both diseases in remission.
SLE
13-years old girl
Lupus nephritis
Microscopic hematuria
Normal kidney function
Glucocorticoids, Cyclophosphamide
Steroid-resistant
Cyclosporin A, MMF, ACE inhibitors
Immunosuppression therapy of the lupus nephritis put both diseases in remission.
SLE, Antiphospholipid syndrome
13-years old girl
SLE with secondary antiphospholipid syndrome
Glucocorticoids
Proteinuria
Microscopic hematuria
Normal kidney function
Glucocorticoids, Cyclophosphamide, MMF, AC inhibitors
Immunosuppression therapy the lupus nephritis put both diseases in remission



SCID – LAD1 deficiency
3-years old boy
Cutaneus ulcers
Hyperleukocytosis
(Leuc >100000/µl)
LAD I type-deficiency
Two hematopoetic stem cell AlloHaploTx
GvHD – with cutaneus and pulmonary manifestation– I-II stage
Glucocorticoids, Cyclosporin A, MMF, Methotrexat
Nephrotic syndrome
Microscopic hematuria
Normal kidney function
Full remission
CVID
14-years old boy
History of frequent infections
Hypertension, obesity
Nephrotic range proteinuria
Microscopic hematuria
Normal kidney function
Hypogammaglobulinemia
Glucocorticoids in the beginning, Immunoglobulin G replacement therapy, ACE inhibitor, Ca antagonist
Low - grade proteinuria
Antiphospholipid syndrome
9-years old boy
Idiopathic thrombocytopeni
Asthma bronchiale
Nephrotic syndrome
Microscopic hematuria
Normal kidney function
Glucocorticoids, Cyclophosphar
Steroid-dependant
Cyclosporin A, ACE inhibitor
Phlegmon on the leg
Mastoiditis
Vasculitis
Anticardiolipin antibodies
Full remission

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THANK YOU

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X SEPNWG MEETING AND TEACHING COURSE 2023
(IPNA Sponsored Teaching Course)

Hypertension in children and adolescents in CKD

Stella Stabouli
Professor of Pediatrics-Pediatric Nephrology
Aristotle University Thessaloniki
1st Department of Pediatrics
Hippokratio Hospital

Aristotle University of Thessaloniki

- **No conflict of interest**

Aims

- Prevalence and definition of hypertension in children and adolescents with CKD
- Associations of BP levels, as well as relevant BP targets for treatment, with kidney and cardiovascular outcomes
- Evidence on the use of antihypertensive medications in children and adolescents with CKD

Prevalence of HTN in pediatric CKD populations

Dialysis patients

- Hypertension was present in **over 2/3** of hemodialysis, peritoneal dialysis, or transplant patients in European pediatric nephrology centers
- BP > 95th percentile was significantly more prevalent in very young patients (under 3 years)

Kramer et al, Kidney Int. 2011 Nov;80(10):1092-8.

Non-dialysis patients

- **54%** of children in the CKiD cohort were either hypertensive (systolic or diastolic BP > 95th percentile for age, sex, and height) or had history of hypertension plus current antihypertensive medication use
- Uncontrolled and/or unrecognized hypertension was common; 37% of participants who had BP > 90th percentile at time study entry

35% uncontrolled HTN | **Nearly 40% unrecognized HTN**

Flynn JT, Hypertension 2008; 52:631–637

Definition of hypertension in children and adolescents with CKD

In retrospective and cohort studies

- BP > 95th percentile for age, gender, and height
- History of hypertension
- Current antihypertensive medication use

In guidelines

- **Diagnosis and initiation** of antihypertensive medication when the BP is **consistently** > 90th percentile for age, sex, and height

  (KDIGO 2012)

Definition-diagnosis of hypertension in children and adolescents

Lurbe et al. J Hypertens 2016;34:1887-1920. **2016 ESH recommendations for the management of high blood pressure in children and adolescents**

Flynn et al, Pediatrics. 2017;140(3):e20171904. **2017 American Academy Pediatrics Clinical Practice Guideline for the management of high blood pressure in children and adolescents**

SBP and/or DBP are persistently ≥95th percentile for age, sex, and height, measured on at least three separate occasions

ESH 2016

Adult BP limit for adolescents≥ 16 years old

AAP 2017

Adult BP limit for adolescents ≥ 13 years old

Definition-diagnosis of hypertension in children and adolescents

Lurbe et al. J Hypertens 2016;34:1887-1920. 2016 ESH recommendations for the management of high blood pressure in children and adolescents

Flynn et al, Pediatrics. 2017;140(3):e20171904. **2017 American Academy Pediatrics Clinical Practice Guideline for the management of high blood pressure in children and adolescents**

Both guidelines did not differentiate BP diagnostic thresholds for children with CKD from those of the general pediatric population

BUT

proposed different BP targets for HTN treatment in children with CKD

Goals of treatment

Prevention CKD progression

Treatment of HTN in children with CKD

Prevention of adverse CVD outcomes

HTN associates with CKD progression

Risk factors for CKD progression
Effect on time to kidney endpoint

Glomerular disease

- Up/c > 0.5 mg/mg (↓94%)
- Hypoalbuminemia (↓71%)
- **Elevated BP (↓67%)**

Non-glomerular disease

- Up/c > 2 mg/mg (↓79%)
- Hypoalbuminemia (↓69%)
- **Elevated BP (↓38%)**
- Dyslipidemia (↓40%)
- Male gender (↓38%)
- Anemia (↓45%)

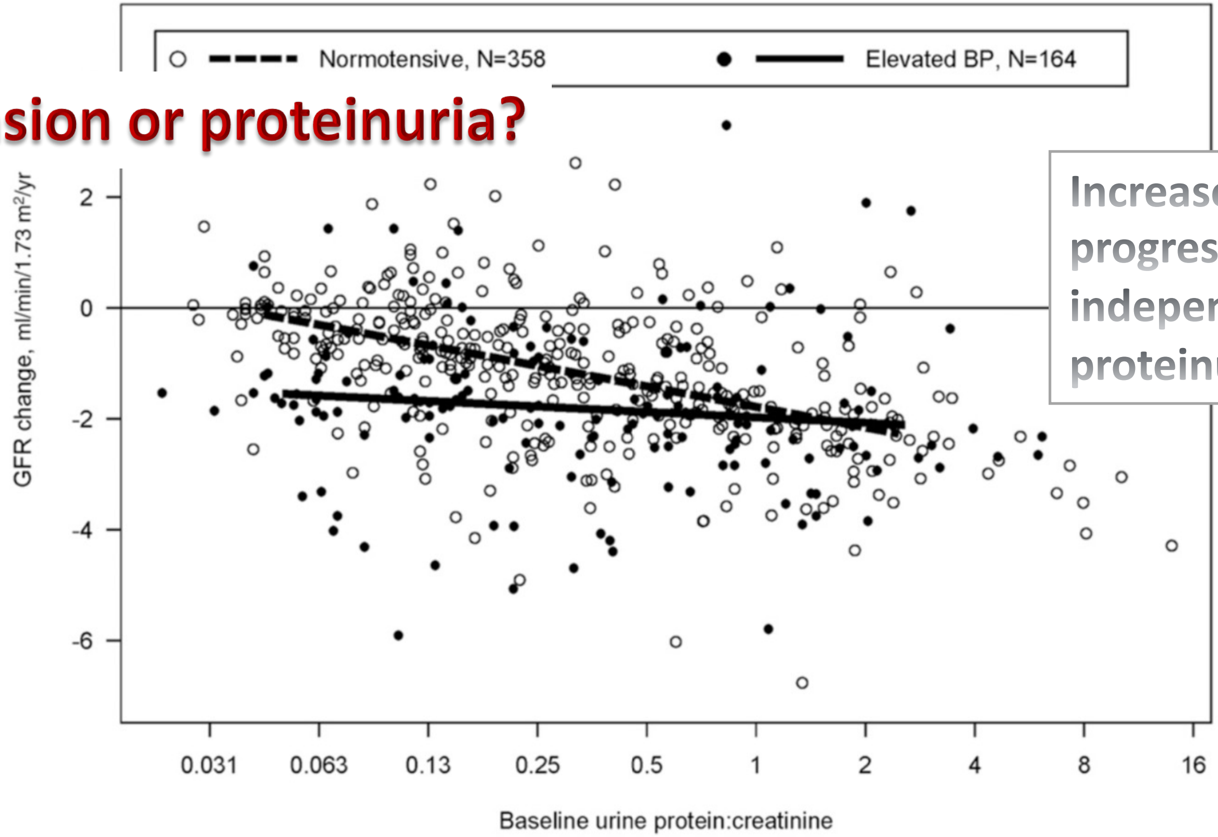
Warady BA, et al. Am J Kidney Dis. 2015 Jun;65(6):878-88.

Progression of pediatric CKD of nonglomerular origin
in the CKiD Cohort

522 children-median age 10 years -follow up > 4 years

HTN= SBP or DBP ≥ 90th percentile for age, sex, and height

Hypertension or proteinuria?

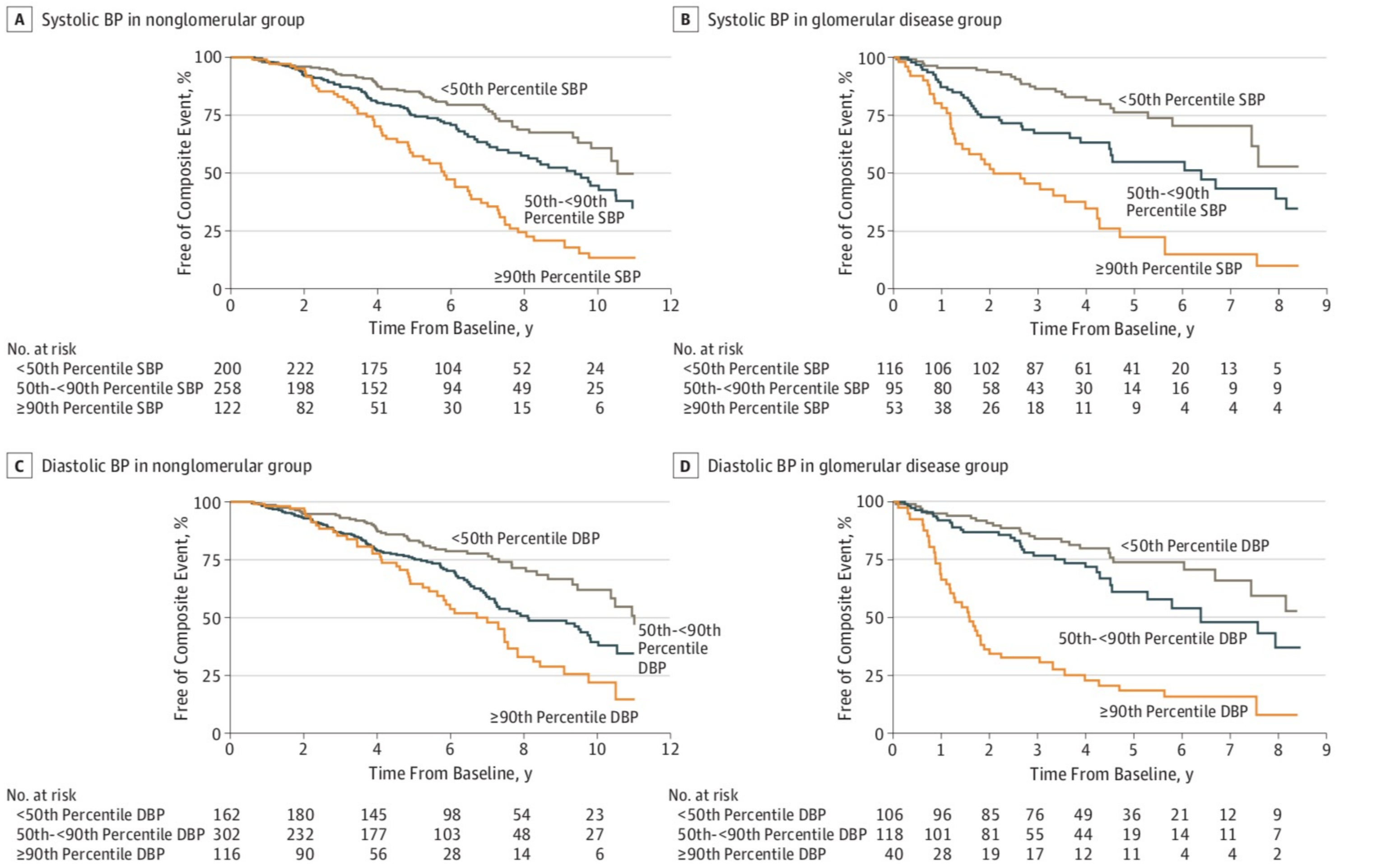


Increased risk of CKD progression in HTN independent of proteinuria

Fathallah-Shaykh et al, Clin J Am Soc Nephrol 2015; 10: 571–577

Which level of office BP?

Figure 1. Unadjusted Survival Curves of Progression to the Composite Renal Outcome by Time-Varying Blood Pressure (BP) Percentile Categories



891 children were enrolled in the CKiD study and contributed 5077 individual visits

Higher HR of kidney outcomes if office BP > 90th pc on long term

Reynolds BC, et al. JAMA Netw Open. 2020 Feb 5;3(2):e1921213.

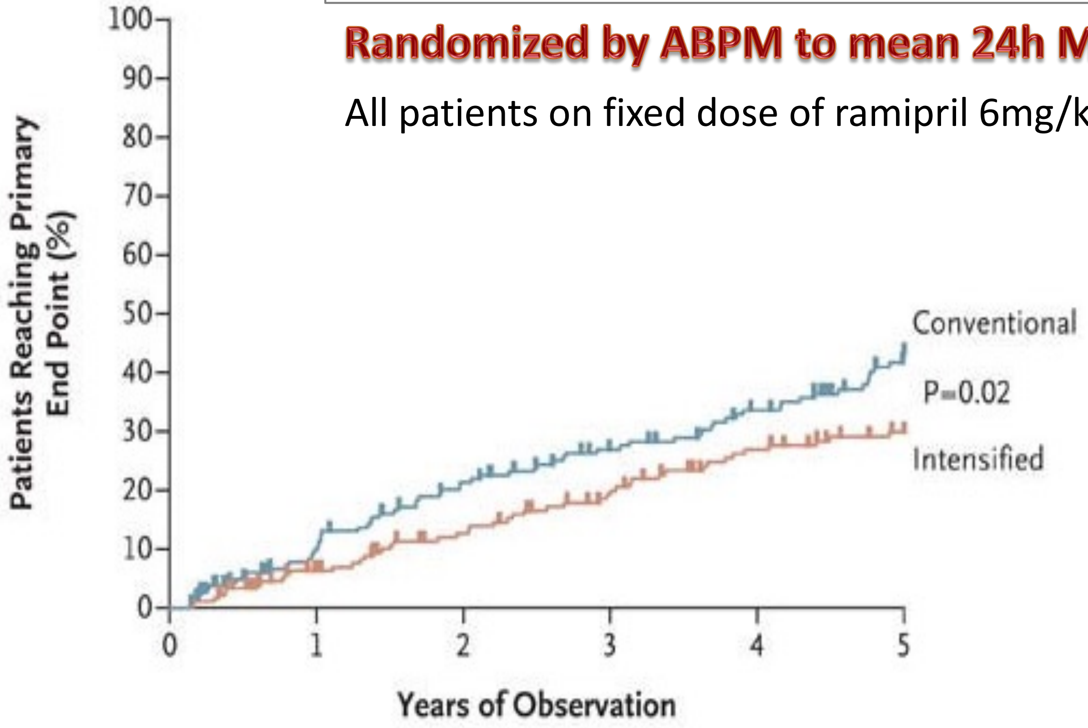
BP control may attenuate CKD progression

Strict blood-pressure control and progression of renal failure in children
The ESCAPE Trial Group

468 children 3-18 years with GFR 15-80 ml/min/1.73m^2

Randomized by ABPM to mean 24h MAP< 50th pc vs 50-95th pc

All patients on fixed dose of ramipril 6mg/kg/m^2



No. at Risk											
Intensified	182	167	152	142	135	126	119	110	102	97	90
Conventional	190	168	154	142	131	122	112	107	97	86	75

HR 0.65 (95%CI 0.44 to 0.94, P=0.02)

Wühl et al. N Engl J Med. 2009;361(17):1639-50.

Unique characteristics of Escape trial

- Prospective multicenter RCT trial on BP control
- Comparing different BP targets on the 2 arms of randomization
- Using out of office measurements-ABPM
- “Hard” end point (decline of 50% in the glomerular filtration rate or progression to end-stage renal disease)

- Not designed to assess the effect of ACEi or any other drug treatment

The mean number of antihypertensive drugs prescribed per patient in addition to ramipril was 0.9±1.1 in the intensified control group as compared with 0.5±0.9 in the conventional-control group (P=0.003)

Published 14 years ago

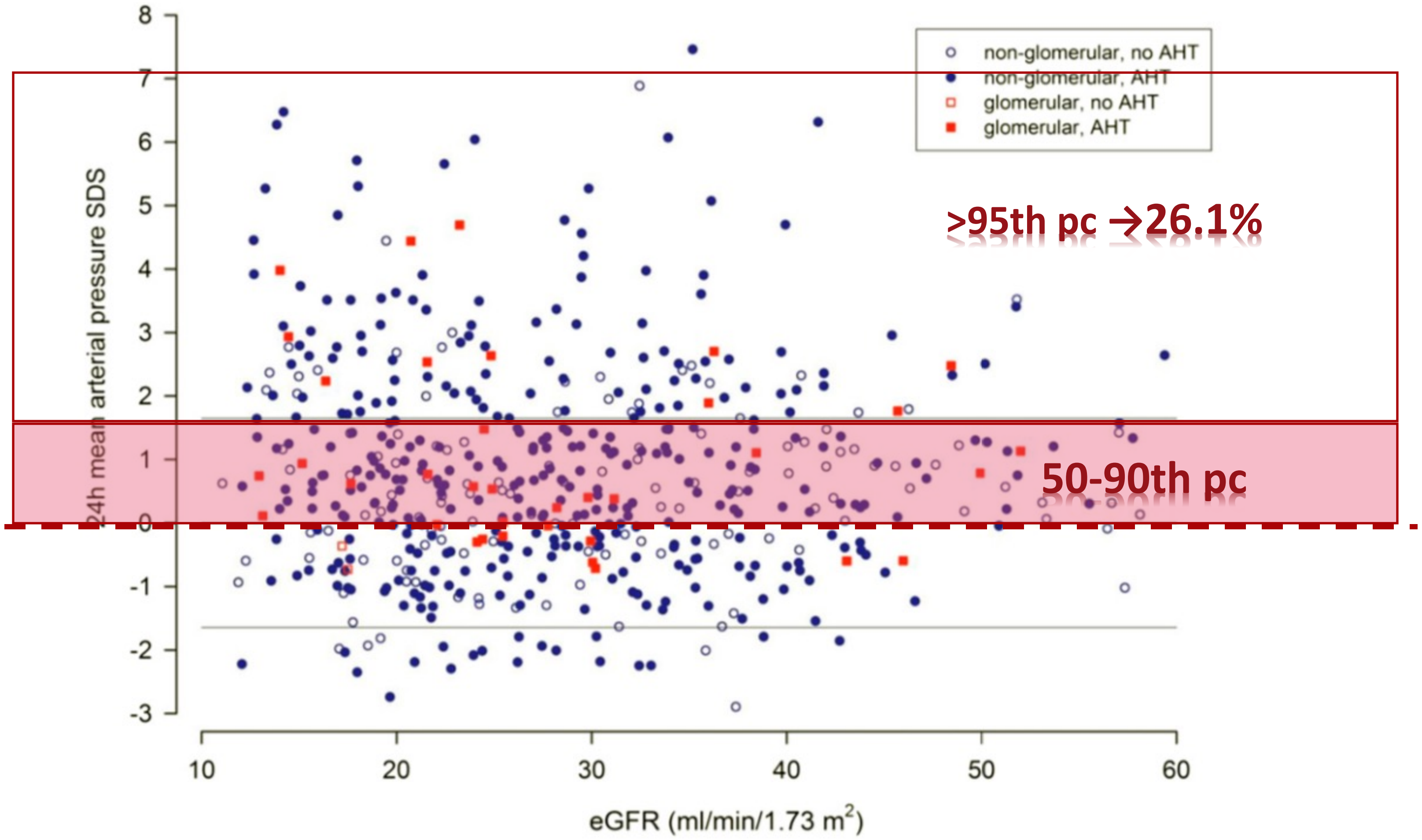
Still the “gold standard”

No further similar studies in pediatric hypertension or pediatric nephrology domain were preformed

Cardiovascular phenotypes

Cardiovascular phenotypes in children with CKD

The Cardiovascular Comorbidity in Children with CKD Study a multicenter, prospective, observational study in children ages 6–17 years old with initial GFR of 10–60 ml/min per 1.73 m^2



Schaefer et al, Clin J Am Soc Nephrol 12: 19–28, 2017

Cardiovascular Phenotypes in Children with CKD

24h BP was examined as continues variable; cut off levels were not assessed for their ability to predict LVMI

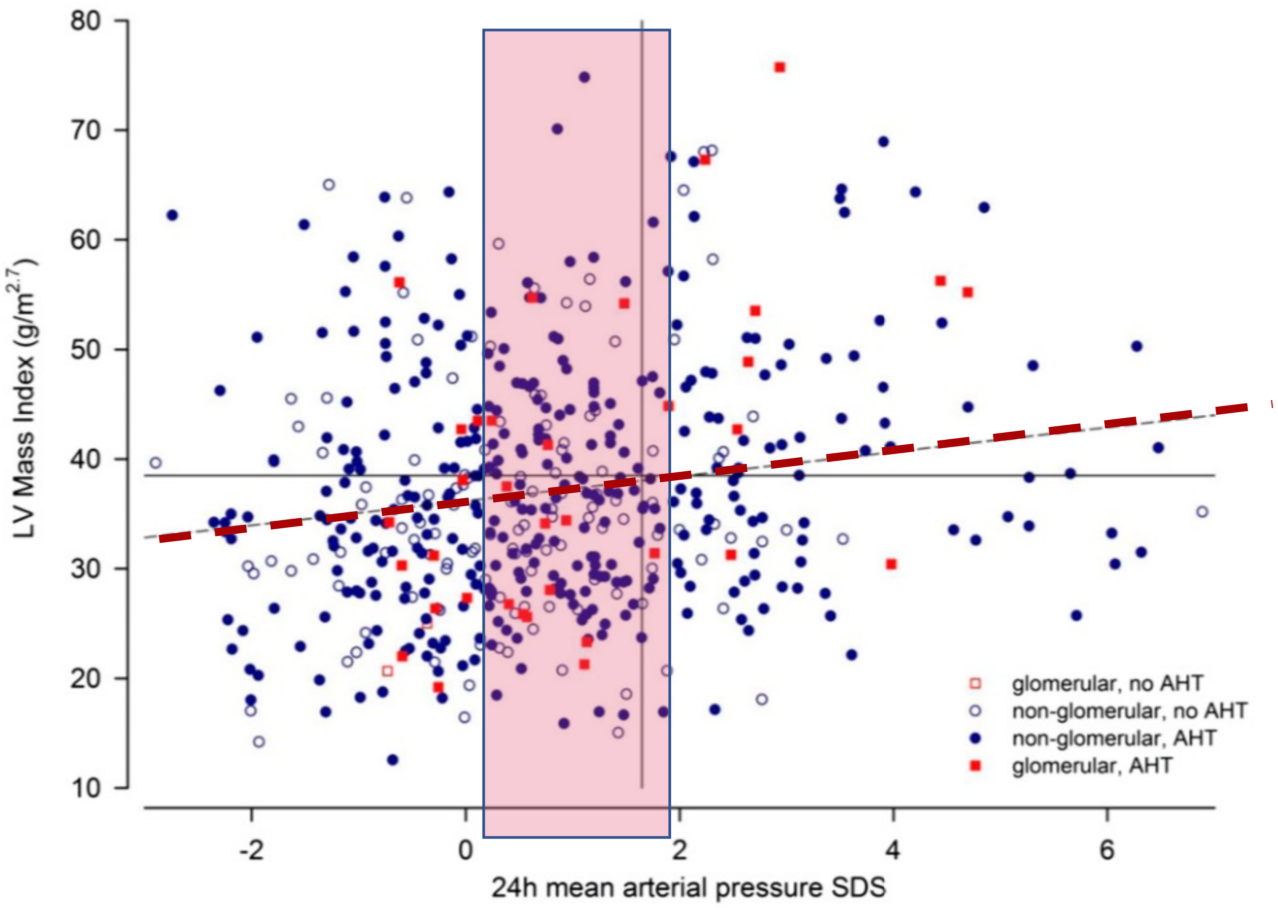


Figure 2. | **24-hour blood pressure and left ventricular mass index in patients with or without antihypertensive treatment.** The 24-hour mean arterial pressure SD scores (SDSs) and left ventricular (LV) mass index in children with underlying glomerular (red squares) and nonglomerular nephropathies (blue circles) with (colored symbols) or without antihypertensive medication (outlined symbols). Vertical and horizontal lines represent 95th reference percentiles of 24-hour mean arterial pressure and LV mass index, respectively. The dashed line represents the linear regression line. AHT, Antihypertensive Treatment.

Schaefer et al, Clin J Am Soc Nephrol 12: 19–28, 2017

What is the BP target?

BP target in children with CKD

ESH 2016

Children <16 years

SBP/DBP (**office, 24-h ABP, home BP**)

<75th pc in non-proteinuric CKD (Recommended)

<50th pc in proteinuric CKD (Recommended)

Adolescents ≥ 16 years

< 130/80 mmHg in non-proteinuric CKD (Recommended)

<125/75 mmHg in proteinuric CKD (Recommended)

Lurbe et al. J Hypertens 2016;34:1887-1920.

AAP 2017

All children and adolescents

24-hour MAP <50th percentile (Grade B, strong recommendation)

Flynn et al, Pediatrics. 2017;140(3):e20171904.

BP target in children with CKD

KDIGO 2021 clinical practice guideline for the management of BP in CKD

Recommendation 5.1: We suggest that in children with CKD, 24-hour mean arterial pressure (MAP) by ABPM should be lowered to ≤50th percentile for age, sex, and height *(2C)*.

Practice Point 5.1: We suggest monitoring BP once a year with ABPM, and monitoring every 3–6 months with standardized auscultatory office BP in children with CKD.

Practice Point 5.2: In children with high BP and CKD, when ABPM is not available, manual auscultatory office BP obtained in a protocol-driven standardized setting targeting achieved SBP <90th percentile for age, sex, and height of normal children is a reasonable approach.

Practice Point 5.3: Use ACEi or ARB as first-line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well tolerated, but they carry the risk of hyperkalemia and have adverse fetal risks for pregnant women.

Kidney International (2021) 99, S1–S87

Which BP measurement?

For diagnosis

For treatment effect monitoring

Ambulatory blood pressure patterns in children with CKD

- Normal BP (42%)
- White-coat HTN(4%)
- **Masked HTN (35%)**
- **Ambulatory HTN (14%)**

- In multivariate analysis, those using an **ACEi were 89% more likely to have a normal ABPM** (odds ratio, 1.89 [95% CI, 1.17–3.04])

Table 4. Descriptive Statistics and Results From Logistic Regression Analysis of Abnormal ABPM on the 1-y Levels and Changes in Iohexol GFR and Urine Protein:Creatinine

Variable	Average	SD	Odds Ratio (95%CI) of Abnormal ABPM for a 1-SD Difference
Geometric mean level of GFR of visits 1 and 2	42.5 mL/min per 1.73 m^2	1.46	0.90 (0.80–1.10) P=0.435
Annual change in GFR (visit 2 level/visit 1 level)	0.96	0.80	1.26 (0.97–1.64) P=0.081
Geometric mean level of uPrCr of visits 1 and 2	0.43 mg/mg of creatinine	3.16	1.16 (0.90–1.51) P=0.246
Annual change in uPrCr (visit 2 level/visit 1 level)	1.08	2.25	1.39 (1.06–1.82) P=0.019

Model was adjusted for age, sex, and CKD diagnosis (glomerular vs nonglomerular underlying cause of CKD). CKD indicates chronic kidney disease; GFR, glomerular filtration rate; ABPM, ambulatory blood pressure monitoring; uPrCr, urine protein:creatinine ratio.

Samuels et al. Hypertension. 2012;60:43-50.

Are BP levels improving in children with chronic kidney disease?

- Comparison of BP control over 2 time periods among participants enrolled in the CKiD study: 2005-2008 (period 1) vs 2010-2013 (period 2)

- Office BP status was categorized as uncontrolled hypertensive (**SBP or DBP ≥95th percentile**)

- Ambulatory hypertension was defined as mean wake and/or sleep SBP or DBP **≥95th percentile for ABPM** and/or SBP or DBP load ≥25%

Barletta et al. Hypertension. 2018;71:444-450.

Main conclusion: Hypertension remains undertreated and under-recognized in children with chronic kidney disease

No difference in office BP

Patient Visits (n)	Time Period		P Value for Difference
	Period 1	Period 2	
	[illegible]	n=408	
	Sum Weights=270.4	Sum Weights=414.0	
Casual SBP *Z* score	0.29 (0.17–0.42)	0.24 (0.13–0.35)	0.54
Casual DBP *Z* score	0.40 (0.29–0.52)	0.44 (0.34–0.54)	0.65
Casual BP status, %			0.87
Normotensive	67	68	
Uncontrolled pre-HTN	15	15	

Hypertension: 18% versus 17%; *P*=0.87

Casual/ABPM hypertension status, %			0.001*
Normotensive	45	37	
White coat HTN	4	0	
Masked HTN	36	49	
Confirmed HTN	15	14	

Higher levels of ABPM

ABPM measurements (N)	Time Period		
	Period 1	Period 2	
	n=169	n=246	
	Sum weights=165.36	Sum weights=249.44	
ABPM HTN, %	51	63	0.036*
Index			
Wake SBP	0.90 (0.89–0.92)	0.92 (0.91–0.93)	0.076
Mean>limit, %	13.2	16.3	0.043
Sleep SBP	0.91 (0.89–0.92)	0.93 (0.92–0.94)	0.038*
Mean>limit, %	13.8	20.1	0.13
Wake DBP	0.87 (0.86–0.89)	0.89 (0.88–0.91)	0.088
Mean>limit, %	11.3	12.3	0.78
Sleep DBP	0.90 (0.88–0.92)	0.93 (0.91–0.94)	0.026*
Mean > limit, %	15.0	22.4	0.094
Load			
Wake SBP	20.5 (16.6–24.3)	22.6 (19.0–26.1)	0.44
>25, %	32.0	32.1	0.98
Sleep SBP	19.3 (14.8–23.8)	26.1 (21.9–30.2)	0.031*
>25, %	26.0	41.0	0.005*
Wake DBP	20.3 (16.6–24.0)	22.3 (18.9–25.7)	0.44
>25, %	29.1	31.8	0.63
Sleep DBP	23.7 (19.5–27.9)	29.9 (26.1–33.8)	0.033*
>25, %	38.8	46.6	0.18

Barletta et al. Hypertension. 2018;71:444-450.

When ABPM is not available?

Limitations of ABPM in children

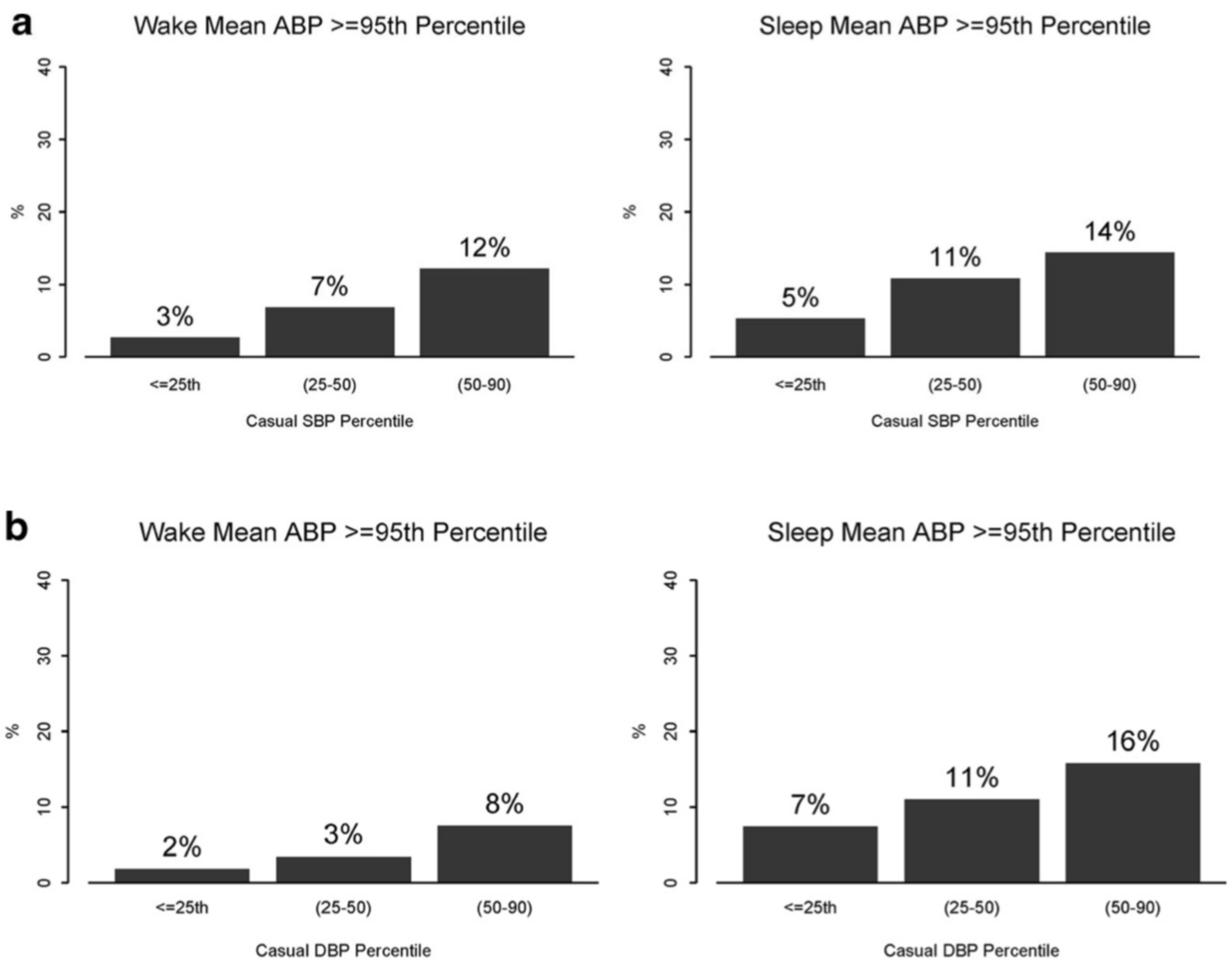
- Limited availability especially in lower resource settings
- Need of staff expertise for application in children and adolescents
- Time consuming for the medical staff and the patient
- Intolerance of the patient

- Lack of normative values for children < 5 years or with a height < 120cm

Can office blood pressure readings predict masked hypertension?

In clinical settings with limited access to ABPM decisions could be made **based on BP obtained during a clinic visit assuming that masked HTN in unlikely in low office BP <25th pc**

This analysis is limited to children with mild-to- moderate CKD



Mitsnefes et al, Pediatr Nephrol (2016) 31:163–166

Home BP

Home, clinic, and ambulatory blood pressure monitoring in children with CKD

118 pediatric patients (3-19 y) with CKD. HBP readings (10.5 ± 5.4 per patient) were averaged for one week around the day of ABPM and CBP

The children were monitored as part of the ESCAPE Study

Table 3. *Sensitivity and specificity of HBP and CBP for detecting hypertension (daytime ABPM as reference)*

	Sensitivity	Specificity	Predictive value	
			Positive	Negative
CBP	0.7	0.7	0.41	0.88
HBP	0.52	0.82	0.47	0.85
CBP or HBP	0.81	0.60	0.38	0.92
CBP and HBP	0.41	0.92	0.61	0.84
Mean of CBP & HBP	0.63	0.87	0.59	0.89

Neither clinic BP nor home BP detected hypertension with enough sensitivity or specificity to replace ABPM

Wulh et al, Pediatr Res 55: 492–497, 2004

KDIGO2021
AAP 2017
ESH 2016

How to measure BP in pediatric patients with CKD

Diagnosis-monitoring

- First line ABPM
- Alternatively office BP

Monitoring

- Home BP
- Complimentary role on treatment monitoring between the ABPM sessions

- **Lack of multicenter large normative data!!!**
- **Need for strict monitoring protocol and use of limited validated devices for HBPM in children!!!**

Which classes of antihypertensive drugs to use?

Evidence on antihypertensive drug classes treatment in children

- The escape trial was not designed to assess the effect of ACEi
- All children were on fixed dose of ramipril 6mg/m^2/day

(Intensified BP control was achieved by addition of further drugs on preference of caring physician)

- There are no head-to-head RCTs comparing antihypertensive drug classes in children with or without CKD
- One Cochrane review

Sparse data informing the use of antihypertensive agents in children, with outcomes reported limited to BP and not end organ damage
No evidence of a consistent dose response relationship for escalating doses of angiotensin receptor blockers, calcium channel blockers or angiotensin-converting enzyme inhibitors
All agents appear safe, at least in the short term

Chaturvedi S et al, Database Syst Rev. 2014 Feb 1;(2):CD008117.

ACEi and ARB

- Mainstay therapy to attenuate CKD progression through BP and proteinuria control and suggested as 1st line treatment in all guidelines

- Evidence **of reducing the risk of RRT** from both adult and pediatric studies

1. **When and how to use?**

2. **What is their role in advanced CKD?**

ACEi and ARB

1. When and how to use

Summary of use of RAASi in paediatric CKD	
Indications	High blood pressure (> = 90th centile) and/or
	Significant proteinuria/albuminuria
	- urinary protein-to-creatinine ratio ≥ 0.5 mg/mg or 50 mg/mmol
	- albumin-to-creatinine ratio ≥ 0.3 mg/mg or 30 mg/mmol
Suggested use specific to CKD stage	CKD I to III: early use and continued use
	CKD IV & V:
	- patients on RAASi: continue treatments if tolerate
	- patients not on RAASi: judicious initiation with close monitoring
Drug of choice	Monotherapy with ACEi
	ARB if ACEi not tolerated
	Avoid combination therapy
Intervention goal	24-h mean arterial pressure less than 50 to 75th centile
	Reduction of proteinuria/ albuminuria
Significant side effects	Decline in GFR, hyperkalaemia, metabolic acidosis, hypotension, angioedema, cough, teratogenicity, impair nephron development
Monitoring	Blood pressure, kidney function, potassium level
	3 to 5 days following drug initiation or dose adjustment
Situations where dose reduction or drug cessation is required	GFR decline
	- CKD I to III: > 30%; CKD IV & V: > 20%
	Uncontrolled hyperkalaemia despite treatment
	Hypotension
Conditions in which RAASi are contraindicated or to be used with caution	Contraindicated in neonates, bilateral renal artery stenosis, pregnancy, hyperkalaemia despite treatment, history of angioedema and allergic reaction related to RAASi
	Cautious use in young infants

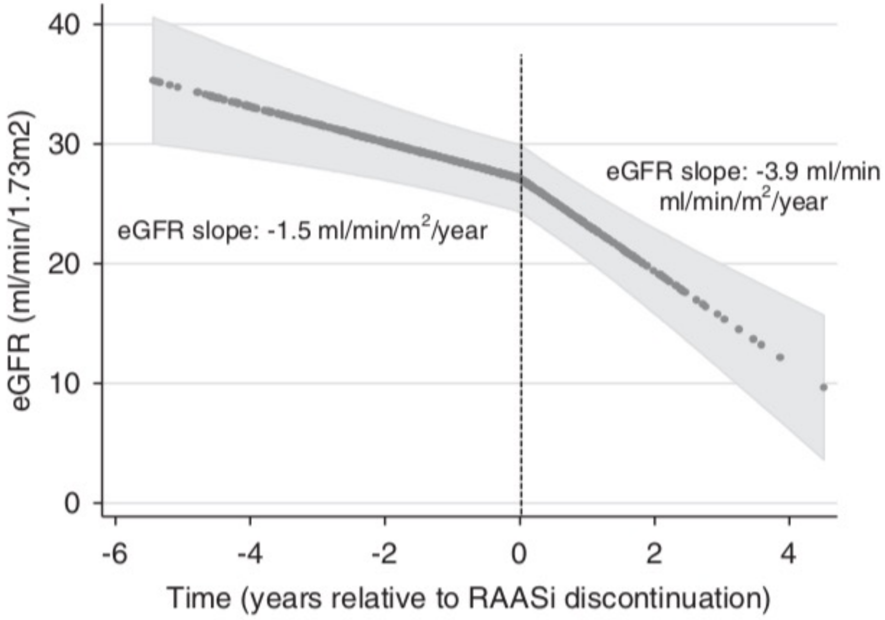
Chan EY, et al. Pediatr Nephrol. 2020

2. What is the role of ACEi and ARB in children with advanced CKD?

Discontinuation of RAS Inhibition in Children with Advanced CKD

380 children, 73 children (19%) discontinued RASi within the 4c cohort

Physician-reported reasons for RASi discontinuation were increase in serum creatinine, hyperkalemia, and symptomatic hypotension



- The rise in albuminuria **by 115%** and associated with progression to the composite kidney end point

- The rise in BP by 2.8 mmHg

van den Belt SM, et al. Clin J Am Soc Nephrol. 2020 May 7;15(5):625-632.

What about other antihypertensive drugs?

- **CCB**

Use of **dhCCBs** (eg. amlodipine) in children with CKD and hypertension in the CKID cohort has been associated with **higher levels of proteinuria** and **was not found to be associated with improved blood pressure control.** The most used 2nd line medication

- **β-blockers**

3rd and 4th line choice in case of resistant hypertension

- **MRA** (Spironolactone, eplerenone)

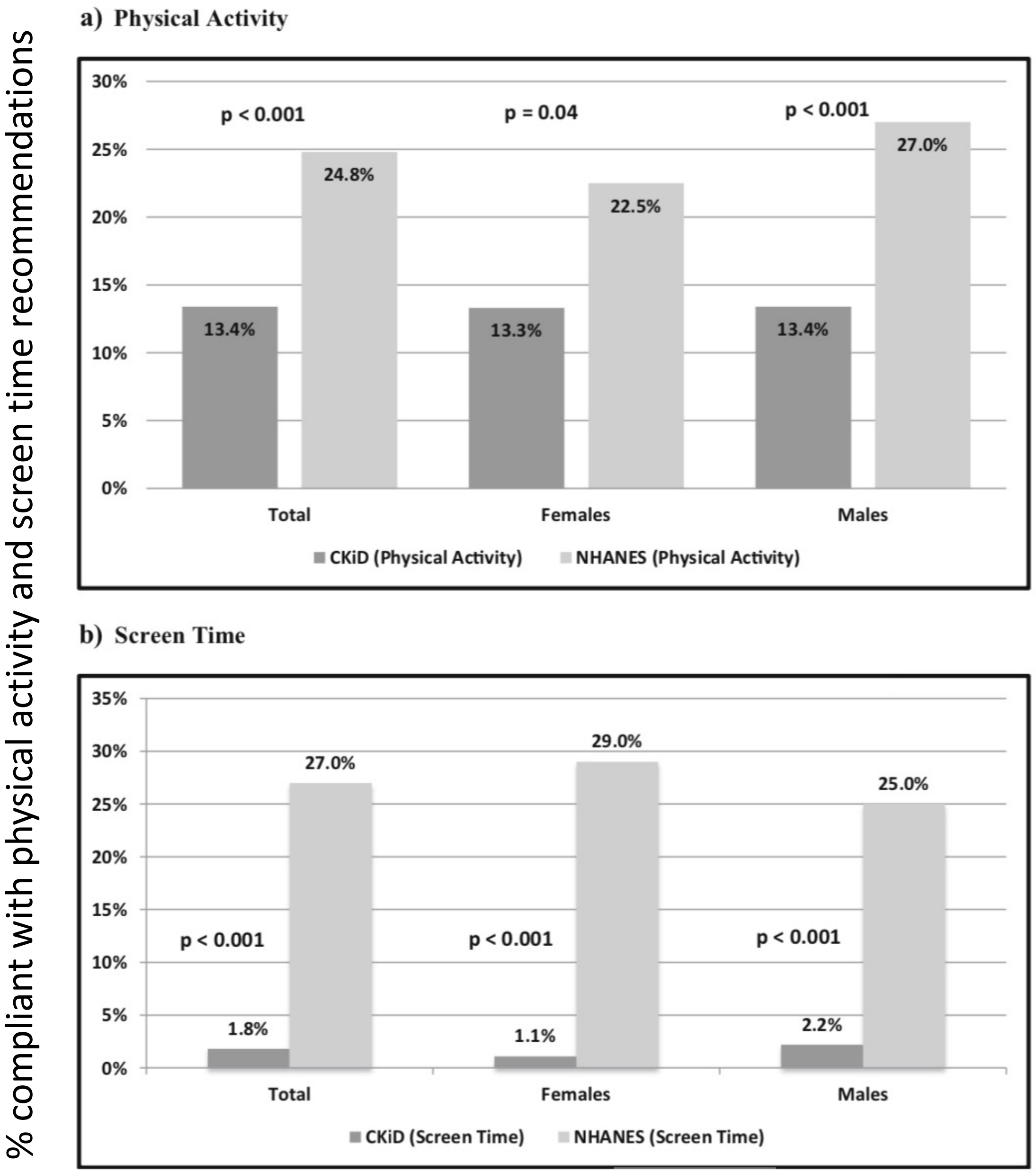
Promising in adults in proteinuria reduction, uncertain the effect on hard outcomes (CKD progression)..

Could be used to treat resistant HTN

Side effects!!

Non-pharmacological treatment should be applied along with antihypertensive treatment

Physical activity and screen time in adolescents in the chronic kidney disease in children (CKiD) cohort



Clark et al, Pediatr Nephrol (2016) 31:801–808

Estimated daily sodium intake in children with CKD

658 children from the North American Chronic Kidney Disease in Children (CKiD) prospective cohort study

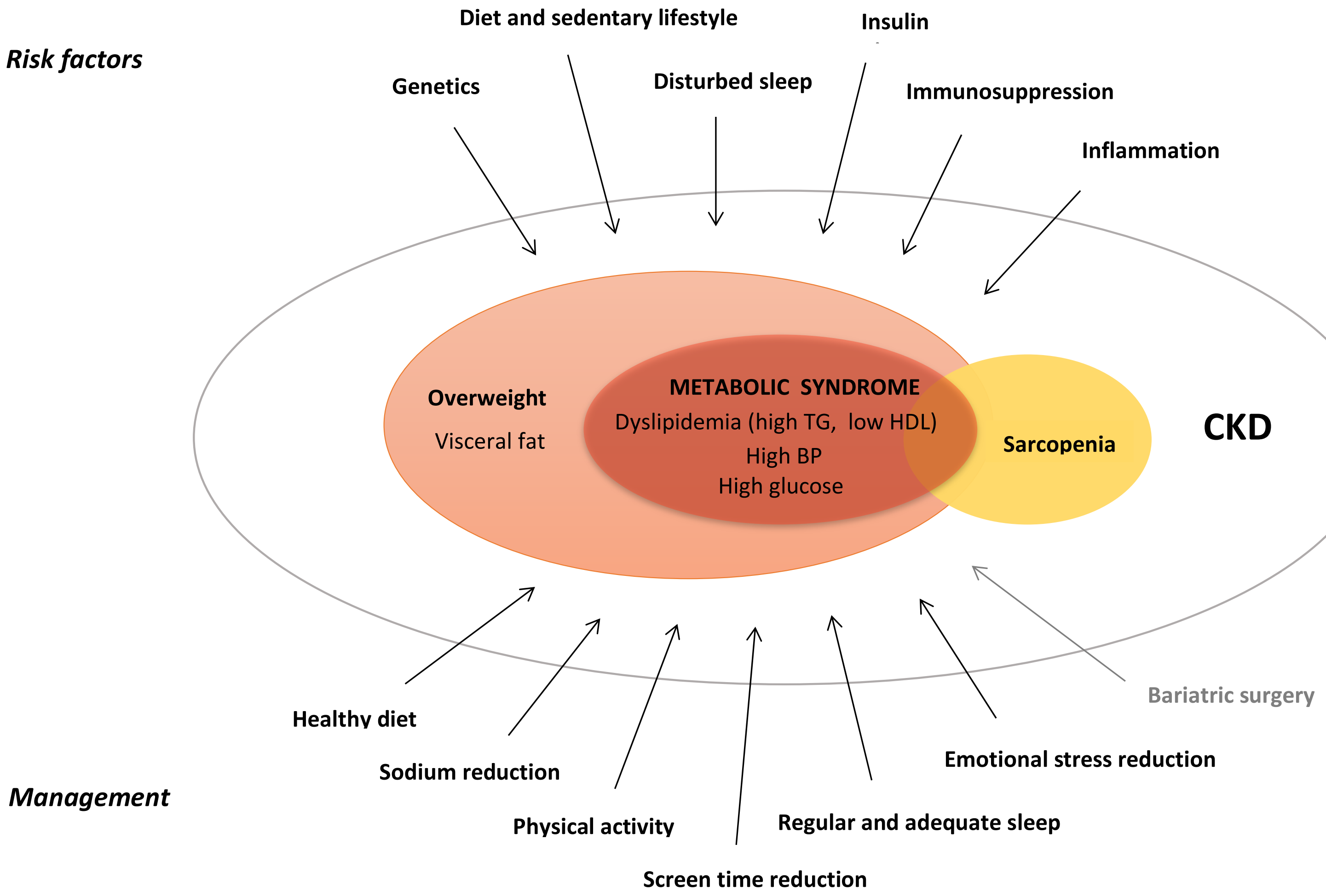
Table 2 Estimated daily sodium intake

Age/years	Recommended maximum total daily intake[a]	All participants
1–3 (*N*=39)	1500	2180 (1690–2805)
4–8 (*N*=164)	1900	2873 (2118–4048)
9–13 (*N*=235)	2200	2937 (2244–3678)
14–18 (*N*=220)	2300	3884 (2854–5150)

Hui et al. Pediatr Nephrol. 2017 Mar;32(3):485-494

Assessment and management of obesity and metabolic syndrome in children with CKD stages 2-5, on dialysis and after kidney transplantation

- clinical practice recommendations from the Pediatric Renal Nutrition Taskforce



Stabouli et al, Pediatric Nephrology 2022

Conclusions

- Lower BP targets are recommended for children and adolescents with CKD
- These targets are mainly supported by evidence on attenuation of CKD progression
- Subclinical CVD endpoints have been associated with BP levels > 90th percentile for age, sex and height
- ABPM and office BP are the mainstay for HTN diagnosis and treatment monitoring in children with CKD
- Current observational data support the use of ACEi/ARBs as first line treatment

- All published guidelines highlight the need for more evidence on the treatment of hypertension in children and adolescents with CKD

- **Thank you very much for your attention**

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

Disasters and Children

F. Lale Sever, M.D.

Emeritus Prof. of Pediatric Nephrology

Istanbul University- Cerrahpaşa School of Medicine, Turkey

10th SEPNWG MEETING AND TEACHING COURSE

1-3 June 2023, Ohrid, Republic of North Macedonia

Macedonian Society for Rare Diseases

LIFE with CHALLENGES Life is a puzzle, collect it.

РЕТКО Е ДА СИ РЕДОК
RRALLË ËSHTË TË JESH I RRALLË
RARE IS TO BE RARE

IPNA Sponsored T

by the Macedonian Pediatri

Outline

- Introduction
- Statistics
  - -Natural disasters
  - -Armed conflicts
- How are children affected by disasters?
- Disasters and kidney problems
  - - Acute kidney injury (Crush syndrome)
  - - Chronic kidney patients during disasters

Disaster - Definition

UNDRR

UN Office for Disaster Risk Reduction

"A serious disruption of the functioning of a community due to hazardous events interacting with conditions of exposure, vulnerability and capacity, leading to human, material, economic and environmental losses"

UNDRR Sendai Framework Terminology on Disaster Risk reduction. https://www.undrr.org/terminology/disaster. Accessed 20 April 2023

The definition includes 3 keywords

"A serious disruption of the functioning of a community due to hazardous events interacting with conditions of exposure, vulnerability and capacity, leading to human, material, economic and environmental losses"

Hazard - triggering event leading to the disater

Natural

Droughts
Floods
Earthquakes
Volcanic activity
Storms
Extreme temparature
Landslides
Wildfires

+ Biological hazards

Man-made

Wars
Terrorist attacks
Nuclear accidents
Fires
Structural collapses

WHO/EHA (2002) Disasters & emergencies. Defnitions. https:// apps.who.int/disasters/repo/7656.pdf. Accessed 4 June 2022

Emergency Disaster Database (EM-DAT) https://ourworldindata.org/natural-disasters. Accessed 15 May 2023

Vulnerability – risk to suffer from the disaster

✓ Some individuals or some segments of the population are unable to resist the hazard or to respond to the disaster.

* Children

** Pediatric Kidney patients,

*** End-Stage Renal Disease

unique sensitive groups

Capacity – ability to manage

Large-scale disasters

Insufficient capacity of local response

Need of help

National

International

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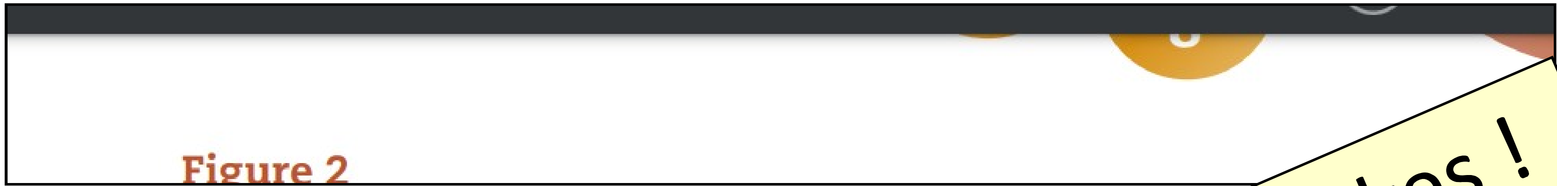
Natural disasters in numbers



✓ Natural disasters are frequent.

Every year, nearly 400 natural disasters occurred gl… …st decade.

✓ Natural disast… …ons.

Every yea… …people are affected by natural disasters.

The most deadly events are earthquakes !

✓ Natural disasters kill thousands.

Natural disasters kill an average of 60.000 people per year.

Centre for Research on the Epidemiology of Disasters CRED. 2022 EM-DAT Report. https://www.emdat.be/publications. Accessed 10 May 2023

Türkiye (Kahramanmaraş) –Syria Earthquake 2023

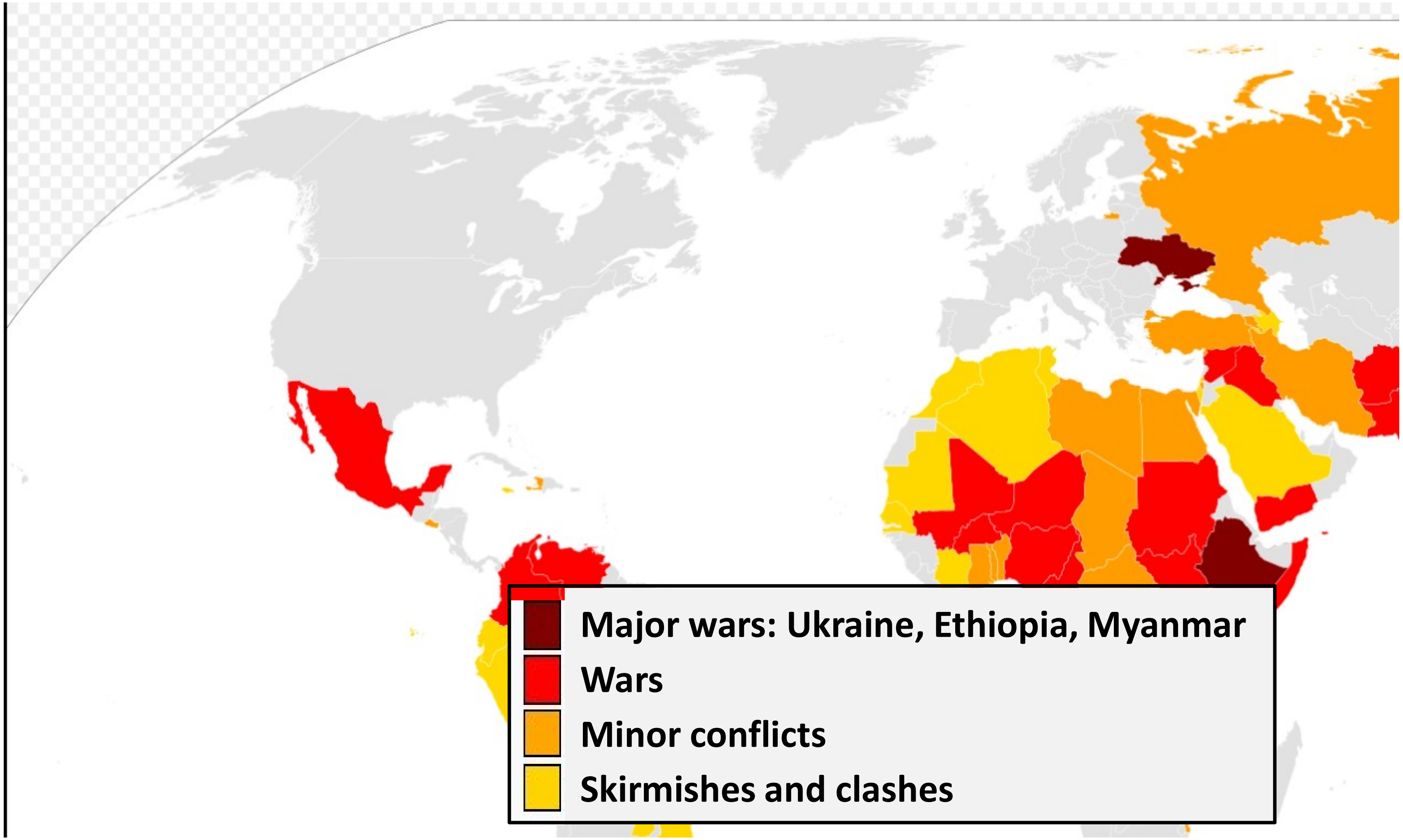
Natural disasters - Children

- ✓ 1 billion children live in countries with high seismic risk
  -prone to be affected by earthquakes-

- ✓ In natural disasters
  up to 43% of injured patients are children.

UNICEF. Children and diasaters. https://www.unisdr.org/we/inform/publications. Accessed 6 May2019
Grindlay J, Breeze KM. J Paediatr Child Health 2016; 52:204-12

Armed conflicts – Ongoing armed conflicts in 2022



Wikipedia. https://en.wikipedia.org/wiki/List_of_ongoing_armed_conflicts Accessed 16 May2023

Armed conflicts - Children

“Save the Children”

Stop the War on Children, 2022 Report – figures from 2021-

- ✓449 million children – globally,
  1 child out of 6 – lives in a conflict zone

- ✓ An average of 22 children being killed or injured a day in 2021.

https://resourcecentre.savethechildren.net/document/stop-the-war-on-children-the-forgotten-ones/

Armed conflicts - Children

"Save the Children"

Stop the War on Children, 2022 Report - figures from 2021-

In 2023, 7.5 million Ukrainian children live in conflict zones

https://resourcecentre.savethechildren.net/document/stop-the-war-on-children-the-forgotten-ones/
Accessed 16 May2023

The most recent armed conflict - Sudan-

- ✓ Nowadays the most dangerous armed conflict continues in Sudan
- ✓ As of 16 May, at least 1,000 people had been killed.

www.aljazeera.com Accessed 22 May2023

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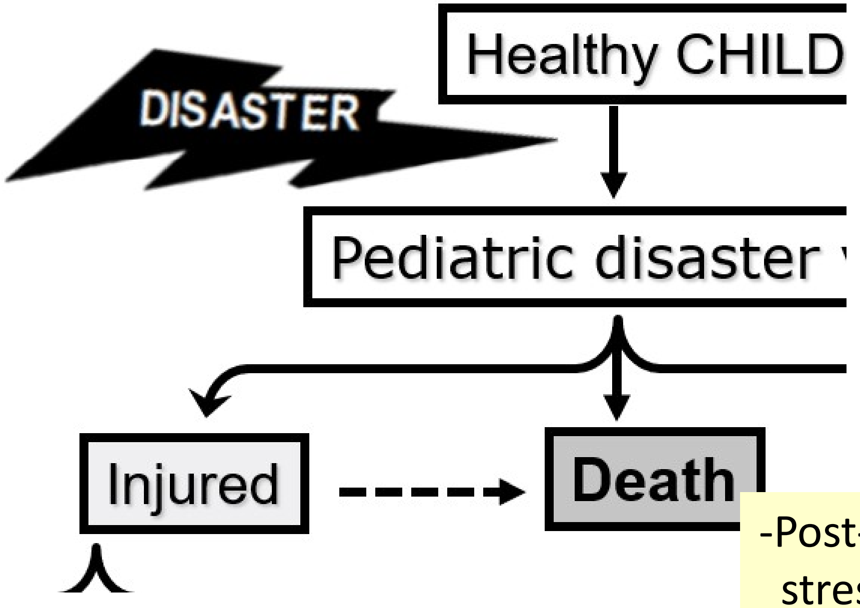
How are children affected by disasters ?
-Health effects-

- ✓ Anatomical and physiological features
- ✓ Limited self-preservation skills
- ✓ Dependence on parents/caregivers



-Post-traumatic stress disorder
-Substance abuse

Grindlay J, Breeze KM. J. Paediatr Child Health 2016; 52:204–12
Sever MS, Sever L, Vanholder R. Pediatr Nephrol 2020; 35:1381-93
Sever L, Balat A. Semin Nephrol 2020; 40:408-20

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Disasters and kidney problems

- Acute kidney injury (AKI) -

Massive bleeding, severe dehydration → **Prerenal**

Direct injury to the kidneys → **Intrinsic renal**

Trauma to the ureters, urethra, pelvic region → **Postrenal**

Prerenal + Intrinsic renal → **Crush Syndrome**

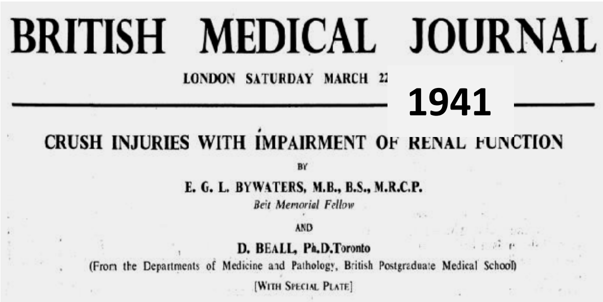
Crush syndrome is the most frequent cause of AKI after destructive disasters.

Sever L, Balat A. Semin Nephrol 2020; 40:408-20

Sever MS, Vanholder R, Lameire N. N Engl J Med 2006; 354:1052-63

Crush syndrome
- A neglected topic in nephrology-

Crush syndrome was described in:


BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 22

1941

CRUSH INJURIES WITH IMPAIRMENT OF RENAL FUNCTION

BY

E. G. L. BYWATERS, M.B., B.S., M.R.C.P.

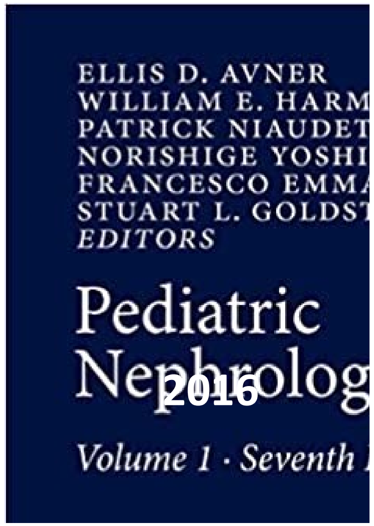
Beit Memorial Fellow

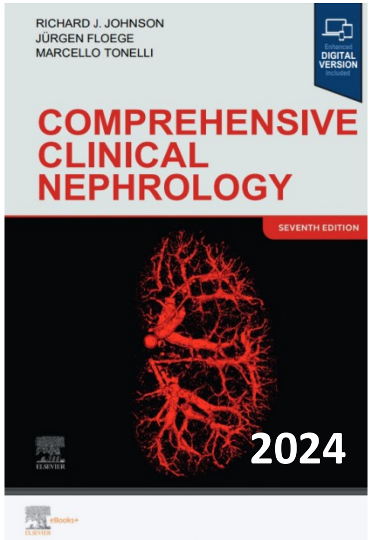
AND

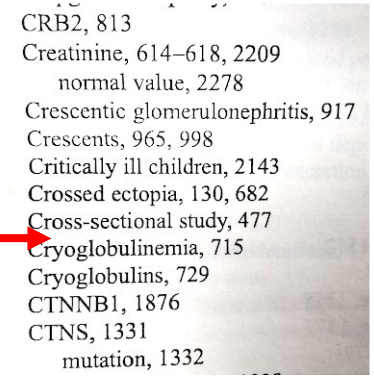
D. BEALL, Ph.D.Toronto

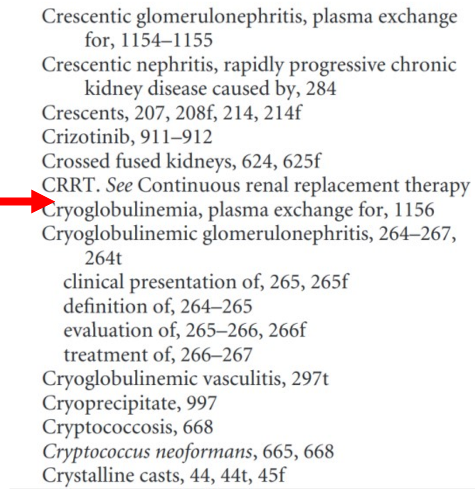
(From the Departments of Medicine and Pathology, British Postgraduate Medical School)

[WITH SPECIAL PLATE]









Crush syndrome

-not listed in the index pages-

Crush syndrome
- Epidemiology-

In earthquakes

- Crush syndrome rate in injured: **2 – 5%[1] (≈ 3%)**
- AKI occurs in more than half of crush syndrome patients[2]

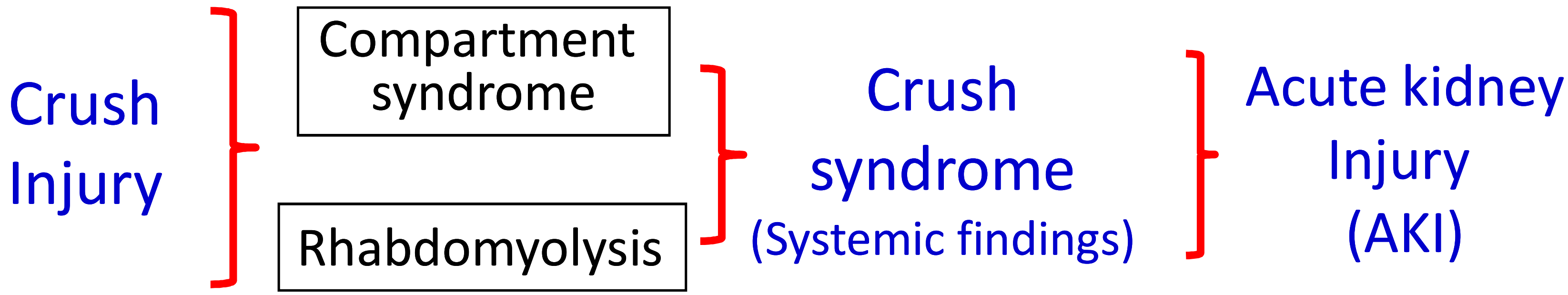
[1] Zhi-Yong S. J Trauma 1987; 27:1130-6
[2] Oda Y, et al. J Trauma 1997; 42:470-6

Pediatric victims

	Crush syndrome (n)	Crush related AKI (n)
Marmara Earthquake 1999[3]	?	**134**
Kahramanmaraş Earthquake 2023[4]	**322**	**264**

[3] Sever MS, et al. Kidney Int 2001;60: 1114-23
[4] Bakkaloğlu SA, et al. Unpublished data 2023

Crush syndrome
- Pathogenesis-



Crush syndrome
- Pathogenesis-

Pressure on muscle ⇒ ↗ sarcolemmal permeability

Ca^{++}
Ca^{+} **Ca^{++}**

Water

Na

Albumin

Ca^{++}

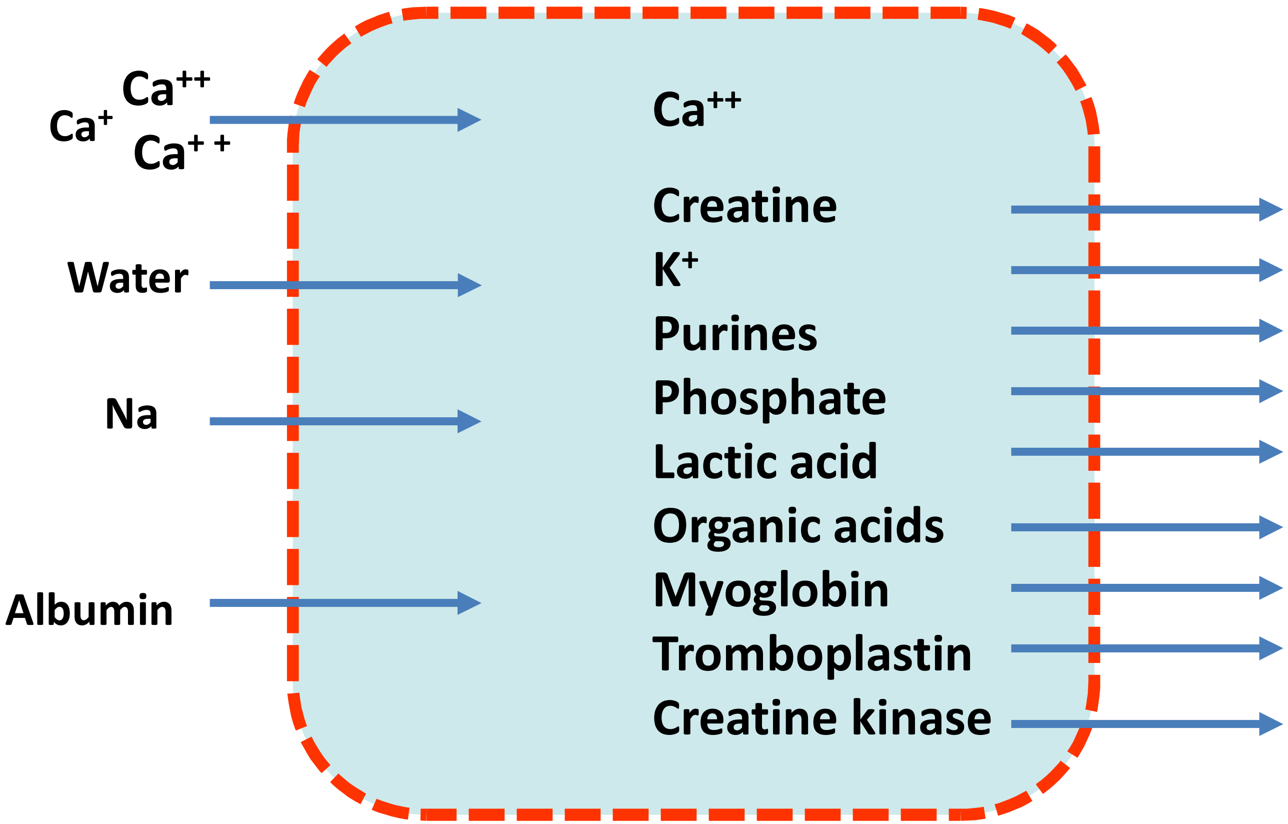
Creatine
K^{+}
Purines
Phosphate
Lactic acid
Organic acids
Myoglobin
Tromboplastin
Creatine kinase

Muscle cell

Better OS, Stein JH. New Engl J Med 1990; 322:825-9

Crush syndrome
- Pathogenesis-

Pressure on muscle ⇒ ↗ sarcolemmal permeability



Muscle cell

Better OS, Stein JH. New Engl J Med 1990; 322:825-9

Crush syndrome
- Pathogenesis-

Compartment syndrome

Hypocalcemia

Ca^{++} Ca^{++} Ca^{++}

Intravascular volume (IVV) ↓

Water

Na

Hypoalbuminemia

Albumin

Creatine → Creatinine ↑

K^{+} → Hyperkalemia

Purines → Hyperuricemia

Phosphate → Hyperphosphatemia

Lactic acid

Organic acids → Acidosis

Myoglobin → Myoglobinuria

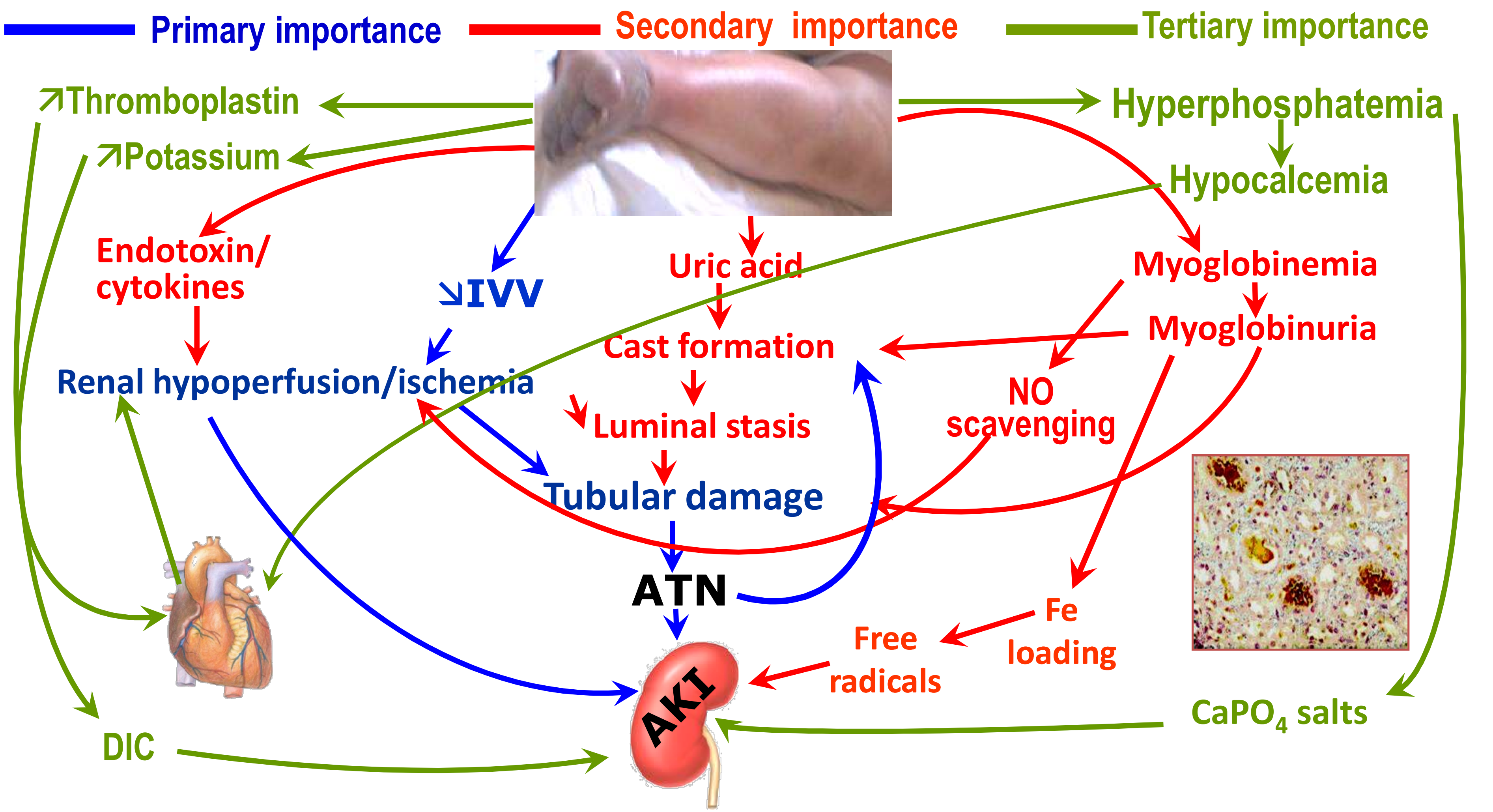
Tromboplastin → DIC

Creatine kinase → Creatine kinase (CK) ↑

Muscle cell → Rhabdomyolysis

Crush syndrome

- Pathogenesis of AKI-

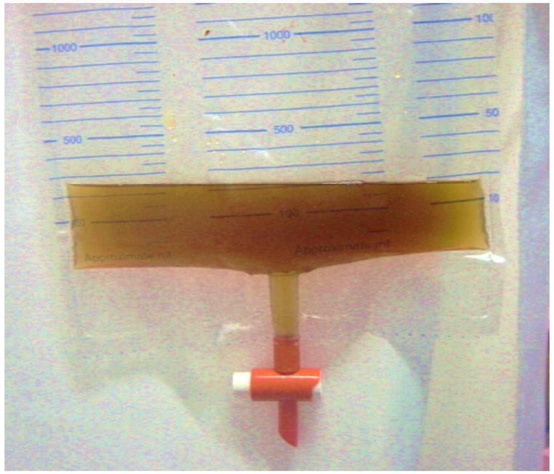


Courtesy of MS Sever

Crush syndrome
- Laboratory findings-

Urine

- Myoglobinuria



Blood tests

- Creatinine ↑
- Acidosis
- Hyperphosphatemia
- Hypocalcemia
- Hyperuricemia

- Hypoalbuminemia
- CK ↑
- Hyperkalemia

⇓

Aggressive dialysis needed

Crush syndrome
- Prevention- fluid therapy-

Turkish Archives of Pediatrics

Canpolat N, Saygılı S, Sever L.

2 / 3

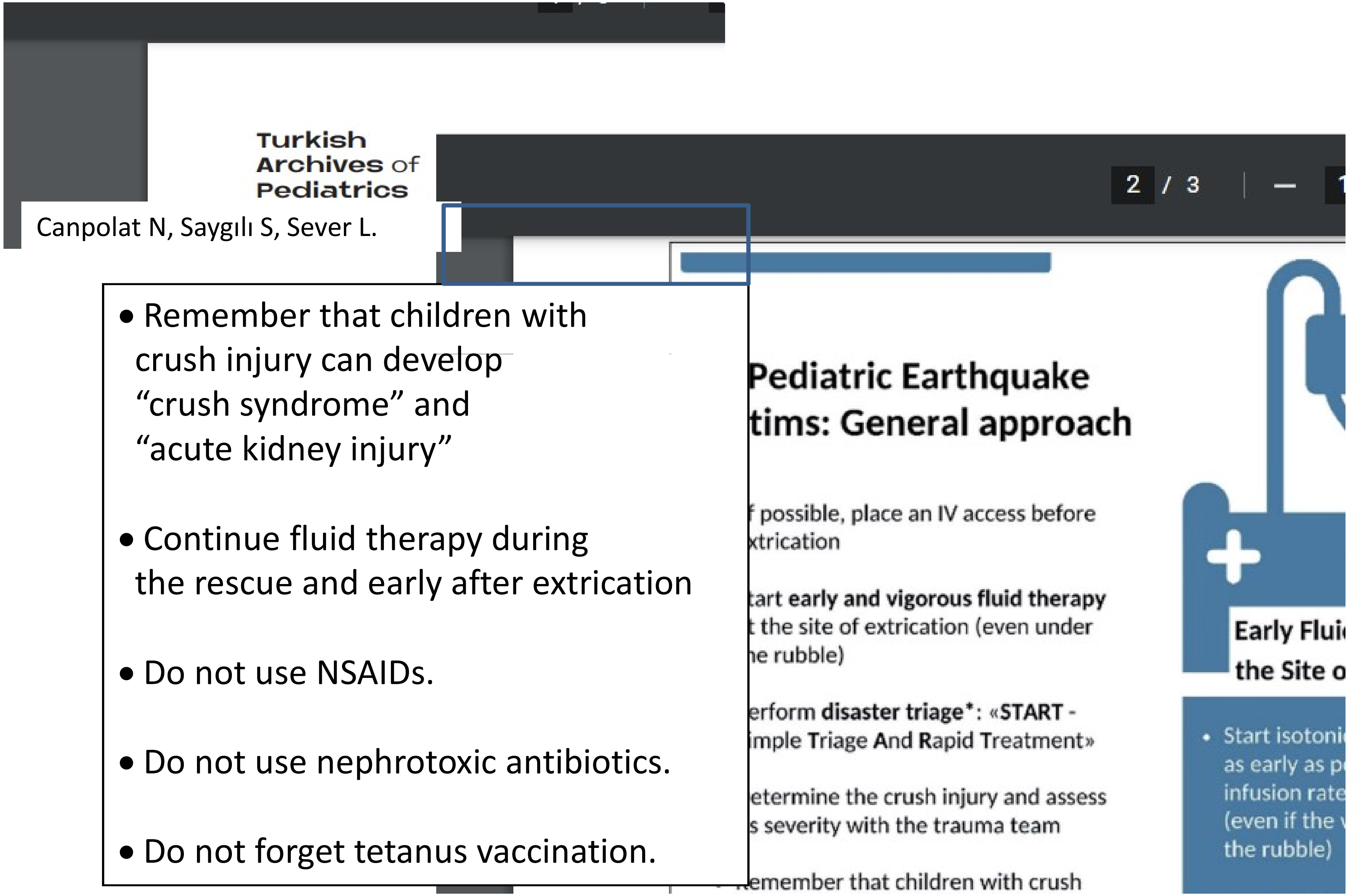
Pediatric Earthquake victims: General approach

- If possible, place an IV access before extrication
- Start **early and vigorous fluid therapy** at the site of extrication (even under the rubble)
- Perform **disaster triage***: «**START** - **Simple Triage And Rapid Treatment**»
- Determine the crush injury and assess its severity with the trauma team
- Remember that children with crush

Early Flui
the Site o

- Start isotoni
as early as p
infusion rate
(even if the
the rubble)

Crush syndrome
- Prevention- fluid therapy-



- Remember that children with crush injury can develop "crush syndrome" and "acute kidney injury"
- Continue fluid therapy during the rescue and early after extrication
- Do not use NSAIDs.
- Do not use nephrotoxic antibiotics.
- Do not forget tetanus vaccination.

Crush syndrome
- Prevention- fluid therapy-

Early fluid therapy at the site of extrication

- Start **isotonic saline (0.9% NaCl)** as early as possible at an infusion rate of **15-20 mL/kg/h** (even if the victim is still under the rubble)
- If extrication takes longer than **2 hours** the infusion rate should be **reduced by half.**
- Continue fluid therapy until the victim reaches the healthcare facility

0.9%NaCl 1500-2000 mL/m^2 in the first 6 hours

- **Do not use** fluids containing **potassium.**

Crush syndrome
- Prevention- fluid therapy-

Maintenance fluid therapy in the healthcare facility

- Monitor the patient's **urine output**
- If patient is **anuric or oliguric**,
  restrict fluid infusion
  400 mL/m^2/day + ongoing losses
- If there is a crush injury +
  the patient has good urine output
  5% dextrose 0.45% NaCl + 50 mEq/L $NaHCO_3$
  3-6 L/m^2/day
- **Avoid adding potassium**,
  without testing serum potassium levels

Crush syndrome related AKI
- Dialysis-

Advantages and drawbacks of various dialysis modalities in disaster victims

Dialysis modality	Advantages	Drawbacks	Comments
IHD	- High clearance rate of low molecular weight solutes (e.g. potassium) - Possibility to dialyze without anticoagulation - P	- Need for experienced personnel and technical assistance - Increased risk of disequilibrium syndrome	- The most practical RRT modality in disaster conditions
CRRT	- B - Lower risk of disequilibrium syndrome - Opportunity to administer more calories - CAVH has the advantage of no need for pumps	- Low removal capacity for small solutes - Treatment restricted to only one patient per machine per day cases, because many patients are hypotensive.	expensive than IHD and PD
PD	- No need for vascular access - Lower risk of disequilibrium syndrome - Simpler technique and less hemodynamic instability - No need for water and electricity - More appropriate than IHD in very small children	- Low clearance of small molecules - Difficulty in maintaining sterile technique - Difficult application if the patient cannot lie down - Bulky, if fluid bags are to be transported to the disaster area	- Difficult to perform in patients with thoracic, pulmonary and abdominal trauma - Can be used as a temporary rescue when IHD is not available - Patients should be closely monitored for hyperkalaemia

Intermittent hemodialysis is preferred because of medical and logistic advantages

Peritoneal dialysis should be considered at least as a temporary rescue in pediatric patients

Sever MS, Sever L, Vanholder R. Pediatr Nephrol 2020; 35:1381-93

Crush syndrome-related AKI
-Prognosis-

Marmara Earthquake 1999

Age groups	Population (n)	Crush- AKI (n)	Deaths (n)	Crush- AKI rate/ 100.000	Mortality rate in Crush AKI%
Overal	2,073,093	572	78	**27.6**	**13.6**
0-9 years	388,130	12	0	**3.1**	**0.0**
10-19 years	436,409	122	12	**28.0**	**9.8**

Crush syndrome- related AKI incidence and mortality is lower in 0-9 year pediatric patients as compared to adults.

[3] Sever MS, et al. Kidney Int 2001;60: 1114-23

Chronic kidney patients during disasters

-Problems-

Disaster

General effects

- Collapse of buildings
- Damage to electrical network
- Damage to water supply
- Destruction of roads, railways, wehicles
- Loss of security
- Damage to communication networks

Damage to medical facilities

- Collapse of hospitals
- Damage to HD and APD machines
- Lack of processed water for HD
- Patients’ and staff transportation difficulties
- Communication failure
- Killed/injured parents and unaccommpained pediatric patients
- İnjuired and overwhelmed personnel
- Shortage of medical supplies and medications

Sever L, et al. Pediatr Nephrol 2023; 38:315-25


AKUT
AMBU
LALE

Chronic kidney patients during disasters
-Problems-

Disaster

Medical problems in patients on kidney replacement therapy

- Increased risk for communicable and infectious diseases
  - Vascular access infections
  - Tunnel infections, peritonitis
- Malnutrition
- Lack of follow-up visits, insufficient laboratory tests
- Underdialysis and interruption in medical treatment
  - Fluid overload
  - Hypertensive emergencies
  - Acid-base, electrolyte disturbances
  - Rejection attacks
- Interruption of KTx programs

Sever L, et al. Pediatr Nephrol 2023; 38:315-25

Chronic kidney patients during disasters
Solutions- Patients

Protection from high blood potassium and fluid overload

Dietary measures

Applies to the patients with
no (or limited) dialysis possibilities

Decrease potassium	Decrease salt	Decrease fluids
Avoid high potassium containing foods 	Cook without salt 	Use small or half full glasses 
Boiling of vegetables and discarding the boling water will reduce the potassium content 	Use pepper, herbs, garlic or citrus to add flavour 	Divide your fluid allowance into parts 
Check labels of ready-to-eat foods for potassium content	Choose whole foods, cut back processed meats	Chewing gum, licking ice or lemon help decrease thirst 
	Check labels of ready-to-eat foods for sodium content	Good oral hygiene help get rid of dry mouth 
	Discard the water of canned foods and wash them 	

Chronic kidney patients during disasters
Solutions- Patients

Consider additional drugs / dosage modifications

Applies to the patients with no (or limited) dialysis possibilities

Risk of hyperkalemia	Warn the patients for dietary measures Consider anti-potassium drugs Consider to stop ACE i / ARB's Prevent acidosis
Risk of acidosis	• Plan to use sodium bicarbonate
Risk of hypervolemia/ Hypertension	Warn the patients for decreasing salt and fluid consumption Check antihypertensive treatment of the patient
Risk of hyperphosphatemia	Check anti phosphate treatment of the patient If needed, increase the dosage of anti phosphate drugs or add new drugs

Sever L, et al. Pediatr Nephrol 2023; 38:315-25

Chronic kidney patients during disasters

Solutions- Patients

Consider treatment modifications

Peritoneal Diaysis	If the patient is on Automated Peritoneal Dialysis (APD): • Connect patients for longer time periods to the cycler, make continuous exchanges; so that you can use the whole volume of big solution bags • If needed, consider manual exchanges (CAPD)
Hemodialysis	If dialysis facilities are limited: Determine patients, who can tolerate lower doses of dialysis If shorter or infrequent dialysis sessions are mandatory: Consider running the blood pump at maximum (tolerated) speed. Consider using dialysers with the largest (tolerated) surface areas
Transplantation	• Consider switching among immunosuppressants in case of unavailability • Switch from MMF to AZA, tacrolimus to cyclosporine or vice versa • If these are impossible, consider adding steroids to the patients with steroid-free regimens or increase dosage of steroids

Sever L, et al. Pediatr Nephrol 2023; 38:315-25

Conclusions

- ✓ Disasters are frequent and affect millions of people.
- ✓ Children, especially those with kidney diseases, constitute the most vulnerable group.
- ✓ Crush syndrome-related AKI is a frequent and potentially life-threatening problem after destructive disasters.
- ✓ Early and aggressive fluid administration may prevent crush-related AKI.
- ✓ Renal replasman therapies are problematic after disasters.

International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

Novel biomarkes in acute kidney injury

Vesna Stojanovic, Prof. MD PhD

Institute for Child and Youth Health Care of Vojvodina, Novi Sad
Serbia

Problems with Creatinine as a marker of AKI

- SCr is a marker of function – not injury
- SCr may not change until 25-50% of the kidney function has been lost
- At lower GFR, SCr will overestimate renal function due to tubular secretion of creatinine
- SCr varies by muscle mass, hydration status, sex, age and gender
- Once a patient receives dialysis, SCr can no longer be used to assess kidney function since SCr is easily dialyzed

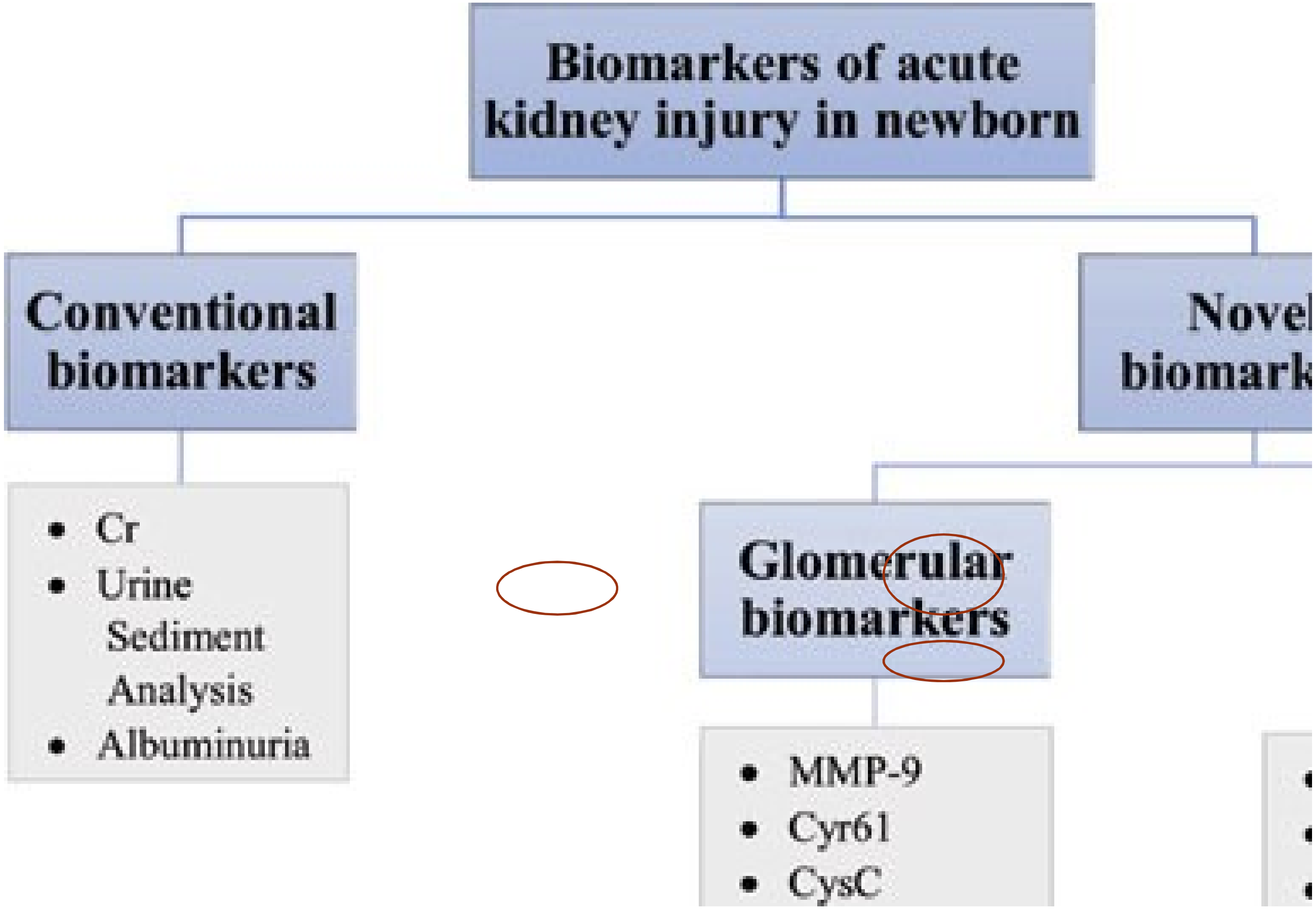
Jetton JG. Curr Opin Pediatr 2012.

Problems with Creatinine as a marker of AKI

- Medication and bilirubin can affect SCr measurements by the Jaffe method
- **Neonatal AKI:**
- Relatively reduced number of Cr measurements
- Variable GFR
- The absence of baseline/reference values
- The measurements of UO are not precise (these patients infrequently have a urinary catheter)

Ferreira Novo AC et al. Clinics 2011.

Novel urinary biomarkers can diagnose AKI within hours of an insult being discovered!



Kamianowska M. et al. Current Drug Metabolism, 20 (5), 2019

Biomarkers

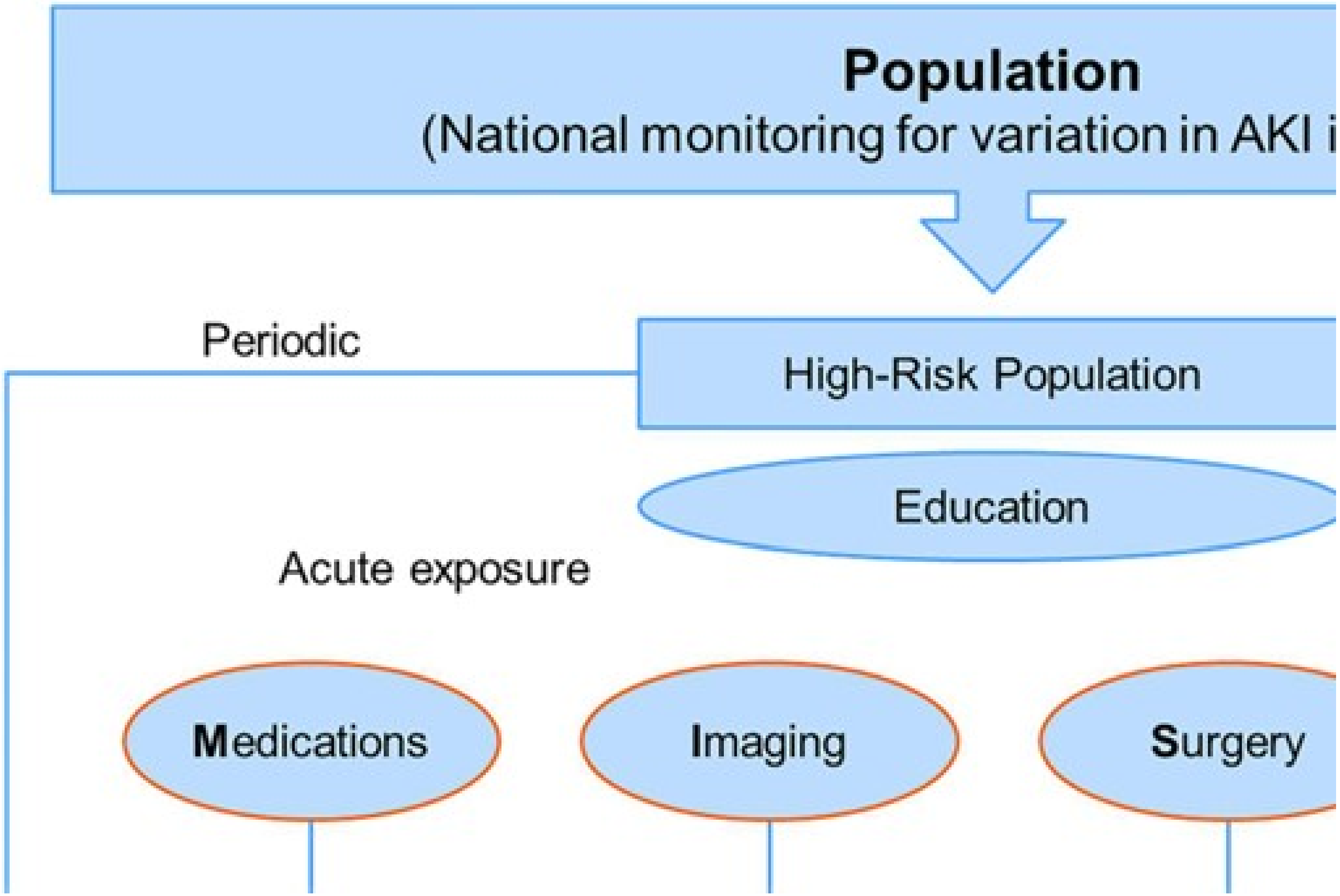
- There are four broad areas, as follows:

(1) AKI risk assessment;
(2) AKI prediction and prevention;
(3) AKI diagnosis, etiology, and management;
(4) AKI progression and kidney recovery.

AKI susceptibility

- Patient factors:

- demographic characteristics,
- comorbidities, and
- previous AKI episodes with the expected intensity of a planned exposure that carries AKI risk.



- Two elective exposures that carry a particularly high AKI risk are major surgery and nephrotoxic medications.

Kashani K. Clin J Am Soc Nephrol, 2019.

The types of functional and/or damage biomarker

- Traditional measures of kidney function include:
- estimated glomerular filtration rate (eGFR) equations,
- serum cystatin C,
- cystatin plus creatinine–based eGFR equations.

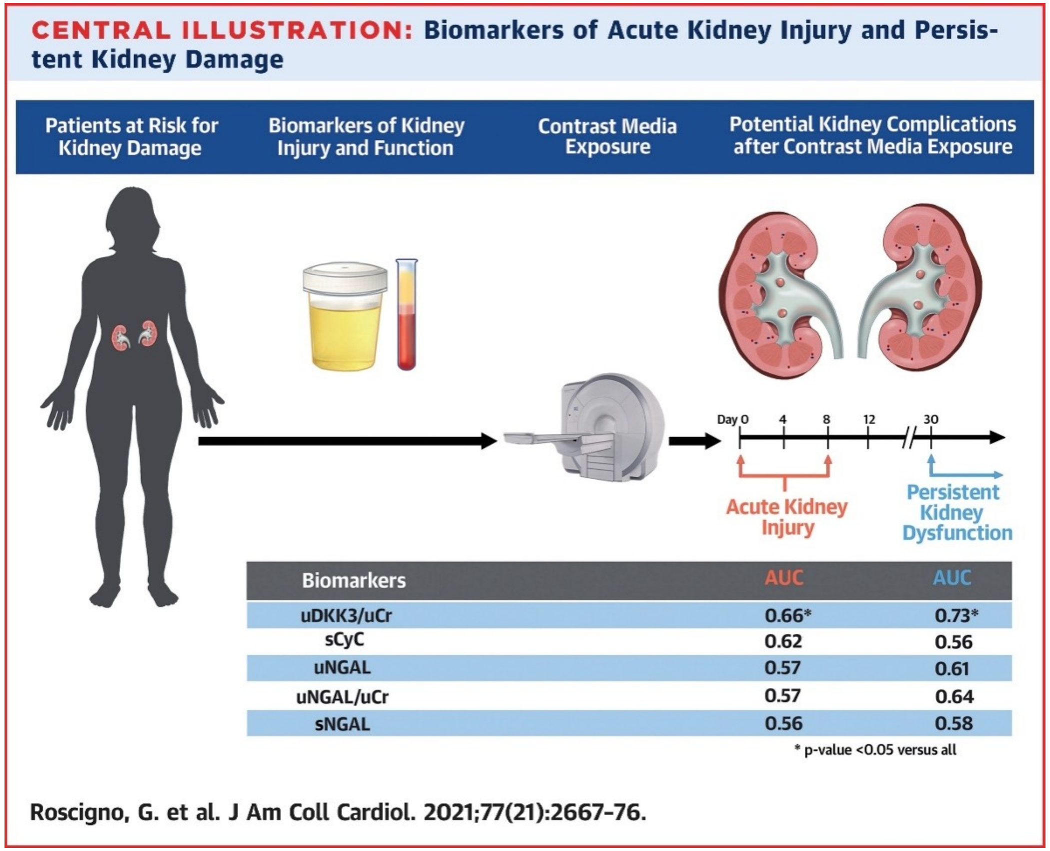
Biomarkers for AKI prediction and prevention

- The biomarkers could be use for identifying the patient populations for whom the preventive interventions have been shown to improve outcomes.

Ostermann M. JAMA Network Open, 2020.

Biomarkers for AKI prediction and prevention

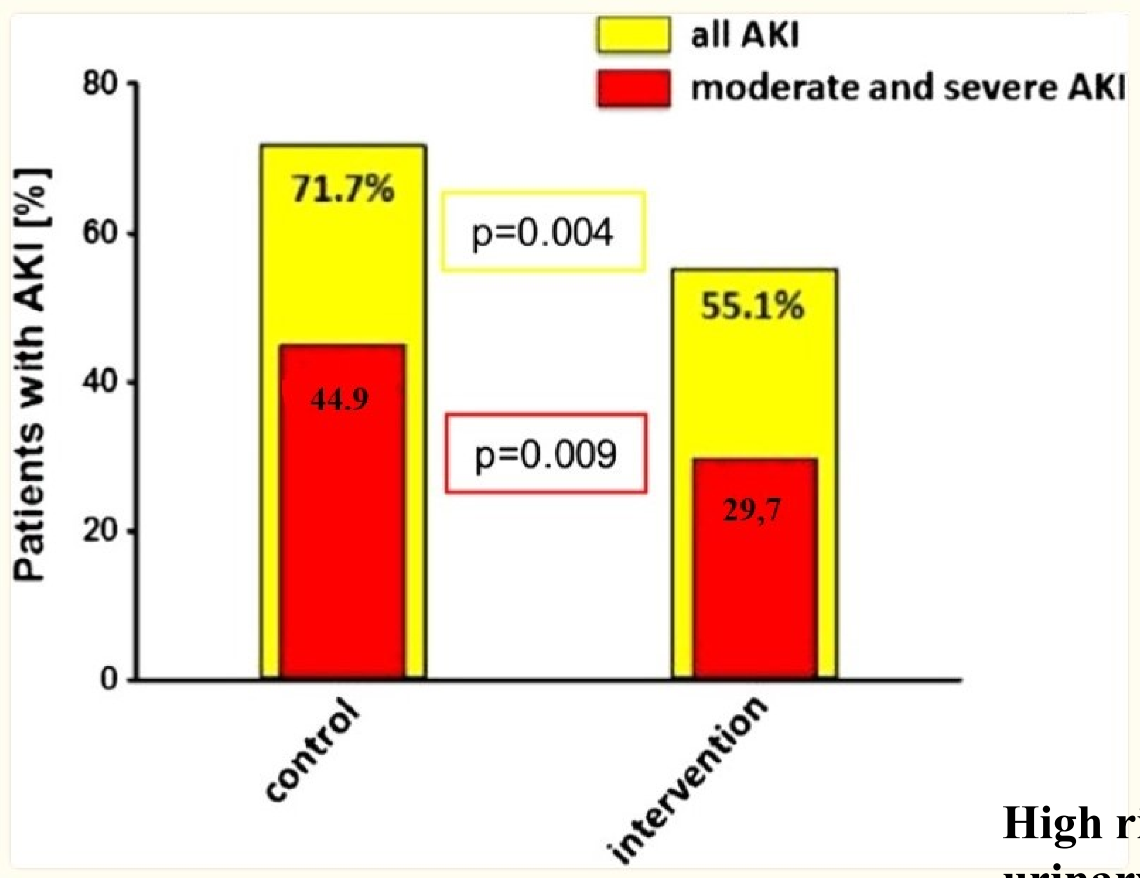
- New biomarkers for prediction of AKI risk.



Biomarkers	AUC	AUC
uDKK3/uCr	0.66*	0.73*
sCyC	0.62	0.56
uNGAL	0.57	0.61
uNGAL/uCr	0.57	0.64
sNGAL	0.56	0.58

Baseline urinary dickkopf-3/creatinine (uDKK3/uCr) was superior to urinary uNGAL, uNGAL/uCr, sNGAL, sCyC for the prediction of both *contrast-associated acute kidney injury* and *persistent kidney dysfunction*.

Different biomarkers were assessed in 458 patients with chronic kidney disease scheduled for invasive cardiovascular procedures requiring CM administration.



Intervention on patients undergoing cardiac surgery – **KDIGO bundle**:

- Optimization of volume status and hemodynamic
- Avoidance of nephrotoxic drugs
- Preventing hyperglycemia
- Discontinuation of ACEi and ARBs for 48h after surgery.

High risk patients are defined as urinary TIMP-2 x IGFBP7 ≥0.3 ng/ml 4h after CPB.

Trials have demonstrated that timely initiation of preventive strategies in patients with positive stress biomarkers after a kidney insult, ie, tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) were effective at preventing AKI within 72h.

Meersch M. Intensive Care, 2017.

Biomarkers for AKI prediction and prevention

- Biomarkers may also optimize ***drug dosing.***
- For decades, sCr has been used for this purpose. However, the use of sCr or any sCr-based estimate requires kidney function to be at a steady state.
- Cystatin C is less reliant on muscle mass and dietary intake and offers an alternative approach to estimate GFR.
- Reports indicate that in a steady state, **eGFR estimated by creatinine–cystatin C** is more precise and accurate at determining a measured GFR than eGFR estimated by creatinine or cystatin C alone.

Frazee EN. Critical Care, 2014.

Most promising biomarkers of nephrotoxicity

Biomarker	Drug
Urinary KIM-1	cisplatin, gentamicin, cyclosporine
Albuminuria	cisplatin
Beta-2 microglobulin	cisplatin, cyclosporin, gentamicin
Clusterin	cisplaitin, gentamicin
Serum cystatin C	aminoglycosides, amphoterin B, radiocontrast dye, high dose methotrexate, vancomycin
Urine NGAL	cisplatin

Griffin B. Ther Drug Monit, 2019.

> Crit Care Med. 2019 Oct;47(10):e820-e826. doi: 10.1097/CCM.00(

Use of Cell Cycle Arrest Biomarkers With Classical Markers of Acute Kic

- The authors examined biomarkers of cell cycle arrest in the settings of oliguria and/or azotemia to improve risk assessment when used with conventional indices in predicting severe AKI or death.

The primary endpoint being development of severe AKI or death within 1 week.

TABLE 2.

Hazard ratios for Stage 3 Acute Kidney Injury or Death by Number of Positive

Number	0.3 Cut-off					
Positive	HR	95% CI Lower	95% CI Upper	*p*	HR	95%
1	2.17	1.03	4.56	0.04	2.89	
2	4.14	2.00	8.55	< 0.001	4.91	

Conclusion 1: Cell cycle arrest biomarkers, TIMP-2 and IGFBP7, improve risk stratification for severe outcomes in patients with stage 1 AKI by urine output, serum creatinine or both, with risk increasing with each AKI indicator.

Joannidis M. Crit Care Med, 2019.

Secondary analysis examined the relationship between TIMP-2 and IGFBP7 and 9-month death or dialysis conditioned on progression to stage 2-3 AKI within 1 week.

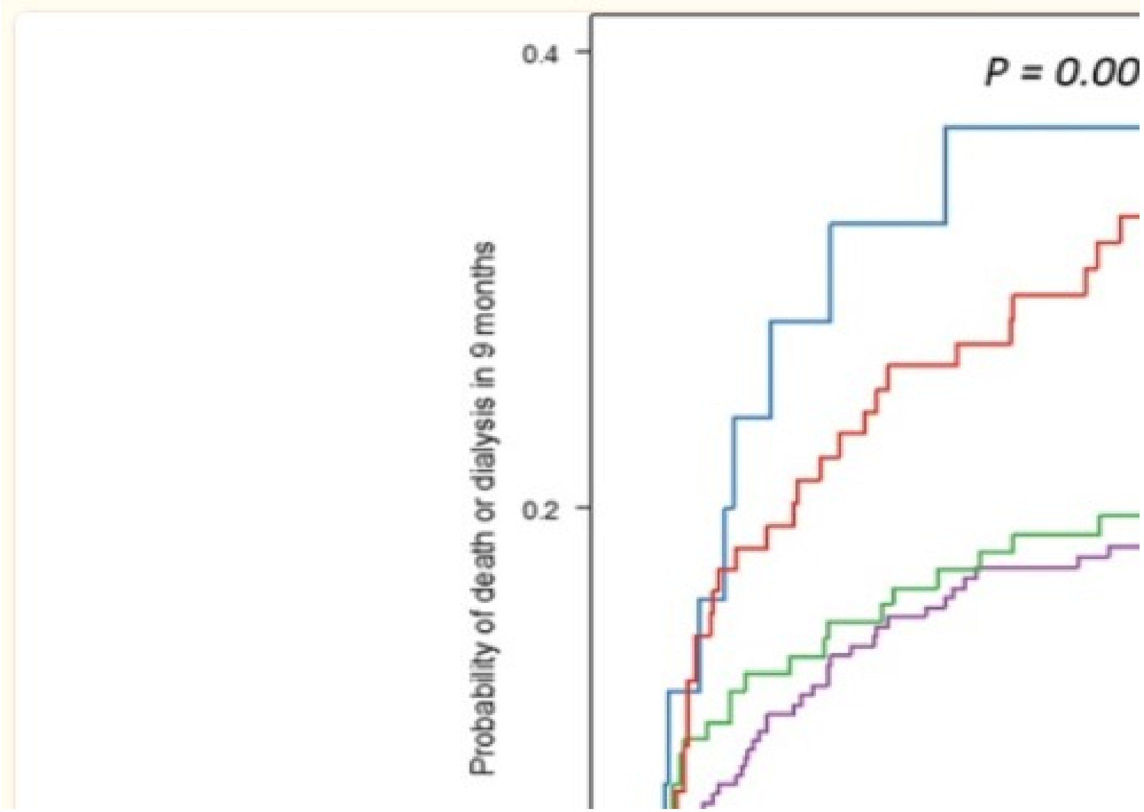


Figure 3. Kaplan-Meier curves for death or dialysis within 9 mo among patients who were alive and dialysis-free at 7 d after enrolment.

Conclusion 2: Longer term outcomes demonstrate that the associated risks of a [TIMP-2]•[IGFBP7] greater than 2.0 is equivalent to AKI progression even where no progression from stage 1 AKI is observed.

Joannidis M. Crit Care Med, 2019.

Biomarkers for AKI prediction (risk of AKI) and prevention

- **Combining clinical assessment** and **validated biomarkers** to triage patients and optimize the timing and type of interventions designed to improve processes of care and patient outcomes.
- The performance of current prediction models to identify patients at risk of AKI is variable. The negative predictive value is generally good, but the positive predictive value of most models is moderate to low.

Ostermann M. JAMA Network Open, 2020.

Biomarkers for AKI diagnosis, etiology, and management

- There is a persistent unmet need for an earlier identification of patients with AKI.
- Furthermore, diagnostic tools that identify the location, mechanism, etiology, severity, and prognosis of AKI are necessary.

- Some patients with positive damage biomarkers do not fulfill traditional AKI criteria, yet, have worse outcomes.

Ostermann M. JAMA Network Open, 2020.

> J Am Coll Cardiol. 2014 Dec 30;64(25):2753-62. doi: 10.1016/j.jacc

Combining functional and tubular d biomarkers improves diagnostic pr kidney injury after cardiac surgery

- This study investigated the value of combining a functional damage biomarker (plasma cystatin C [**pCysC**]) with a tubular damage biomarker (urine neutrophil gelatinase-associated lipocalin [**uNGAL**]), forming a composite biomarker for prediction of discrete characteristics of AKI.
- Data from 345 children after cardiopulmonary bypass were analyzed.

Basu R. J Am Coll Cardiol, 2014.

TABLE 2. Prediction of Severe AKI by Biomarker Composites

Marker	Sensitivity	Specificity	PPV	NPV
ASCr+	22 (13-35)	94 (91-96)	45 (27-64)	85 (80-89
uNGAL– pCysC–	5(1-14)	46 (41-52)	2 (0-6)	69 (62-76
uNGAL– pCysC+	23 (13-35)	57 (50-63)	10 (6-17)	77 (71-82
uNGAL+	24 (14-37)	98 (96-99)	75 (51-91)	75 (51-91

uNGAL and pCysC demonstrate significantly improved **prediction of severe AKI** compared to the change in serum creatinine (ΔSCr) from pre-operative to first post-operative value (cutoff value for positivity of ≥50% increase).

Basu R. J Am Coll Cardiol, 2014.

TABLE 3. Prediction of AKI >2 Days by Biomarker Composites

Marker	Sensitivity	Specificity	PPV	NPV
Δ SCr+	31 (15-51)	93 (90-96)	29 (14-48)	93 (90-96)
uNGAL– pCysC–	7 (1-23)	52 (46-58)	1.3 (0.2-4.6)	86 (80-90)
uNGAL– pCysC+	0(0-16)	57 (51-62)	0 (0-3)	89 (83-93)
uNGAL+	24 (10-44)	96 (93-98)	35 (15-59)	93 (90-96)

uNGAL and pCysC demonstrate significantly improved **prediction of the duration of severe AKI** compared to the ΔSCr from pre-operative to first post-operative value (cutoff value for positivity of ≥50% increase).

Basu R. J Am Coll Cardiol, 2014.

TABLE 4. Prediction of Transient AKI by Biomarker Composites

Marker	Sensitivity	Specificity	PPV	NPV
ΔSCr 0%-24%	42 (25-61)	59 (39-77)	54 (33-74)	47 (30
ΔSCr 25%-49%	24 (11-42)	83 (64-94)	62 (32-86)	49 (34
ΔSCr ≥50%	15 (5-32)	69 (49-85)	36 (13-65)	42 (28
uNGAL– pCysC–	3(0-16)	93 (77-99)	33 (5-88)	46 (33
uNGAL– pCysC+	42 (25-61)	100 (88-100)	100 (77-100)	60 (45

For patients who developed AKI (62 of 345), uNGAL and pCysC demonstrate the ability to use composite biomarker panels to **identify transient injury.** Prediction was significantly superior to that afforded by any ΔSCr from pre-operative to first post-operative value.

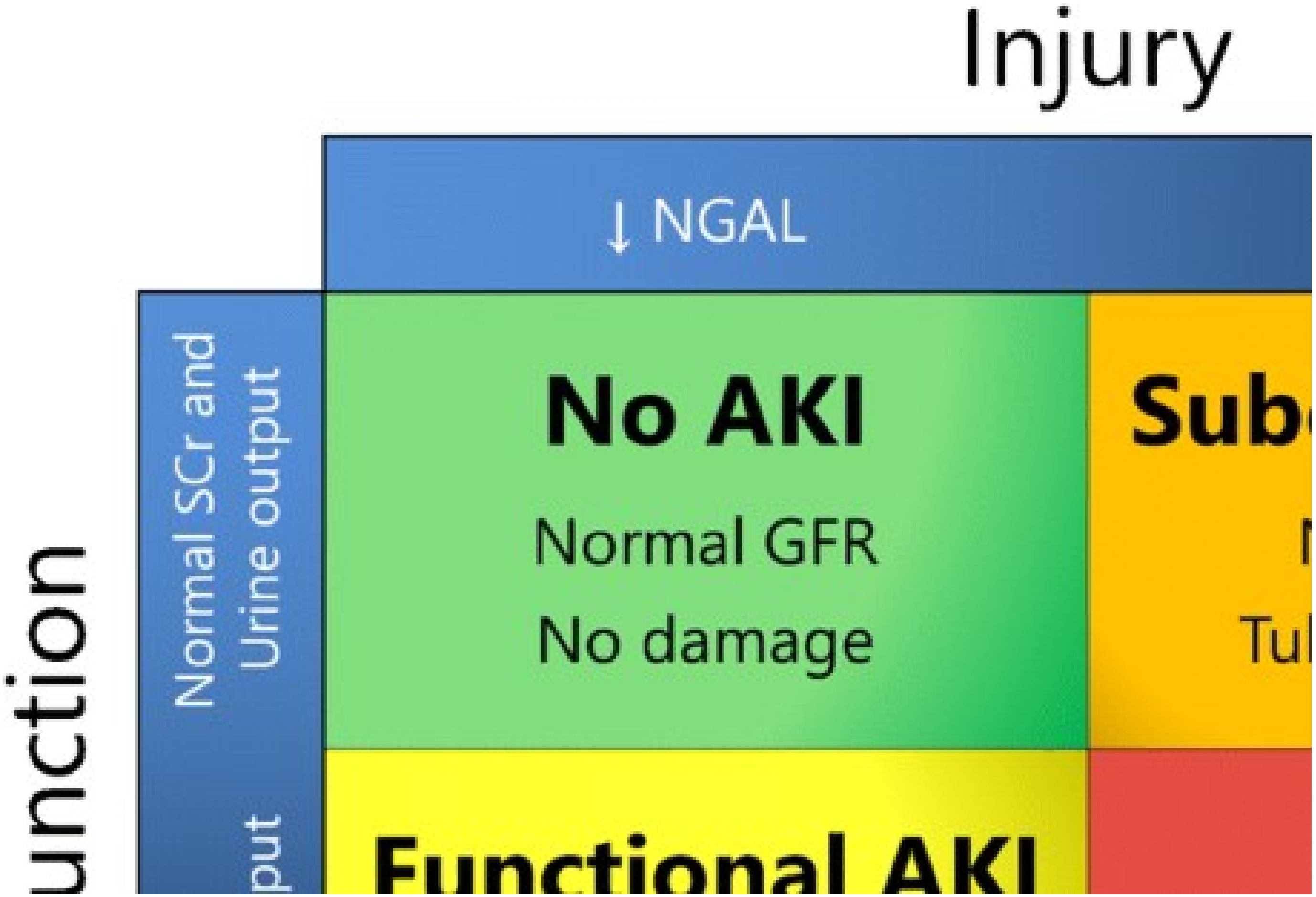
Basu R. J Am Coll Cardiol, 2014.

Biomarkers for AKI diagnosis, etiology, and management

- Combination of damage and functional biomarkers, along with clinical information, be used to improve the diagnostic accuracy of AKI, to recognize the different pathophysiological processes, to discriminate AKI etiology, and to assess AKI severity.
- Transient AKI, formerly known as "pre-renal" AKI, falls into the category of loss of function without damage.
- Damage with loss of function is a combination of functional and tubular injury.

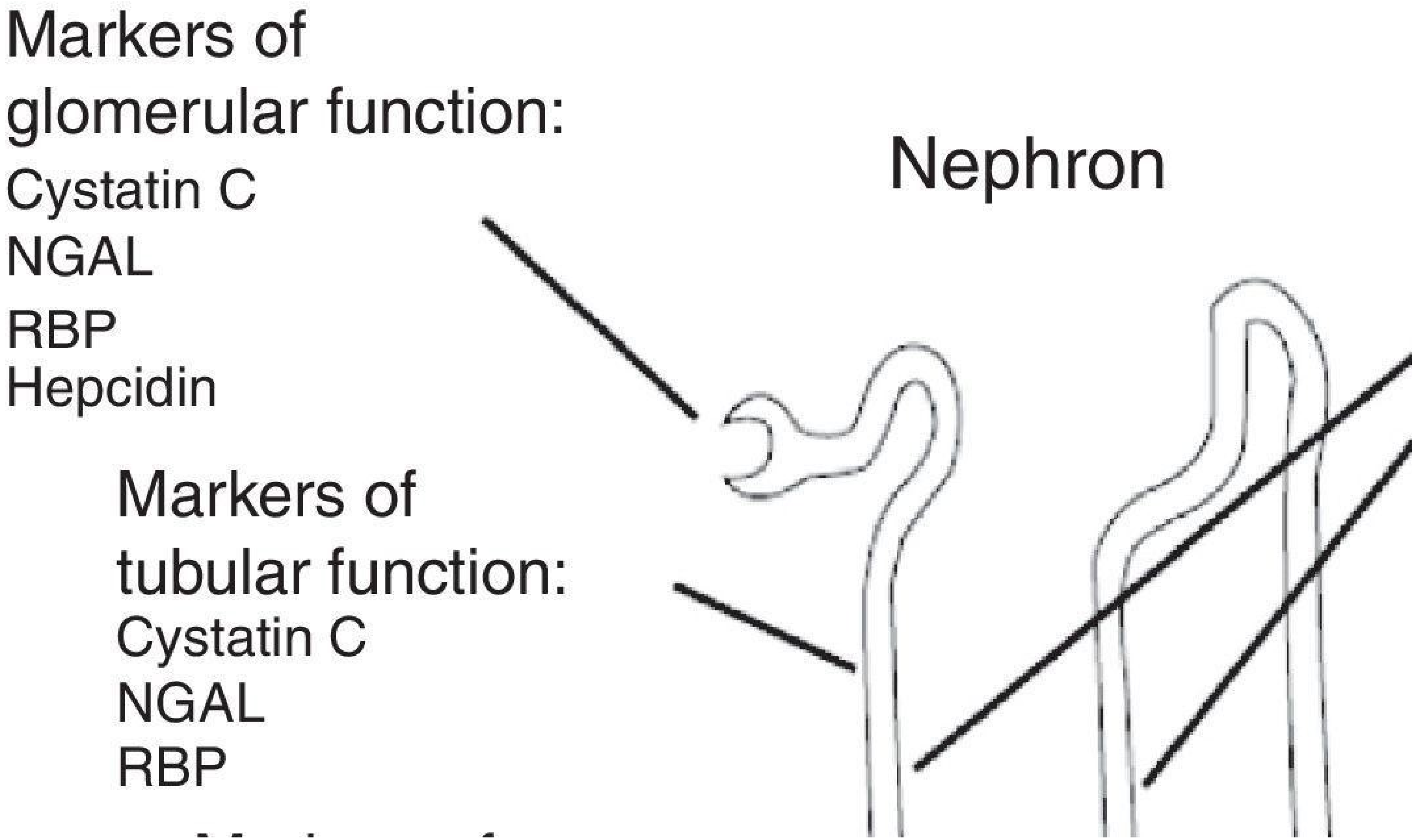
Ostermann M. JAMA Network Open, 2020.

Biomarkers for AKI diagnosis, etiology, and management



Roy RP. Ind J Pediatr, 2020.

Biomarkers for AKI diagnosis, etiology, and management



Biomarkers for AKI diagnosis, etiology, and management

- Clinical information enriched by damage and functional biomarkers could lead to more sensitive AKI definitions.
- The ADQI suggest a modification of KDIGO stage 1 AKI to reflect 3 substages (1S, 1A, and 1B) and to subcategorize stages 2 and 3 AKI by presence of biomarkers.

- *ADQI - Acute Disease Quality Initiative (Workgroup)

Ostermann M. JAMA Network Open, 2020.

Proposed New Definition of Acute Kidney Injury

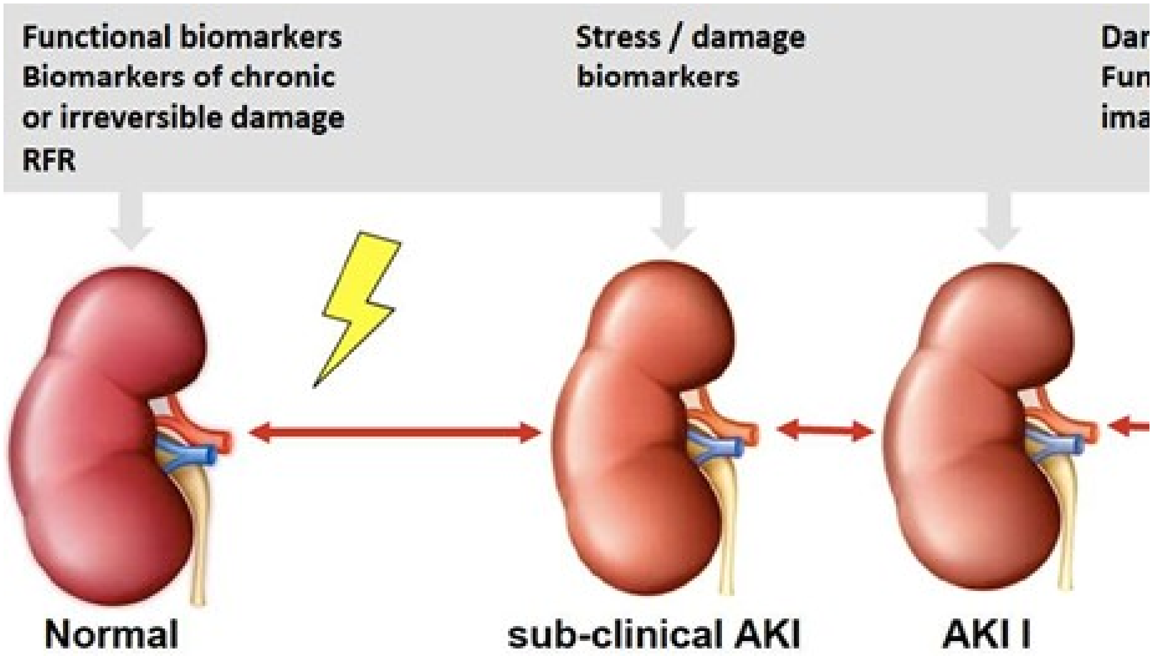
Functional criteria	Stage
No change or sCr level increase <0.3 mg/dL and no UO criteria	1S
Increase of sCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A
	1B
Increase of sCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A
	2B

Functional markers include serum creatinine (sCr) and urine output (UO) but new functional markers may also be included.

Ostermann M. JAMA Network Open, 2020.

Biomarkers for AKI diagnosis, etiology, and management

- A **combination of biomarkers** may assist the planning of therapy and management of AKI.

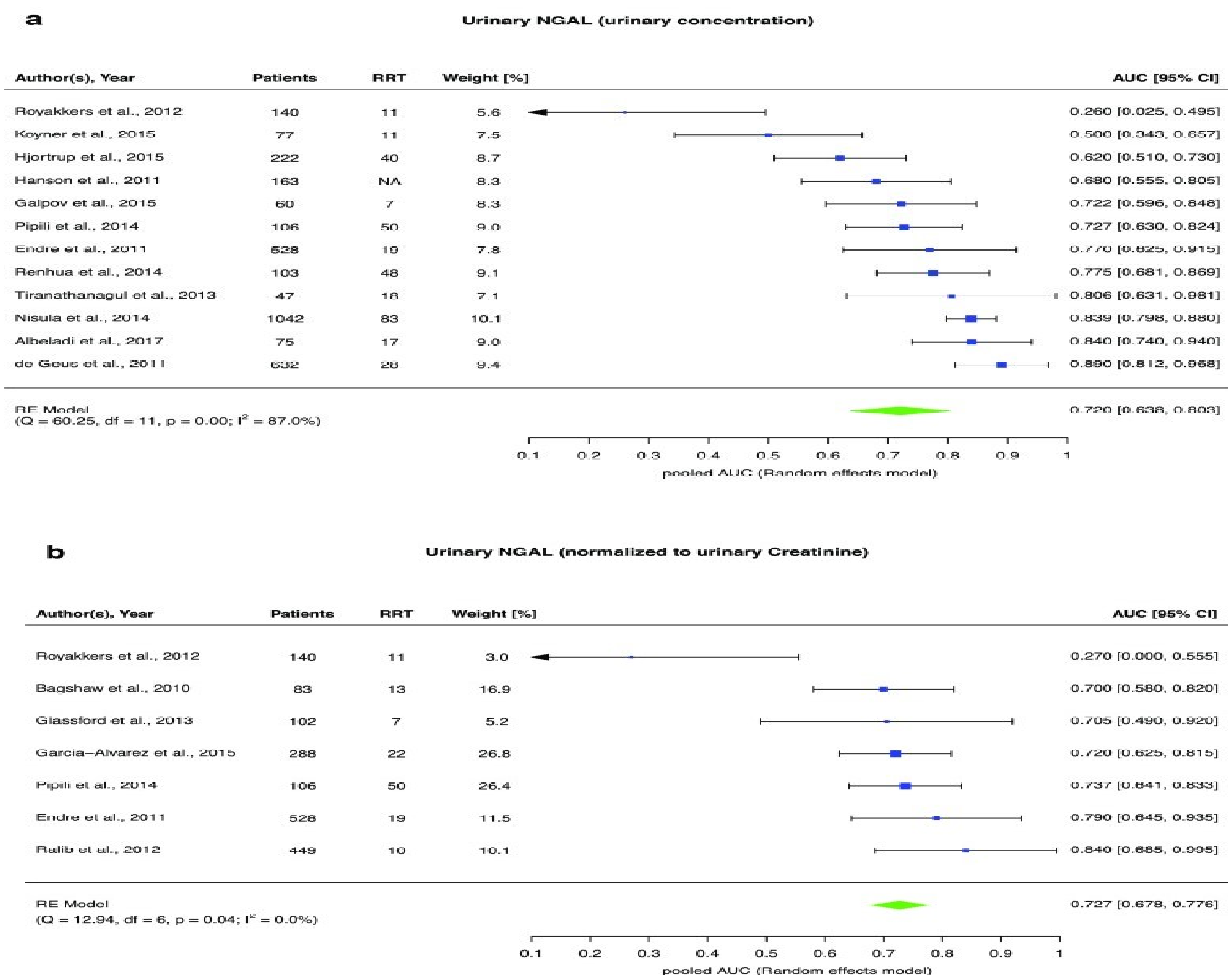


Acute Disease Quality Initiative 23 (https://www.ADQI.org)

Biomarkers and need for KRT and optimal timing of KRT initiation

- Currently, the decision to start KRT is based on clinical judgement and conventional criteria.
- Several studies have evaluated different biomarkers in predicting the need for KRT with variable results.

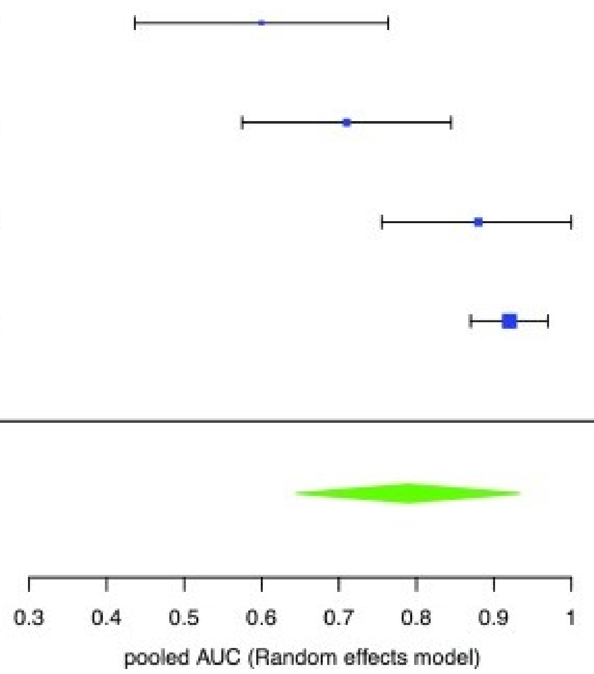
Ostermann M. JAMA Network Open, 2020.



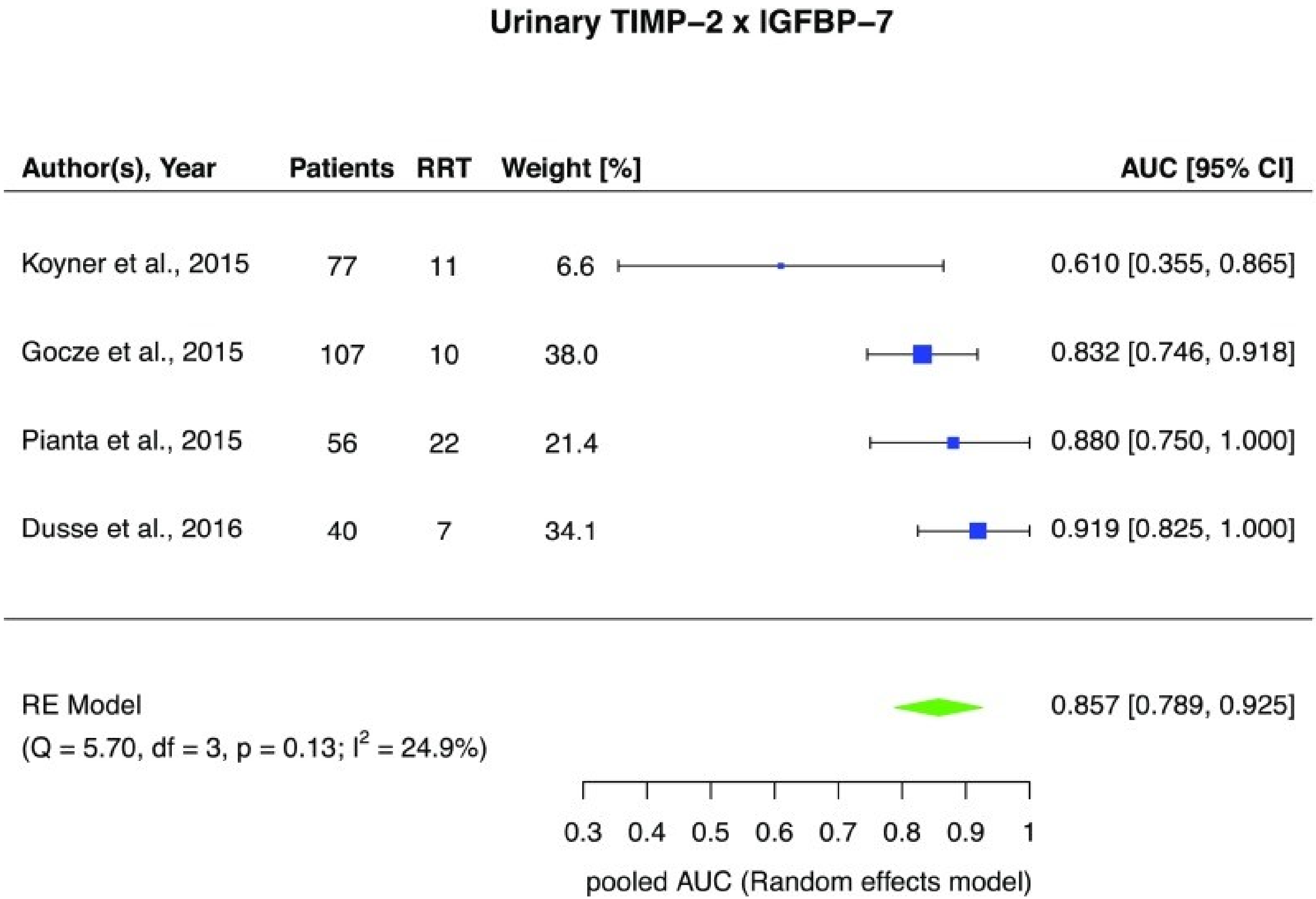
Klein S. Intensive Care Med, 2018.

Urinary Cystatin C (normalized to urinary Creatinine)

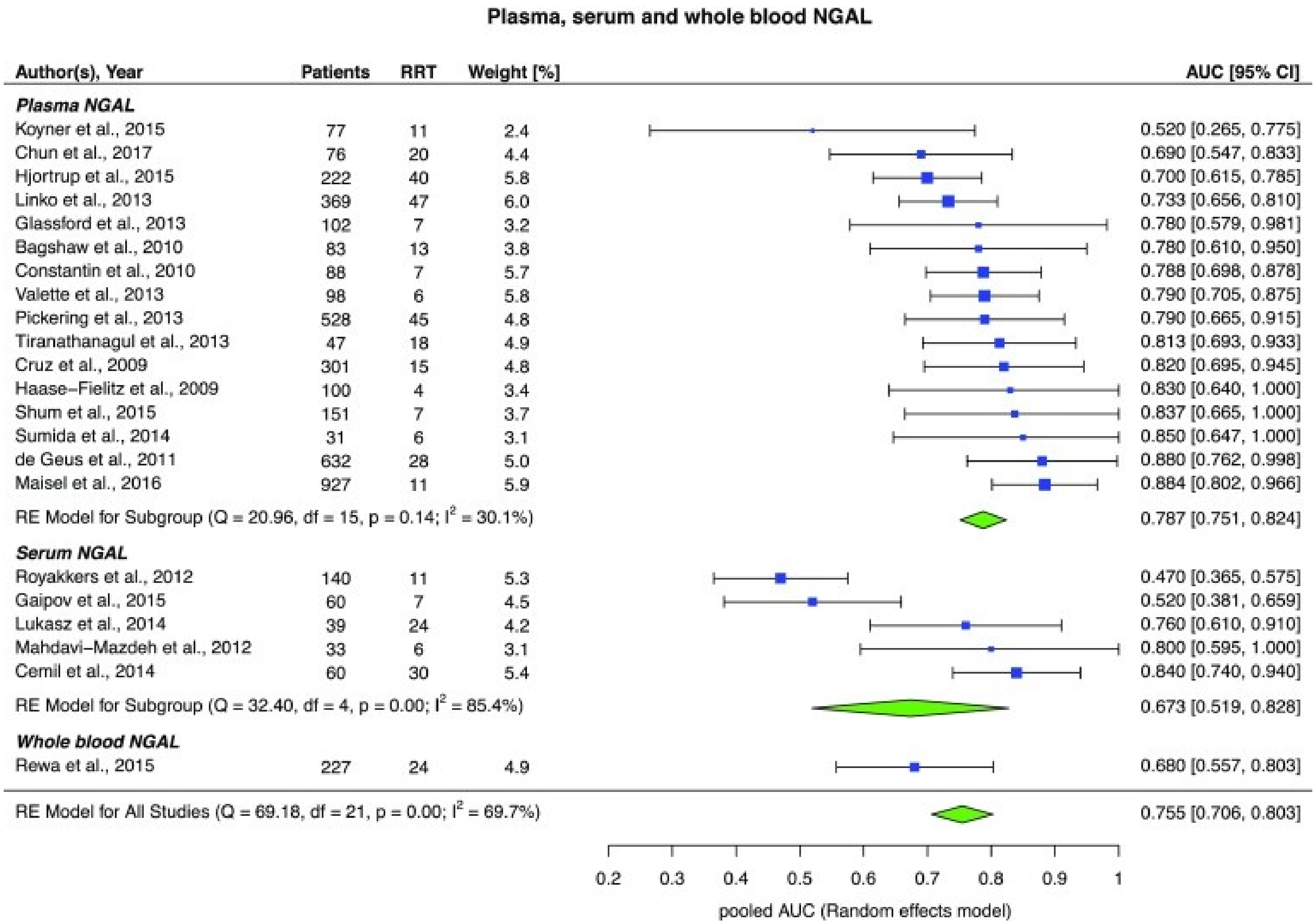
Author(s), Year	Patients	RRT	Weight [%]	AUC [95% CI]
Roaykkers et al., 2011	151	14	21.9	0.600 [0.436, 0.764]
Endre et al., 2011	528	19	24.0	0.710 [0.575, 0.845]
Ralib et al., 2012	480	12	24.8	0.880 [0.755, 1.000]
Herget–Rosenthal, Poppen et al., 2004	73	26	29.3	0.920 [0.870, 0.970]
RE Model (Q = 19.70, df = 3, p = 0.00; I^2 = 85.2%)				0.790 [0.645, 0.934]



Klein S. Intensive Care Med, 2018.



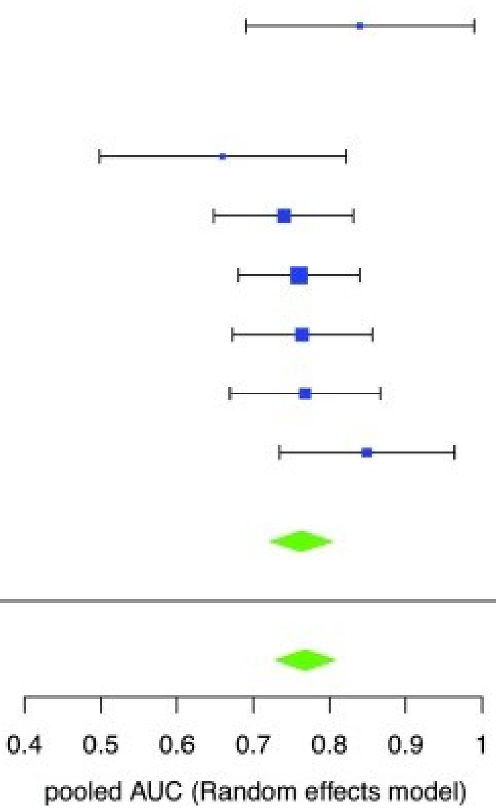
Klein S. Intensive Care Med, 2018.



Klein S. Intensive Care Med, 2018.

Plasma and serum Cystatin C

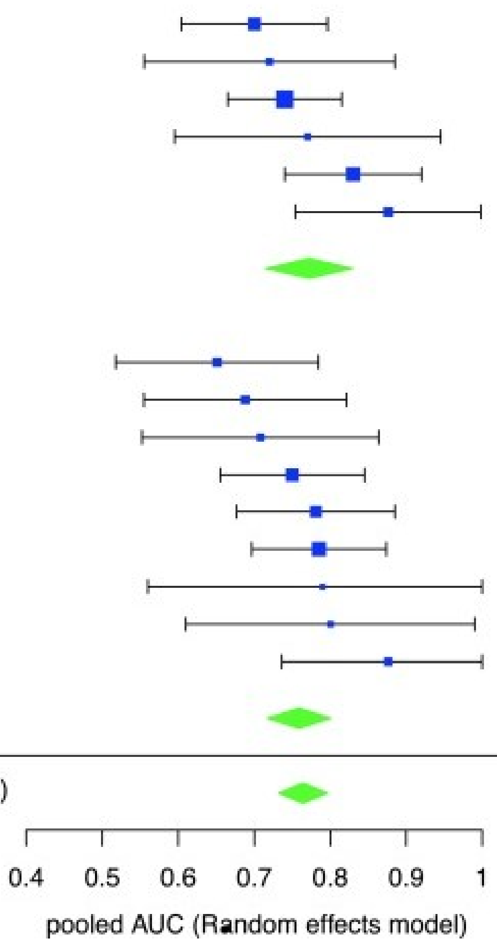
Author(s), Year	Patients	RRT	Weight [%]	AUC [95% CI]
Plasma Cystatin C				
Nejat et al., 2010	444	14	6.8	0.840 [0.690, 0.990]
Serum Cystatin C				
Royakkers et al., 2011	151	14	5.8	0.660 [0.498, 0.822]
Koziolek et al., 2012	120	52	18.2	0.740 [0.649, 0.831]
Herget–Rosenthal et al., 2004	85	17	23.8	0.760 [0.680, 0.840]
Pipili et al., 2014	106	50	18.0	0.764 [0.672, 0.856]
Renhua et al., 2014	103	48	15.7	0.768 [0.670, 0.866]
Kiessling et al., 2014	70	NA	11.5	0.849 [0.734, 0.964]
RE Model for Subgroup (Q = 3.96, df = 5, p = 0.56; I^2 = 0.0%)				0.763 [0.723, 0.803]
RE Model for All Studies (Q = 4.90, df = 6, p = 0.56; I^2 = 0.1%)				0.768 [0.729, 0.807]



Klein S. Intensive Care Med, 2018.

Plasma and serum Creatinine

Author(s), Year	Patients	RRT	Weight [%]	AUC [95% CI]
Plasma Creatinine				
Koziolek et al., 2012	120	52	9.5	0.700 [0.604, 0.796]
Pickering et al., 2012	484	NA	3.6	0.720 [0.555, 0.885]
Hjortrup et al., 2015	222	40	14.2	0.740 [0.665, 0.815]
Nejat et al., 2010	444	14	3.2	0.770 [0.595, 0.945]
Hanson et al., 2011	163	NA	10.6	0.830 [0.740, 0.920]
Maisel et al., 2016	927	11	6.2	0.876 [0.754, 0.998]
RE Model for Subgroup (Q = 7.62, df = 5, p = 0.18; I^2 = 38.0%)				0.772 [0.715, 0.829]
Serum Creatinine				
Gaipov et al., 2015	60	7	5.3	0.651 [0.518, 0.784]
Drey et al., 2015	61	NA	5.3	0.688 [0.555, 0.821]
Tiranathanagul et al., 2013	47	18	4.0	0.708 [0.552, 0.864]
Valette et al., 2013	98	6	9.7	0.750 [0.655, 0.845]
Renhua et al., 2014	103	48	8.3	0.781 [0.677, 0.885]
Pipili et al., 2014	106	50	10.9	0.785 [0.696, 0.874]
Sumida et al., 2014	31	6	1.9	0.790 [0.560, 1.000]
Mahdavi–Mazdeh et al., 2012	33	6	2.7	0.800 [0.610, 0.990]
Kiessling et al., 2014	70	NA	4.8	0.876 [0.736, 1.000]
RE Model for Subgroup (Q = 7.48, df = 8, p = 0.49; I^2 = 0.0%)				0.759 [0.717, 0.800]
RE Model for All Studies (Q = 15.23, df = 14, p = 0.36; I^2 = 10.6%)				0.764 [0.732, 0.796]



Klein S. Intensive Care Med, 2018.

Biomarkers and need for KRT and optimal timing of KRT initiation

- In a meta-analysis of more than 15 000 patients, the pooled AUROCs for urine and blood **NGAL** for prediction of KRT were 0.72 (95% CI, 0.64-0.80) and 0.76 (95% CI, 0.71-0.80), respectively.
- **sCr** and **cystatin C** had pooled AUROCs of 0.76 (95% CI, 0.73-0.80) and 0.77 (95% CI, 0.73-0.81), respectively.
- Urine biomarkers **interleukin-18, cystatin C**, and **TIMP-2 × IGFBP7** showed pooled AUROCs of 0.67 (95% CI, 0.61-0.73), 0.72 (95% CI, 0.58-0.87), and 0.86 (95% CI, 0.79-0.93), respectively.

Klein S. Intensive Care Med, 2018.

Biomarkers and need for KRT and optimal timing of KRT initiation

- Most studies evaluating the role of biomarkers to guide **KRT discontinuation** have relied on urine output, urinary Cr, or urea clearance.

Ostermann M. JAMA Network Open, 2020.

KRT discontinuation

Prospective, observational study of 110 patients who had received CRRT and were weaned after renal recovery.

Table 2. AUC for biomarkers and clinical factors at cessation of CRRT fc
At the time of CRRT cessation. Abbreviations: AUC, area under the rece
CRRT, continuous renal replacement therapy; SE, standard error; CI, cc
Spe, specificity; CysC, cystatin C; NGAL, neutrophil gelatinase-associated

Parameter	AUC	SE	95% CI
Creatinine (mg/dL)	0.601	0.074	0.455–0.747

Conclusion: The study showed that serum CysC, at the time of CRRT cessation, is an independent predictor of the successful weaning from CRRT in critically ill patients with AKI.

Kim CS. Kidney Blood Press Res, 2018.

Biomarkers to assess AKI progression and kidney recovery

- Studies have found that complete and sustained reversal of AKI episodes within 48 to 72 hours of onset was associated with better outcomes than persistent AKI.
- Persistent AKI is the AKI that lasts more than 48 hours.

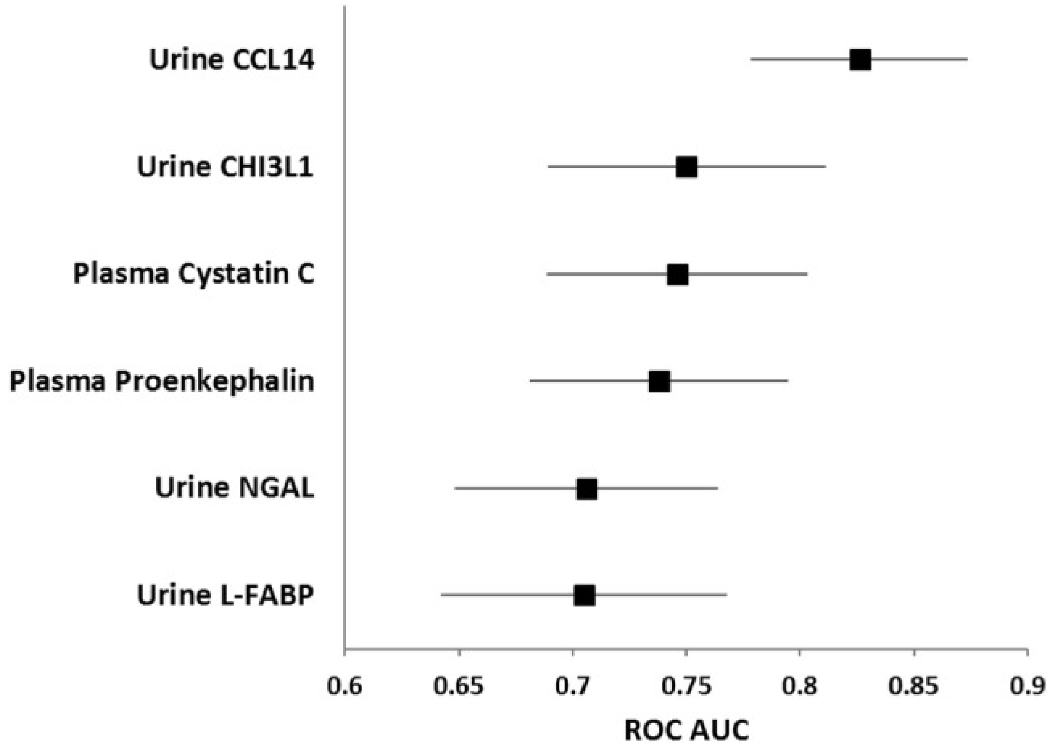
Biomarkers to assess AKI progression and kidney recovery

- 956 patients with sepsis
- Median **sCr level** on day 1 was significantly lower in patients who recovered kidney function within 48 hours compared with those who did not recover (2.9 [2.5-3.3] mg/dL vs 3.2 [2.6-4.2] mg/dL; P = .006).
- Median day 1 plasma **proenkephalin-A** concentration was also significantly lower (137 [89-188] pmol/L) compared with patients without kidney recovery (226 [145-352] pmol/L).
- **The increase in proenkephalin-A concentrations preceded elevation of sCr levels in patients with worsening kidney function, and with persistent AKI.**

Caironi P. Clin Chem, 2018.

Biomarkers to assess AKI progression and kidney recovery

- A study of 331 critically ill patients with AKI stage 2 or 3 demonstrated that **urinary C-C motif chemokine ligand 14** was predictive of persistent AKI.



Hoste E. Intensive Care Med, 2020.

Bomarkers to refine acute kidney disease staging

- There is insufficient evidence to recommend the routine use of novel biomarkers to refine acute kidney disease (AKD) staging.

- Studies have evaluated the long-term prognostic value of biomarkers for predicting KRT dependence and death among critically ill patients with AKI.

Ostermann M. JAMA Open, 2020.

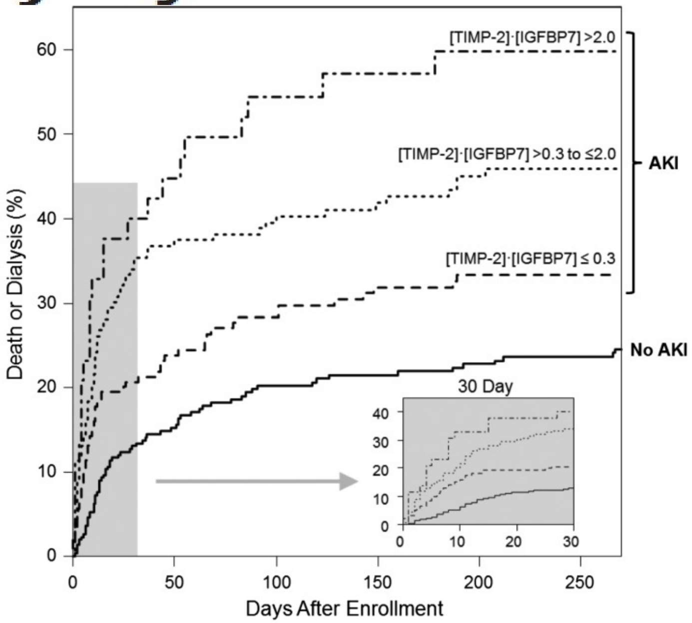
Biomarkers predictive of CKD staging and progression

- The study evaluated **serum osteopontin, IL-6**, and **cystatin C** for kidney recovery among 102 patients with AKI requiring KRT.
- Lower levels of osteopontin and IL-6 were associated with greater odds of 60-day survival with AUROCs of 0.81 and 0.74, respectively.
- **The AUROC value for predicting survival reached its highest level when all biomarkers were combined with urine output and sCr upon discontinuation of KRT(AUROC = 0.88).**

Yang T. Hemodial Int, 2018.

Multicenter Study > J Am Soc Nephrol. 2012 May;23(5):905-1
Epub 2012 Mar 1.

Biomarkers predict progression of injury after cardiac surgery



	0	50	100	150	200	250	300
	Number At Risk						
No AKI	310	223	207	177	173	165	164
AKI							
≤0.3	178	118	102	95	92	92	92
>0.3 to ≤2.0	160	91	83	74	69	69	69
>2.0	44	23	20	17	16	16	16

Conclusion: [TIMP-2]·[IGFBP7] > 2.0 measured early in the setting of critical illness may identify patients with AKI at increased risk for mortality or receipt of RRT over the next 9 months.

Routine measurement of these biomarkers may help to identify a population of patients in the ICU who are at highest risk for adverse outcomes.

Koyner JL. J Am Soc Nephrol, 2015.

Conclusions

- Considerable progress has been made in the field of AKI biomarkers, which has resulted in a better understanding of the pathophysiology of AKI and improved outcomes with biomarker-guided management.

- However, the prospect of clearer identification of high-risk patients and different AKI subphenotypes and the integration of appropriately selected biomarkers in routine clinical practice hold the key to further improvement in AKI care.

Table. Description and Characteristics of Common Biomarkers of AKI

AKI biomarker	Biological role	Source	Stress marker[a]	Damage marker[b]	Functional marker[c]	Potential role in clinical practice				
						Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI	Kidney recovery
Alanine aminopeptidase; alkaline phosphatase; γ-glutamyl transpeptidase	Enzymes located on the brush border villi of the proximal tubular cells; released into urine after tubular damage	Coca et al,[2] 2008		Urine				X	X	
Calprotectin	Cytosolic calcium-binding complex; derived from neutrophils and monocytes; detectable in urine in intrinsic AKI	Charlton et al,[3] 2014; Heller et al,[4] 2011		Urine				X		
C-C motif chemokine ligand 14	Pro-inflammatory chemokine; released into urine following stress or damage of tubular cells	Hoste et al,[5] 2020		Urine						X
Chitinase 3-like protein 1	39 kDa intracellular protein of glycoside hydrolase family; expressed by endothelial cells, macrophages, and neutrophils	De Loor et al,[6] 2016		Urine and plasma				X		
Cystatin C	13 kDa cysteine protease inhibitor produced by nucleated human cells; freely filtered	Coca et al,[2] 2008; Ho et al,[7] 2015; Ravn et al,[8] 2019			Plasma			X	X	
Dickkopf-3	38 kDa stress-induced, kidney tubular epithelia-derived glycoprotein; secreted into urine under tubular stress conditions	Schunk et al,[9] 2019	Urine			X	X			
α glutathione S-transferase	Cytoplasmic enzyme in proximal tubule	Koyner at al,[10] 2010		Urine				X		
π glutathione S-transferase	Cytoplasmic enzyme in distal tubules	Coca et al,[2] 2008; Charlton et al,[3] 2014		Urine				X		
Hepatocyte growth factor	Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	Heller et al,[4] 2011; Vaidya et al,[11] 2008		Plasma					X	X
Hepcidin	2.78 kDa peptide hormone predominantly produced in hepatocytes; freely filtered	Ho et al,[7] 2015		Urine and plasma				X	X	
Tissue metalloproteinase-2; insulin-like growth factor binding protein-7	Metalloproteinases released during cell cycle arrest	Kashani et al,[12] 2013; Ostermann et al,[13] 2018; Joannidis et al,[14] 2019	Urine				X	X	X	
Interleukin-18	18 kDa pro-inflammatory cytokine; released into urine following tubular damage	Coca et al,[2] 2008; Ho et al,[7] 2015		Urine			X	X		
Kidney injury molecule-1	Transmembrane glycoprotein produced by proximal tubular cell; released into urine after tubular damage	Coca et al,[2] 2008; Ho et al,[7] 2015; Koyner et al,[10] 2010		Urine			X	X	X	
Liver-type fatty acid-binding protein	14 kDa intracellular lipid chaperone; freely filtered and reabsorbed in proximal tubule; urinary excretion after tubular cell damage	Ho et al,[7] 2015		Urine and plasma				X		
MicroRNA	Endogenous single-stranded non-coding nucleotides; >50 individual microRNAs are expressed in AKI, especially in association with inflammation, apoptosis and fibrosis	Fan et al,[15] 2019		Urine and plasma				X		

Ostermann M. JAMA Network Open, 2020.

Table. Description and Characteristics of Common Biomarkers of AKI

						Potential role in clinical practice				
AKI biomarker	Biological role	Source	Stress marker[a]	Damage marker[b]	Functional marker[c]	Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI	Kidney recovery
Monocyte chemoattractant peptide-1	Peptide expressed in tubular epithelial cells, kidney mesangial cells and podocytes; released into urine	Moledina et al,[16] 2017		Urine					X	
N-acetyl-β-D-glucosaminidase	>130 kDa lysosomal enzyme; released into urine after tubular damage	Charlton et al,[3] 2014		Urine				X		
Neutrophil gelatinase-associated lipocalin	At least 3 different types: (1) monomeric 25 kDa glycoprotein produced by neutrophils and epithelial tissues, including tubular cells; (2) homodimeric 45 kDa protein produced by neutrophils; (3) heterodimeric 135 kDa protein produced by tubular cells	Coca et al,[2] 2008; Ho et al,[7] 2015; Charlton et al,[3] 2014		Urine and plasma				X	X	
Netrin-1	50-75 kDa laminin-related molecule minimally expressed in proximal tubular cells of normal kidneys; released into urine after tubular cell damage	Ramesh et al,[17] 2010		Urine				X		
Osteopontin	Glycoprotein expressed in tubular cells and interstitial infiltrating cells in areas of tubulointerstitial damage	Lorenzen et al,[18] 2011		Plasma				X	X	
Proenkephalin A	Endogenous polypeptide hormone in adrenal medulla, nervous system, immune system and renal tissue; freely filtered	Legrand et al,[19] 2019			Plasma			X	X	X
Retinol binding protein	21 kDa glycoprotein; synthesized by liver; filtered by glomeruli and reabsorbed by proximal tubules; released into urine following tubular damage	Charlton et al,[3] 2014		Plasma						
Tumor necrosis factor	Pro-inflammatory cytokine; released after tubular damage	Ho et al,[7] 2015		Plasma				X		

Abbreviation: AKI, acute kidney injury.

[a] Stress markers indicate cell stress; cell stress can resolve or progress to damage or alter kidney function.

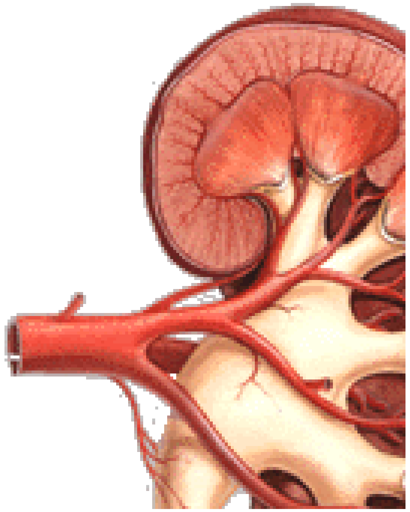
[b] Damage markers indicate structural damage that may or may not be associated with reduced kidney function. These molecules include constitutive proteins released by the damaged kidney, molecules upregulated in response to injury, or nonkidney tissue products that are filtered, reabsorbed, or secreted by the kidney.

[c] Functional markers reflect changes in glomerular filtration.

Ostermann M. JAMA Network Open, 2020.

Further studies and investigations are required to come to the final conclusions!!!

THANK YOU FOR YOUR ATTENTION!



MITOCHONDRIAL CYTOPATHIES

YAACOV FRISHBERG, MD
DIVISION OF PEDIATRIC NEPHROLOGY
SHAARE ZEDEK MEDICAL CENTER
JERUSALEM, ISRAEL

X SEPNWG MEETING AND TEACHING COURSE, SKOPJE, JUNE 1-3, 2023

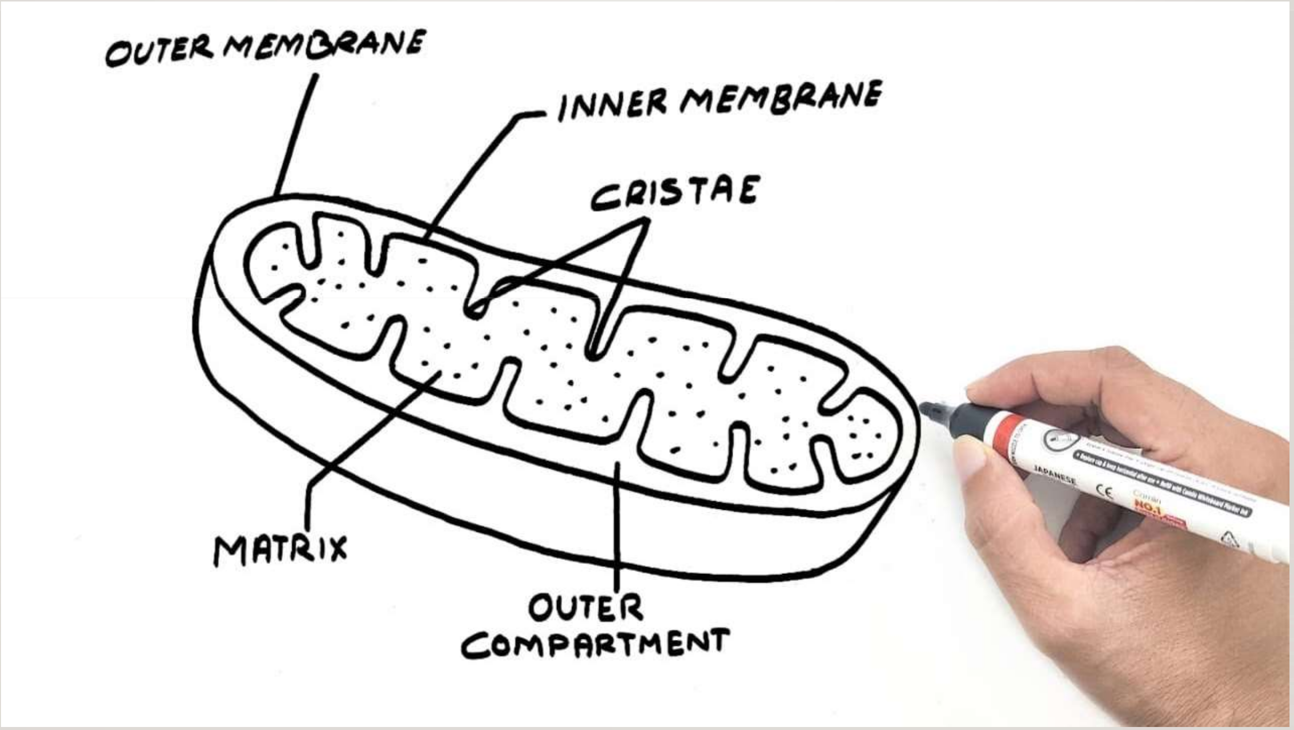
DISCLOSURES

- None with respect to this talk

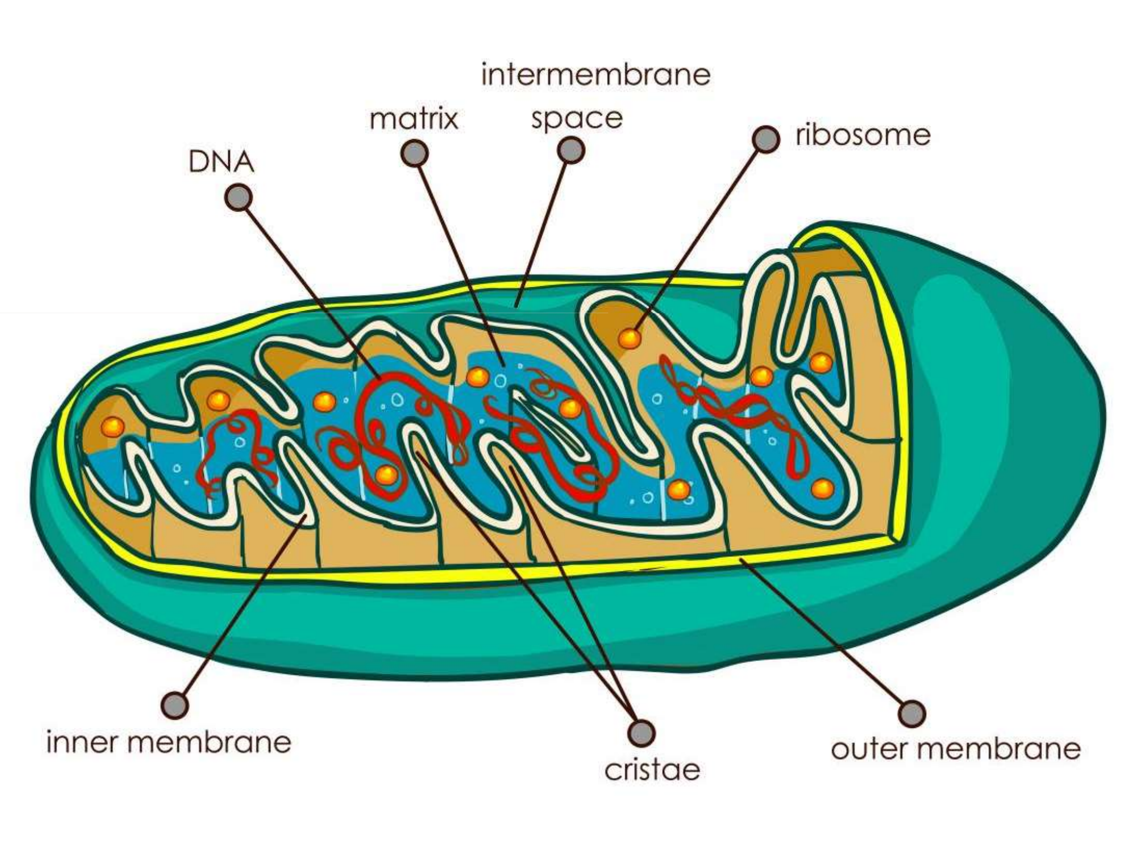
MITOCHONDRION

- Intra-cellular organelle
- Gram negative oxidative bacteria which began endosymbiotic process with glycolytic progenitors of eukaryotic cells more than 2 billion years ago
- Energy production through oxidative phosphorylation (OXPHOS)
- Accomplished by the respiratory chain = ATP producing "power houses"
- 100-1000 mitochondria/cell
- RBC rely on anaerobic metabolism contain no mitochondriae

MITOCHONDRION



MITOCHONDRION



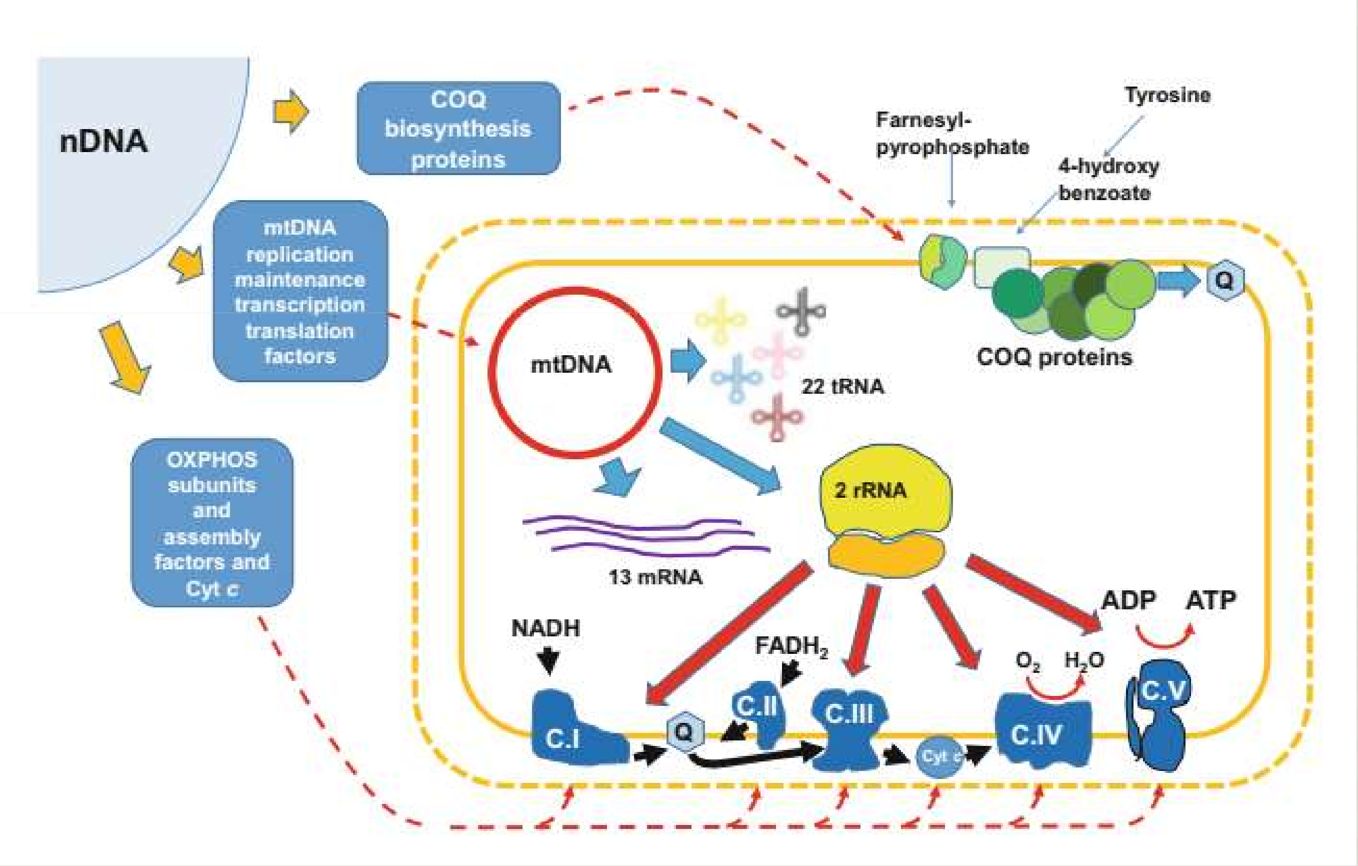
ADDITIONAL MITOCHONDRIAL FUNCTIONS

- Pyrimidine, ß oxidation and heme biosynthesis pathways
- Calcium homeostasis
- Calcium signaling
- Control of apoptosis
- Tissue injury and repair

MITOCHONDRIAL DNA

- The mtDNA - 16,569 BP long circular molecules
- No introns
- Genetic code for translation distinct from the universal code
- Highly susceptible to damage and mutations
- Most genes required for mitochondrial function are encoded by the nucleus
    - Out of > 80 OXPHOS subunits, only 13 are encoded by mtDNA
- Tissues that rely on aerobic metabolism are most severely affected
    - Nervous system, cardiac, kidney and skeletal muscles

OXPHOS BIOGENESIS REQUIRES COORDINATION BETWEEN NUCLEAR AND MITOCHONDRIAL DNA



MITOCHONDRIAL DNA

- Maternal inheritance
- Heteroplasmy = wild type and mutant mtDNA co-exist in different proportions within cells of the same tissue
- Threshold effect = mutations must affect a critical proportion of the total mtDNA in order to cause a phenotype
- Random drift = mtDNA molecules segregate randomly in daughter cells at cell division
- Post-mitotic cells, as opposed to those with high turnover, are more likely to accumulate mutations (neurons, kidney cells)

CASE PRESENTATION

- A 4 month old baby boy referred to our ED for acute bronchiolitis and FTT
- Born at 34 weeks of gestation to healthy unrelated Palestinian parents
- Renal failure (BUN/creatinine 44 and 0.99 mg/dl, respectively)
- Anemia, hyperuricemia, hypochloremic alkalosis, mild lactemia
- u/a SG 1.010, mild proteinuria and normal sediment
- US – normal sized echogenic kidneys
- Renal failure persisted despite recovery from the acute illness
- A procedure was performed….

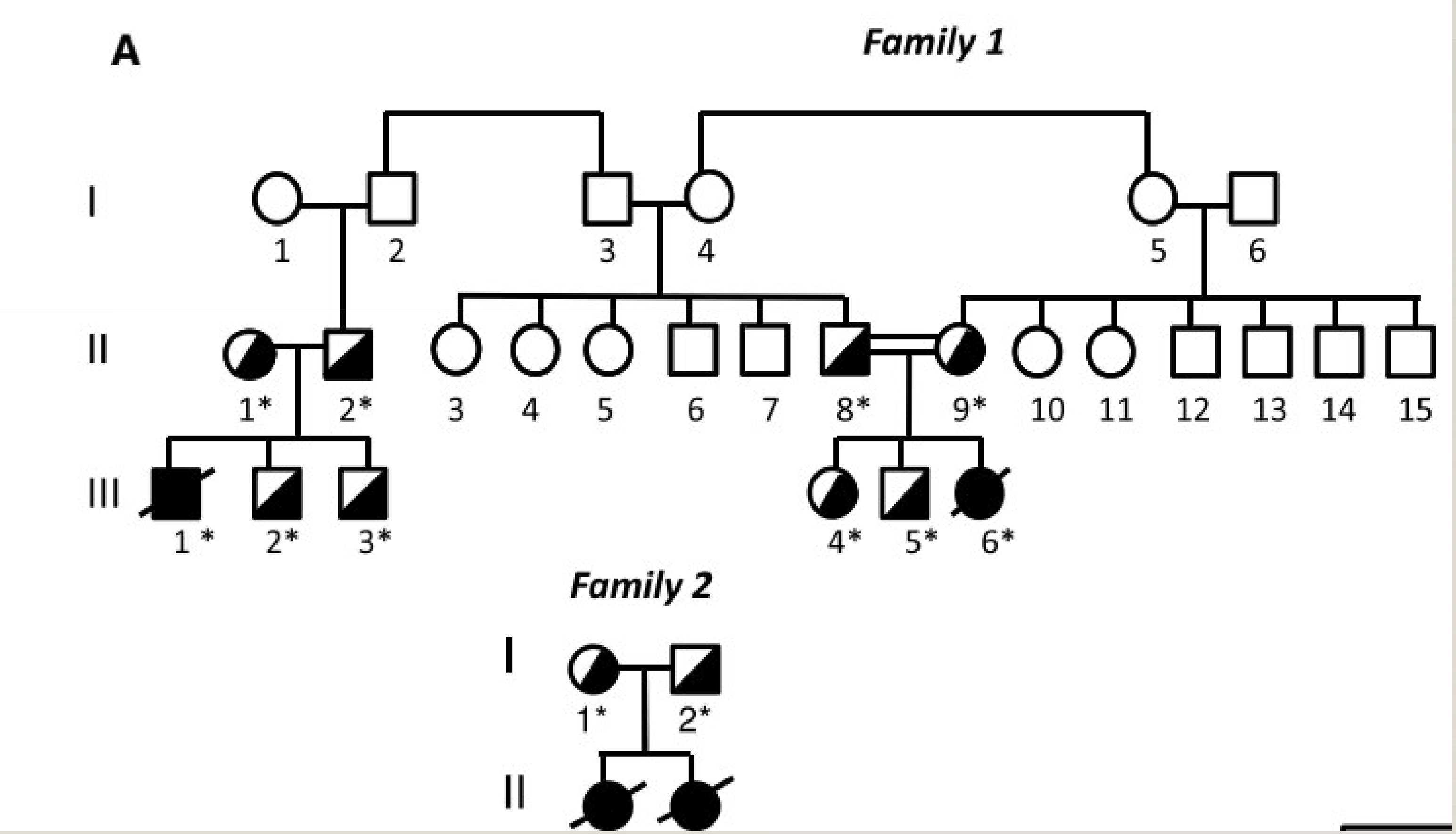
KIDNEY BIOPSY

- Immature normal glomeruli
- Non-specific tubulo-interstitial changes: dedifferentiated atrophic tubules with thickened BM or denuded tubules
- Hyperplastic areteriolitis in the interstitium
- IF staining – negative
- Diagnosis?

HE SUBSEQUENTLY DEVELOPED…

- Pancytopenia with normal bone marrow biopsy
- Feeding problems
- Global developmental delay (brain US normal)
- Diabetes mellitus
- Pulmonary hypertension
- Kidney failure
- Succumbed at 14 months of age
- **H**yper**U**ricemia, **P**ulmonary hypertension, **R**enal failure, **A**lkalosis =HUPRA syndrome

HUPRA SYNDROME



CLINICAL CHARACTERISTICS - KIDNEY

Table 1. Clinical Characteristics of Patients with the HUPRA Syndrome

	Patient F1:III-1	Patient F1:III-6	Patient F2:II-2
Renal Disease			
Hyperuricemia	+	+	+
Low FeUA	+	+	+
Salt wasting	+	+	+
Polyuria	+	ND	+
Elevated BUN (disproportionate to serum creatinine)	+	+	+
Hypochloremic metabolic alkalosis	+	+	+
Hypomagnesemia	+	+	+
High FeMg	+	+	+
Progressive renal failure	+	+	+

EXTRA-RENAL MANIFESTATIONS

Extrarenal Manifestations			
Prematurity	+	+	+
Pulmonary hypertension	+	+	+
Elevated serum lactate	+	+	+
Failure to thrive	+	+	+
Global developmental delay	+	+	+
Diabetes mellitus	+	±	+
Pancytopenia	+	-	-

Abbreviations: FeUA, fractional excretion of uric acid; FeMg, fractional excretion of magnesium; ND, not determined; plus and minus signs, stress hyperglycemia.

WHAT'S THE DIAGNOSIS?

- Autosomal recessive inheritance
- Compromised energy production
- Muscle biopsy – reduced activities of complex I, III, IV; complex II was preserved
- Mitochondrial deletion was excluded
- Defect in the synthesis of the mtDNA encoded proteins?

- Homozygous mutation c.1169A>G (p.Asp390Gly) in SARS2, encoding mitochondrial seryl tRNA-synthetase
- Targeted screening: 1:15 carriers among inhabitants of the village

CONSERVED AMINO ACID

```
SARS2 HUMAN           ILTELGLHFRVLDMPTQELGLPAYRKFDIEAWMPGRGRFGEVTSASNCTD 427
SARS2 BOVINE          ILTELGLHFRVLDMPTQELGLPAYRKFDIEAWMPGRGRFGEVTSASNCTD 427
SARS2 MOUSE           ILTELGLHFRVLDMPTQELGLPAYRKFDIEAWMPGRGRYGEVTSASNCTD 427
SARS2 RAT             ILTELGLHFRVLDMPTQELGLPAYRKFDIEAWMPGRGRYGEVTSASNCTD 427
SARS2 ZEBRAFISH       IFSSLKLHYRVLDMPTQELGPPAYRKFDIEAWMPGRGSFGEISSASNCTD 428
SARS2 YEAST           IVQGLGLSVRVLDMPTEELGASAHRKYDMEAWMPGRGKWGEITSTSNCTD 407
SARS2 RICE            LYASLGLHFKTLDMATGDLGAPAYRKFDIEAWMPGLDRYGEISSASNCTD 425
                      :   * *  :.***.* :** .*:**:*:****** . :**::*:*****
```

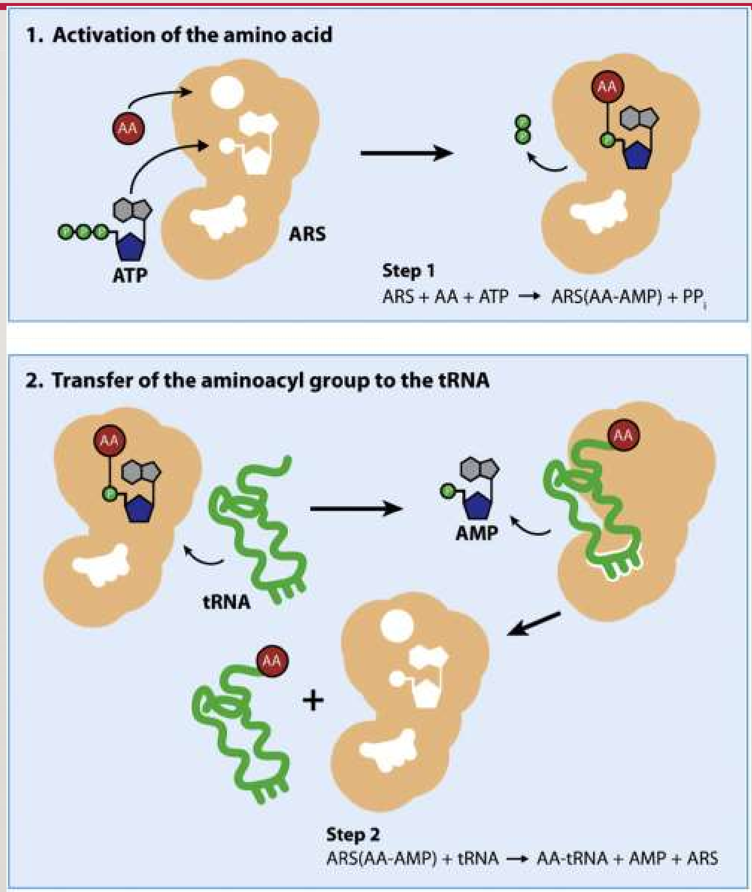
KIDNEY BIOPSY - EM

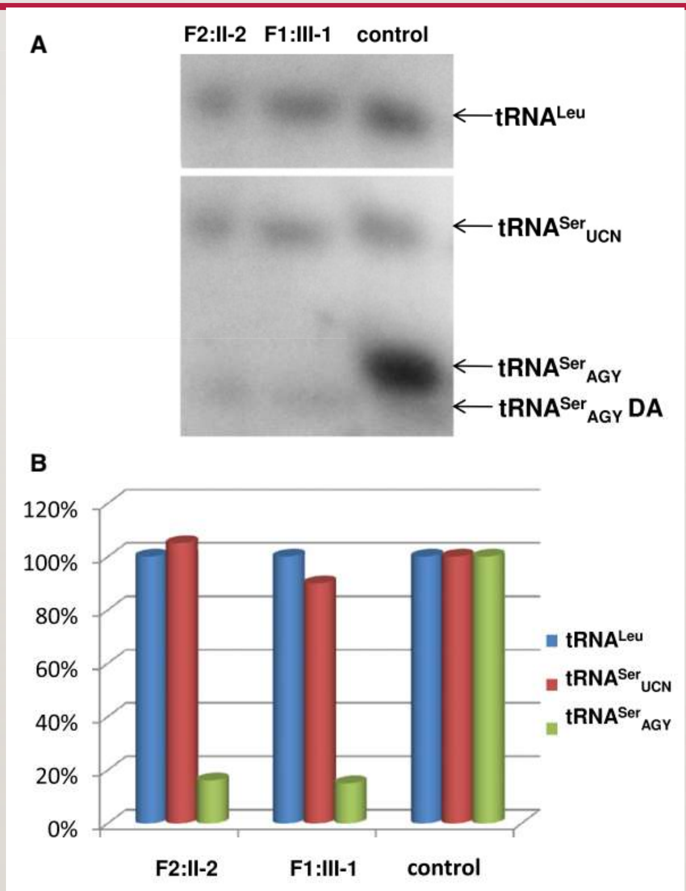
- A portion of the tubular epithelial cells contained markedly enlarged mitochondria with paracrystalline lesions

MITOCHONDRIAL TRANSLATION MACHINERY

- 22 tRNA encoded by mtDNA
- 18 correspond to one amino acid, each
- Leucine and serine acylate 2 tRNA isoacceptors, each
- 20 amino-acyl tRNA synthetases (ARS), each one corresponding to a single amino acid are encoded by nDNA
- The product is imported into the mitochondria
- ARS provide the specific attachment of amino acids to the 3'-ends of their cognate tRNA

THE ROLE OF T-RNA SYNTHETASE





A
F2:II-2
F1:III-1
control
tRNA^Leu
tRNA^Ser_UCN
tRNA^Ser_AGY
tRNA^Ser_AGY DA
B
120%
100%
80%
60%
40%
20%
0%
F2:II-2
F1:III-1
control
tRNA^Leu
tRNA^Ser_UCN
tRNA^Ser_AGY

- Mutations in mitochondrial ARS

- Decreased aminoacylation by the corresponding amino acid

- Dysfunctional mitochondrial translation system
- Derangement in energy supply

THICK ASCENDING LIMB AND MITOCHONDRIA

- Thick ascending limb has high energy requirements
- Primarily to support NA-K-ATPase cotransporter activity
- Features of TAL dysfunction (similar to loop diuretics):
  - Salt wasting
  - Magnesium wasting
  - Concentration defect
  - Elevated BUN disproportionate to serum creatinine

AM J HUM GENT 2011: 88: 193

Mutations in the Mitochondrial Seryl-tRNA Synthetase Cause Hyperuricemia, Pulmonary Hypertension, Renal Failure in Infancy and Alkalosis, HUPRA Syndrome

Ruth Belostotsky,[1] Efrat Ben-Shalom,[1,3] Choni Rinat,[1,3] Rachel Becker-Cohen,[1,3] Sofia Feinstein,[1,3] Sharon Zeligson,[2] Reeval Segel,[2] Orly Elpeleg,[4] Suheir Nassar,[5] and Yaacov Frishberg[1,2,*]

1 Mitochondrial kidney disease: examples of molecular mechanisms

cular t	Gene(s)	Inheritance	Renal manifestations	Other clinical phenotypes
IA-encoded				
-scale ngements DNA	Multiple	Sporadic	Fanconi-type tubulopathy, tubulointerstitial nephritis	Pearson and Kearns-Sayre syndromes, PEO
NA point ions ted ples)	*MT-TL1*	Maternal	FSGS	MELAS, MIDD
	MT-TK	Maternal	Tubulointerstitial nephritis	MERRF
	MT-TF	Maternal/ sporadic	Tubulointerstitial nephritis	Encephalomyopathy
	MT-ND5	Maternal/ sporadic	Glomerulocystic disease	Leigh syndrome, MELAS
ear-encoded				
zyme Q_{10} nthesis	*COQ2, COQ6, COQ8B, PDSS1, PDSS2*	AR	Steroid resistant nephrotic syndrome	Seizures, ataxia, hearing loss, ar multisystem disease
	COQ9	AR	Tubulopathy	Encephalomyopathy, HCM
plex I	*NDUFAF2*	AR	Renal tubular acidosis	Leigh syndrome

MITO DNA DEFECTS AND KIDNEY DISORDERS

- Point mutations or gene rearrangement (large deletions most common)
- May affect the structural subunits, tRNA or rRNA
- Isolated or complex syndromes (kidney phenotype may precede other systems)
- Decrease in ATP production and increase in generation of reactive oxygen species
- Increased apoptosis
- Phenotypic variability may be partly explained by complex inheritance and transmission
- Lack of animal models

PROXIMAL AND DISTAL TUBULES

- High energetic demand
- Rich in mitochondria
- Proximal phenotypes range from complete Fanconi syndrome to RTA, glycosuria, LMW proteinuria, aminoaciduria, and Bartter-like syndromes
- Distal tubulopathies: specific electrolyte imbalance: Hypo-K/Mg

THE GLOMERULUS

- The glomerulus relies less on OXPHOS since anaerobic glycolysis can maintain GFR
- Podocyte are susceptible to oxidation or change in podocyte metabolism distinct from OXPHOS dysfunction
- m3243A>G mutation $tRNA^{leu}$
- Glomerular phenotype in MELAS/MIDD syndromes
- Proteinuria, NS, CKD
- FSGS and rarely tubulo-interstitial nephritis or cystic disease

NUCLEAR-ENCODED MITOCHONDRIAL KIDNEY DISORDERS: COENZYME Q10 DEFICIENCIES

- Primary coenzyme Q10 (CoQ10) deficiencies result from defects in components of the CoQ10 biosynthesis pathway
- CoQ10 is a lipid component of the respiratory chain and an electron carrier
- AR inheritance
- A number of genes are involved in CoQ10 biogenesis [altogether responsible for 1% of SRNS)
- Kidney phenotype: isolated or syndromic
- Proteinuria ± hematuria, SRNS
- Histologic findings – non-specific, FSGS (occasionally DMS), dysmorphic mitochondria in podocytes
- Amenable to CoQ10 supplementation

COENZYME Q2 NEPHROPATHY

- Defects in the enzyme catalyzing the second step in CoQ10 biogenesis
- Very rare
- Onset < 2.5 years (appearance during 2nd decade)
- Clinical phenotypes:
  - Isolated NS
  - Cerebro-renal disease
  - Multi-system disease
- Early supplementation may improve proteinuria but not neurological involvement

COENZYME Q6 NEPHROPATHY

- Interferes with hydroxylation of the quinone ring in CoQ10 synthesis
- Very rare
- SRNS progressing to ESKD
- Sensory-neural hearing loss
- Multiple neurological deficits
- Median age of diagnosis – 1.2 yrs
- CoQ10 supplementation may improve renal but not extra-renal manifestations

COENZYME Q8B NEPHROPATHY

- Reduced cellular CoQ10 content
- More common
- SRNS/FSGS or CKD in adolescence (often asymptomatic) → late diagnosis
- Usually isolated kidney phenotype
- Occasionally extra-renal manifestations: neurological involvement, hypertrophic cardiomyopathy, pulmonary hypertension
- May benefit most from CoQ10 supplementation
- In KO animals impaired podocyte motility improved with CoQ10 supplementation

KIDNEY INT 2022: 102:592

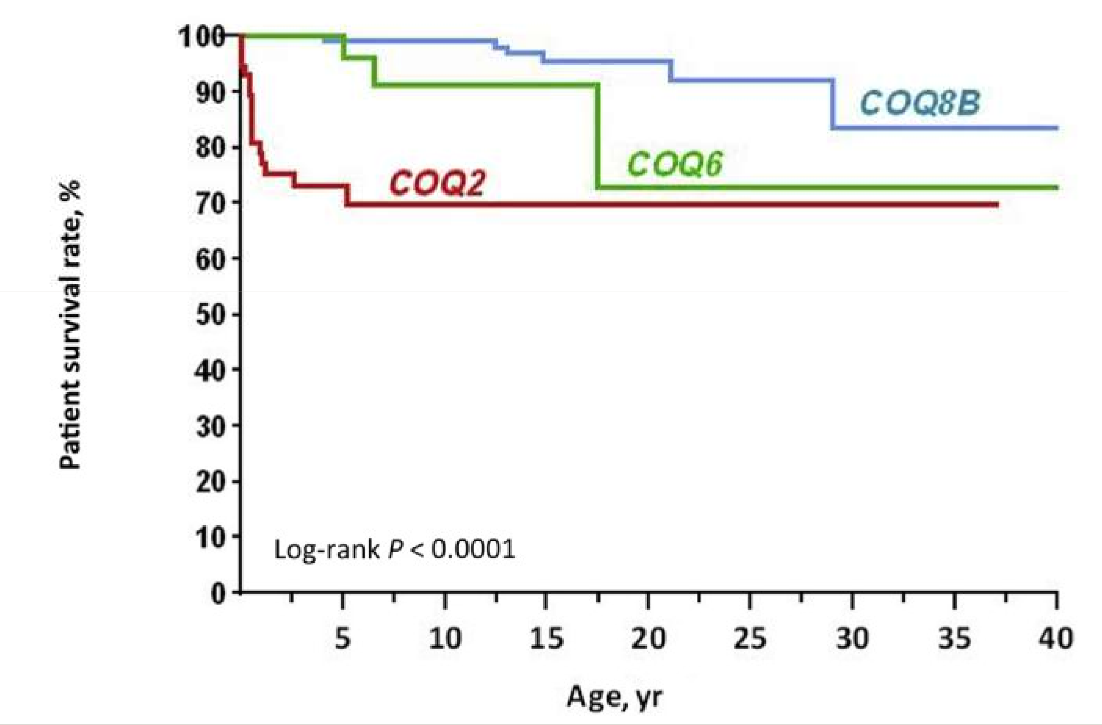
- Systematic review of 251 cases (173 previously reported and 78 new cases)

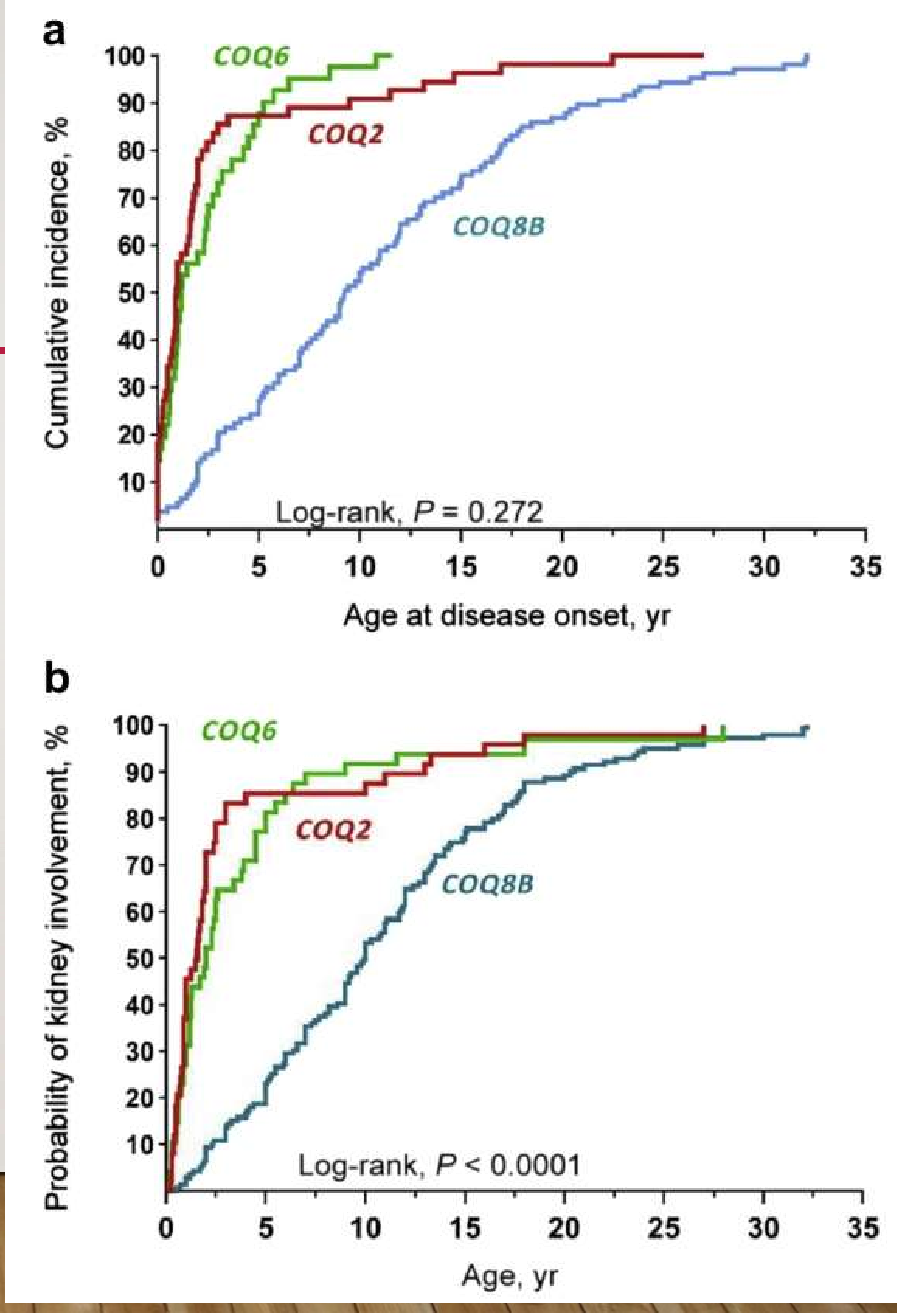
Variation of the clinical spectrum and genotype-phenotype associations in Coenzyme Q10 deficiency associated glomerulopathy

1 | Patient characteristics and clinical outcomes

characteristic	COQ2	COQ6	COQ8
mber of patients (females)	63 (30)	48 (16)	140 (65)
ease manifestation			
irst symptoms, yr	1 (0.3–2)	1.2 (0.6–3.4)	9.8 (5–1
nvolvement	93.6 (59/63)	97.9 (47/48)	100 (140
disease presentation			
irst kidney disease manifestation, yr	1 (0.5–2)	2 (0.9–4.5)	9.9 (5.3–
ic range proteinuria	85.7 (36/42)	86.1 (31/36)	71.7 (86/1
phrotic range proteinuria	14.3 (6/42)	13.9 (5/36)	28.3 (34/1
omatic proteinuria	0 (0/63)	18.7 (9/48)	23.6 (33/1
nsion	28.6 (12/42)	21 (4/19)	39 (32/8
	86.6 (39/45)	47.8 (11/23)	40.2 (33/8
maturia	6.8 (4/59)	8.5 (4/47)	18 (13/7
ge 1	71.8 (23/32)	42.1 (8/19)	34.3(35/1
ge 2–4	18.7 (6/32)	36.8 (7/19)	32.3 (33/1
	9.4 (3/32)	21 (4/19)	33.3 (34/1
istopathologic findings			
	69.4 (25/36)	72.2 (26/36)	77.1 (64/8
S, not otherwise specified	76 (19/25)	88.4 (23/26)	89 (57/6
S, collapsing subtype	24 (6/25)	11.5 (3/26)	9.4 (6/64
S, tip-lesion	0 (0/25)	0 (0/26)	1.5 (1/64
l glomerulosclerosis	11.1 (4/36)	8.3 (3/36)	15.6 (13/8
ngioproliferative glomerulonephritis	11.1 (4/36)	5.6 (2/36)	7.2 (6/83
al change disease	5.6 (2/36)	5.6 (2/36)	0 (0/83
orphic mitochondria	30.5 (11/36)	25 (9/36)	10.8 (9/83
nal features			
xtrarenal involvement	77.9 (46/59)	89.1 (41/46)	29.3 (41/1
terine abnormalities/preterm delivery	13.6 (8/59)	2.2 (1/46)	0.7 (1/14
[illegible]	[illegible]	[illegible]	[illegible]

KIDNEY DISEASE/ SURVIVAL





KIDNEY INT 2022: 102: 604

- Real life study
- 116 patients received CoQ10 supplements for primary CoQ10 deficiency
- In half treatment was initiated only after they progressed to ESRD
- Ubiquinone (oxidized form) or ubiquinol (reduced form) was prescribed (wide range of dosage: 3-60 mg/Kg/d)
- Median duration of follow up on treatment – 1.1-2.0 yrs

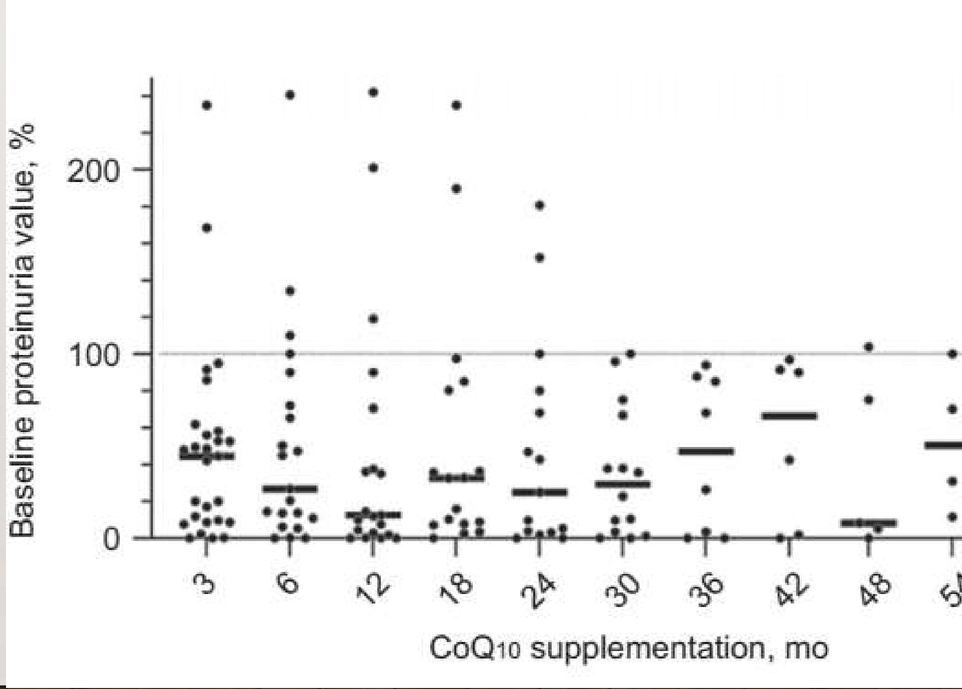
Oral Coenzyme Q10 supplementation leads to better preservation of kidney function in steroid-resistant nephrotic syndrome due to primary Coenzyme Q10 deficiency

2| Characteristics of the treated cohort, treatment strategies, and response to oral CoQ_{10} supplementation

	CoQ_{10}-treated cohort ($n = 116$)		
teristic	*COQ2* ($n = 32$)	*COQ6* ($n = 24$)	*COQ8B* (*n*
start of CoQ_{10} supplementation, yr	2.6 (1–12.9)	5 (1.8–8.15)	11 (8.1-
om disease onset to CoQ_{10} start, yr	0.8 (0.2–1.75)	3 (0.9–6.6)	1.8 (0.4-
t start of CoQ_{10} supplementation (ml/min per 1.73 m^2)[a]	100 (96–100)	100 (100–100)	91 (75–
age			
	41 (13/32)	58 (14/24)	30 (18/
	0 (0/32)	0 (0/24)	10 (6/6
	3 (1/32)	0 (0/24)	8 (2/6
	6 (2/32)	0 (0/24)	0 (0/6
	34 (11/32)	37 (9/24)	47 (28/
wn eGFR	16 (5/32)	4 (1/24)	10 (6/6
at start of CoQ_{10} supplementation	25 (8/32)	33 (8/24)	40 (24/
withdrawal during CoQ_{10} supplementation	0 (0/8)	37 (3/8)	4 (1/2
py at start of CoQ_{10} supplementation	37 (12/32)	29 (7/24)	17 (10/
drawal during CoQ_{10} supplementation	50 (6/12)	43 (3/7)	20 (2/1
ation (ubiquinone/ubiquinol/unknown)	16/6/10	14/0/10	35/1/
dose, mg/kg per day	30 (30–30)	29 (20–30)	20 (15–

CHANGE IN PROTEINURIA – COQ10 SUPPLEMENTS

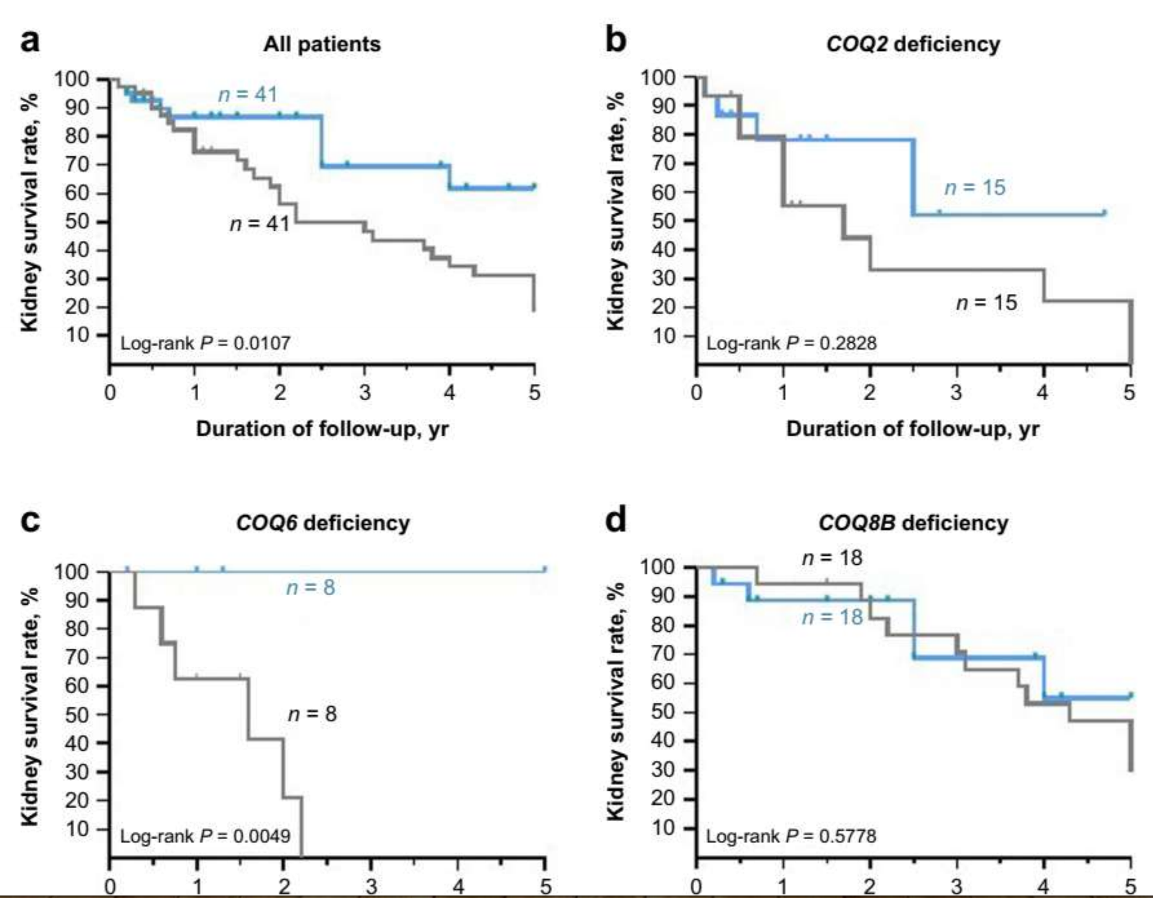
- Proteinuria diminished by a median of 88% by the end of the first treatment year
- Remained at 40% of baseline by the end of 5 years



COMPLETE REMISSION

- Complete remission in 23% of patients with CKD 1-4
- Complete remission in 58% of patients with bi-allelic mutations in CoQ6
- Rarely in the other forms

KIDNEY SURVIVAL –COQ10 SUPPLEMENT



EXTRA-RENAL RESPONSE TO TREATMENT

- Not uniform
  - 10-20% showed improvement
  - In others, new-onset and progressive neurological involvement during treatment
- Serum CoQ10 concentration and leukocyte levels do NOT correlate with disease course

APPROACH TO DIAGNOSIS

- Consider the diagnosis of mitochondrial disorder if:
  - Multi-system syndrome including kidney and/or neurologic system
  - Non-specific proteinuria → SRNS → CKD
  - Proximal tubulopathy: Complete Fanconi syndrome or isolated abnormalities
  - Electrolyte wasting or RTA
- Elevated serum and/or CSF lactate levels
- Neuro-imaging: focal lesions in deep grey matter (basal ganglia), strokes
- Muscle biopsy: histology and/or enzymatic activities (pitfall – heteroplasmy)

FURTHER WORKUP

- Next generation sequencing for nuclear- and mitochondrial DNA
- Consider extracting DNA from urine sediment

THANK YOU!

BREAKING DOWN LUPUS NEPHRITIS: THE POWER OF KIDNEY BIOPSY

ADRIAN LUNGU
ROMANIA

ERKNet The European Rare Kidney Disease Reference Network
European Reference Networks
Funded by the European Union

What proportion of children have abnormal renal function on presentation with SLE ?

A. 10%
B. 20%
C. 30%
D. 60%
E. 90%

What proportion of children have abnormal renal function on presentation with SLE ?

A. 10%
B. 20%
C. 30%
D. 60%
E. 90%

Pediatric Nephrology
https://doi.org/10.1007/s00467-022-05859-w

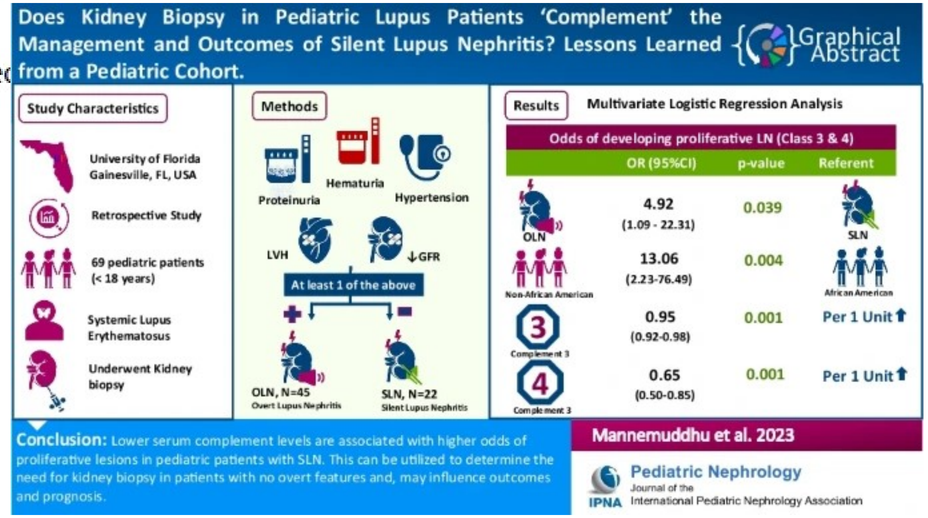
ORIGINAL ARTICLE

Check for updates

Does kidney biopsy in pediatric lupus patients "complement" the management and outcomes of silent lupus nephritis? Lessons learned from a pediatric cohort

Sai Sudha Mannemuddhu[1,2,3] · Lawrence R. Shoemaker[1] · Shahab Bozorgmehri[4] · R. Ezequiel Borgia[5,6] · Nirupama Gupta[1,7] · William L. Clapp[8] · Xu Zeng[8] · Renee F. Modica[5]

Received: 1 March 2022 / Revised: 10 December 2022 / Accepted: 10 Dec



Silent lupus nephritis (SLN) is systemic lupus erythematosus (SLE) without clinical and laboratory features of kidney involvement but with biopsy-proven nephritis

This concept of SLN, apparent only upon kidney biopsy, has been recognized since 1977, with a few published studies mainly in the adult population

> Int Arch Allergy Appl Immunol. 1977;55(1-6):420-8. doi: 10.1159/000231953.

Silent renal involvement in systemic lupus erythematosus

W M Bennett, E J Bardana, D C Houghton, B Pirofsky, G D Striker

PMID: 338507 DOI: 10.1159/000231953

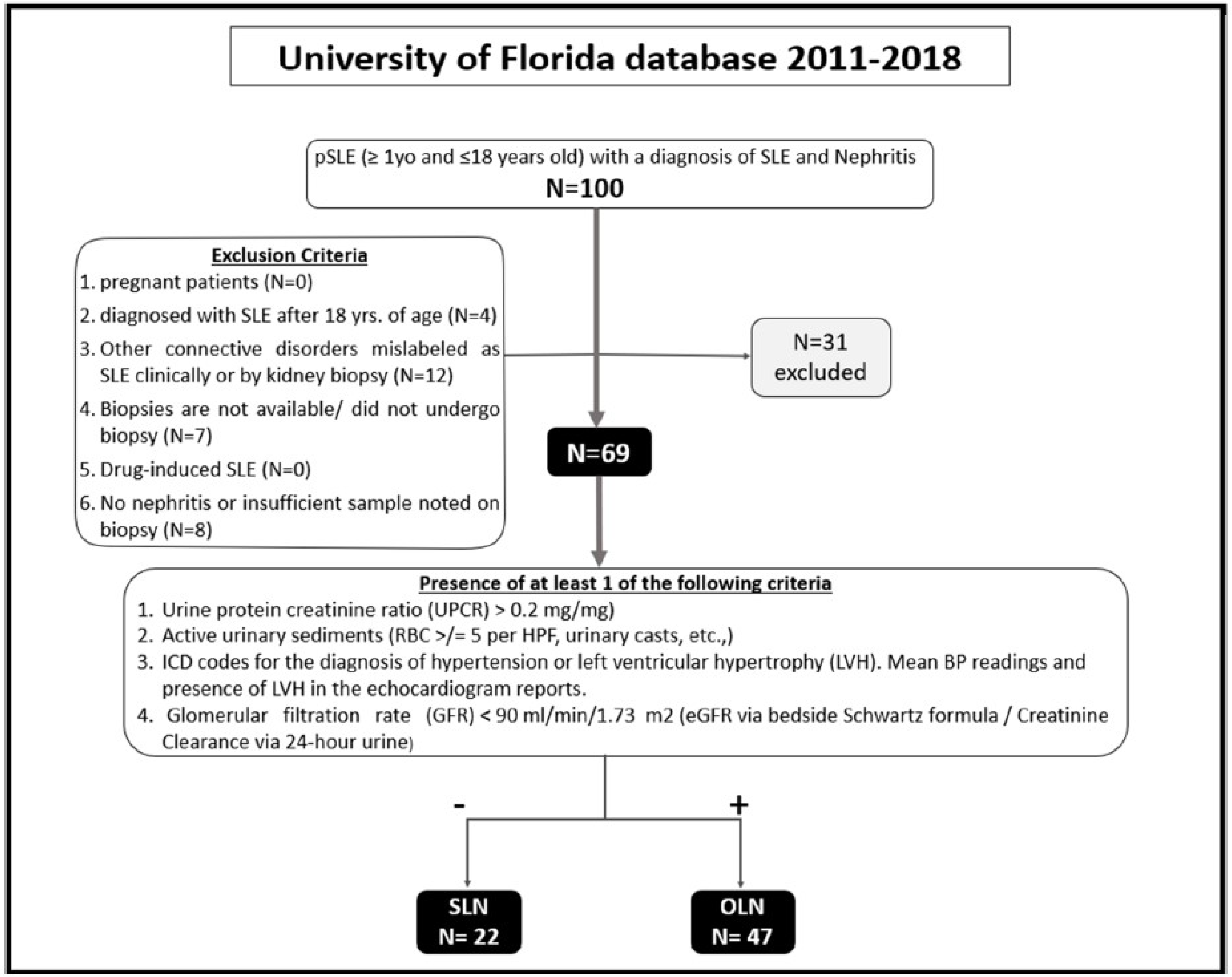
Abstract

20 patients with active SLE without clinical evidence of renal involvement underwent percutaneous renal biopsy. 12 had varying proliferative changes on light microscopy. Of 19 ultrastructural examinations performed only 3 had no electron-dense deposits. Serum C3 and C4 levels were 63 +/- 8 and 8 +/- 2 mg% in patients with subendothelial deposits, compared to 142 +/- 27 and 27 +/- 6 mg%, respectively, in patients without deposits (p less than 0.01). All patients with diffuse proliferative changes had subendothelial deposits; however, one with normal light microscopy and another with focal proliferation also had them. It is concluded that no variant of lupus nephropathy can be excluded on clinical grounds alone.

To identify pSLE patients with nephritis, **some centers have instituted baseline kidney biopsy at SLE diagnosis in children with the significant clinical and serologic activity of SLE**, **regardless of the presence or absence of overt kidney involvement**

Early identification and treatment of patients with LN correlate with early remission

Sixty-nine patients met the inclusion criteria - between 2011 and 2018. University of Florida



Silent vs. overt lupus nephritis				
Factor		Silent lupus nephritis	Overt lupus nephritis	*P*-value
N		22	47	
Female		18 (82%)	40 (85%)	0.737
Race	Asian	0	1 (2%)	0.307
	African-American	13 (59.5%)	25 (53%)	
	Hispanic	4 (18%)	9 (19%)	
	Other	4 (18%)	3 (7%)	
	Caucasian	1 (4.5%)	9 (19%)	
Age, mean (*SD*)	At diagnosis	12.6 (4.5)	13.5 (3.2)	0.358
	At biopsy	13 (4.6)	14 (3.4)	0.219
Complement (mg/dL), median (IQR)	C3	59.5 (34–77)	48 (37–74)	0.984
	C4	6.5 (3–8)	7 (4–10)	0.403
dsDNA positive		18 (82%)	36 (77%)	0.759
Anti-Smith Ab		17 (77%)	33 (70%)	0.628
Anti-RNP Ab		20 (91%)	33 (70%)	0.05
Anti-SSA Ab		11 (50%)	24 (51%)	0.8
Anti-SSB Ab		15 (68%)	29 (62%)	0.4
Anti-phospholipid Ab		15 (68%)	37 (79%)	0.7
eGFR (mL/min/1.73m^2), median (IQR) at biopsy		126 (116–138)	111.5 (84–136)	0.041
Hypertension		0	9 (19%)	0.0489
Random UPCR mg/mg, median (IQR)		0.12(0.07–0.17)	1.2(0.3–3.3)	<0.001
Biopsy results	Class I	3 (14%)	1 (2%)	
	Class II	11 (50%)	10 (21%)	
	Class III	4 (18%)	8 (18%)	
	Class IV	2 (9%)	19 (40%)	
	Class V	2 (9%)	9 (19%)	
	Class VI	0	0	

Demographics, antibody panel, eGFR, hypertension, urinary findings, and histopathology findings in SLN vs. OLN patients. OLN was seen in 68% of patients, and SLN in 32%. eGFR is normalized to BSA

eGFR, estimated glomerular filtration rate; *IQR*, interquartile ranges; *UPCR*, urine protein creatinine ratio

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	Referent	Odds ratio (95% CI)	*P*-value
Overt LN	Silent LN	4.92 (1.09–22.31)	**0.039**
Age	per one year	1.00 (0.82–1.24)	0.975
Female	Male	5.93 (0.57–61.74)	0.137
Not African-American	African-American	13.06 (2.23–76.49)	**0.004**
dsDNA Ab, positive	Negative	1.08 (0.20–5.86)	0.927
Anti-Smith Ab, positive	Negative	0.29 (0.05–1.67)	0.165
C3	Per one unit	0.95 (0.92–0.98)	**0.001**
eGFR	Per one unit	0.99 (0.97–1.01)	0.294

Multivariate logistic regression analysis demonstrating the association between baseline demographics, laboratory features, pathology findings, and proliferative nephritis. Values in bold indicate significant association

[*] C3 is included in the model, but C4 is not included due to multicollinearity

Table 2 Predictors of proliferative nephritis on multivariable logistic regression analysis with C3[*]

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Table 2 Predictors of proliferative nephritis on multivariable logistic regression analysis with C3*

In this study, 1 out of every 2.7 patients without any biochemical or clinical findings of kidney involvement who underwent kidney biopsy and were found to have proliferative or membranous SLN, which is very significant

Currently, kidney biopsy is the gold standard for diagnosing lupus nephritis

decreased levels of complement components C1q, C3, C4, and CH50 tend to correlate with disease activity in patients with active OLN

Was observed that none of the serologic auto-antibody markers in our study could accomplish this in light of prior reports suggesting an association of high levels of ds-DNA and anti-Sm antibodies with SLN

Upon multivariate logistic regression, only lower C3 and C4 levels were associated with higher odds of proliferative nephritis

Low C3 represents immune consumption and deposition in the kidneys; however, a primary complement deficiency seen in a subset of pSLE patients can be a confounding factor, particularly with low C4 levels

CASE 1

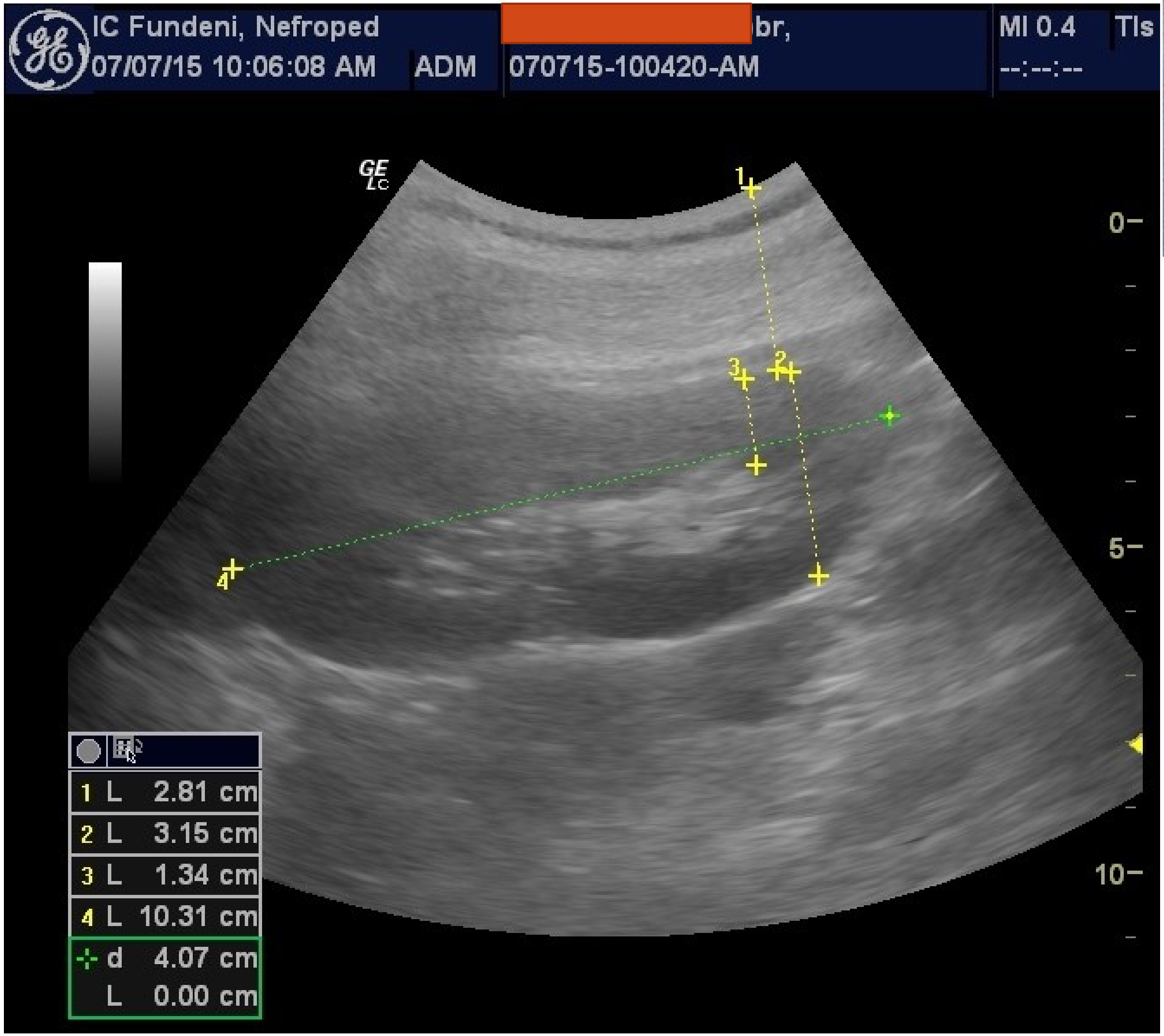
- Denisa-13 years old
- SLE diagnosed in a local hospital is transferred to my clinic for accentuated butterfly erythema, intermittent joint pains.
- characteristic facies with intense butterfly erythema, maculo-erythematous elements at the level of the hands, arms, upper chest, discoid lupus type intermittent pain in the sacroiliac joint
- present diuresis, normochromic urine,

BUTTERFLY ERYTHEMA

- Pictures with family and patient approval

PARACLINIC

- **WBC 3120/mm3**
- Hb 13.9g/dl
- **PLT 144000/mm3**
- **Anti ds DNA >200u/ml (intens +)**
- **Intense positive ANA**
- **Intense Positive aniti C1Q**
- **C3 28.4 mg/dl**
- **C4 2.12 mg/dl**
- **NORMAL URINE SEDIMENT**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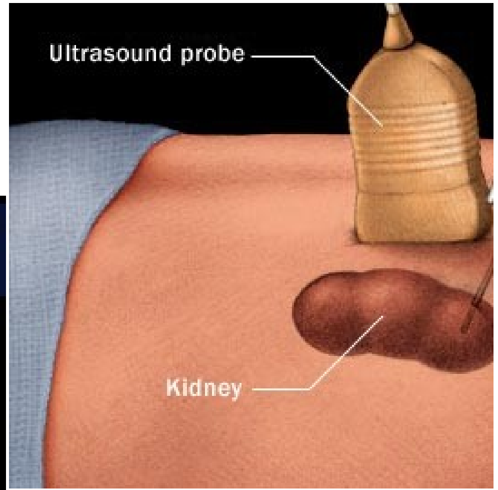
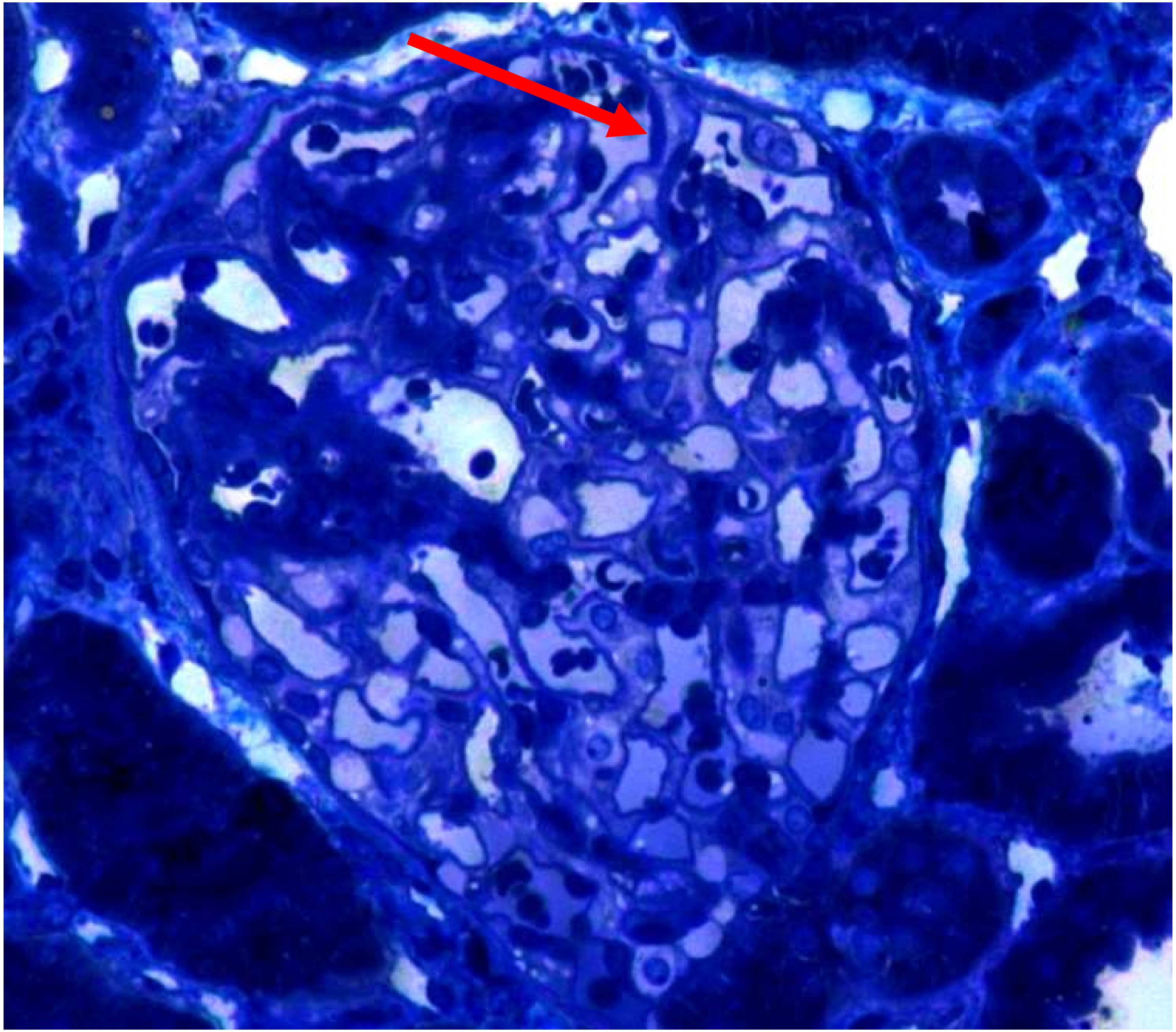
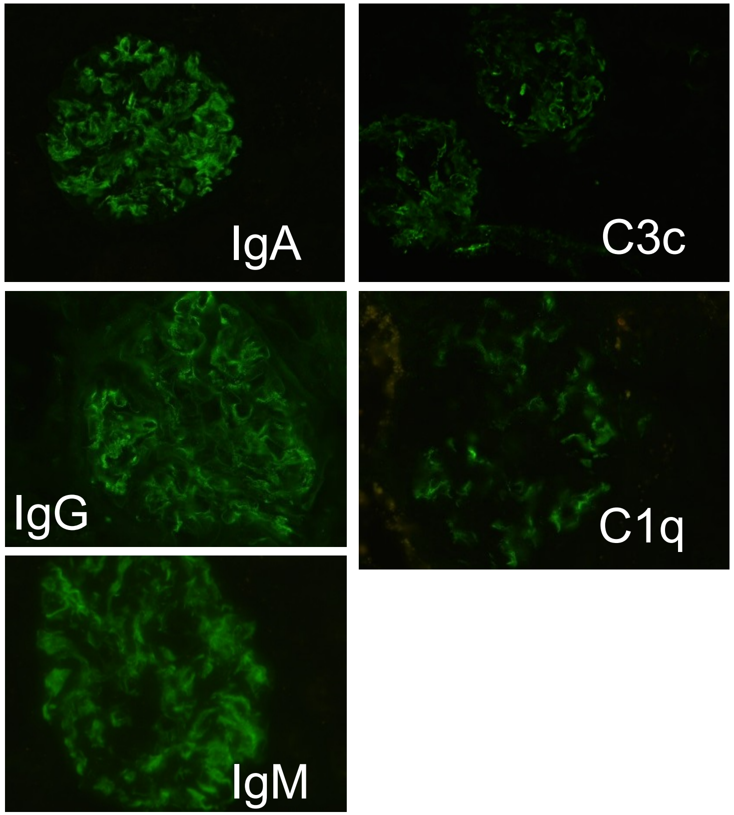

Ultrasound probe
Kidney

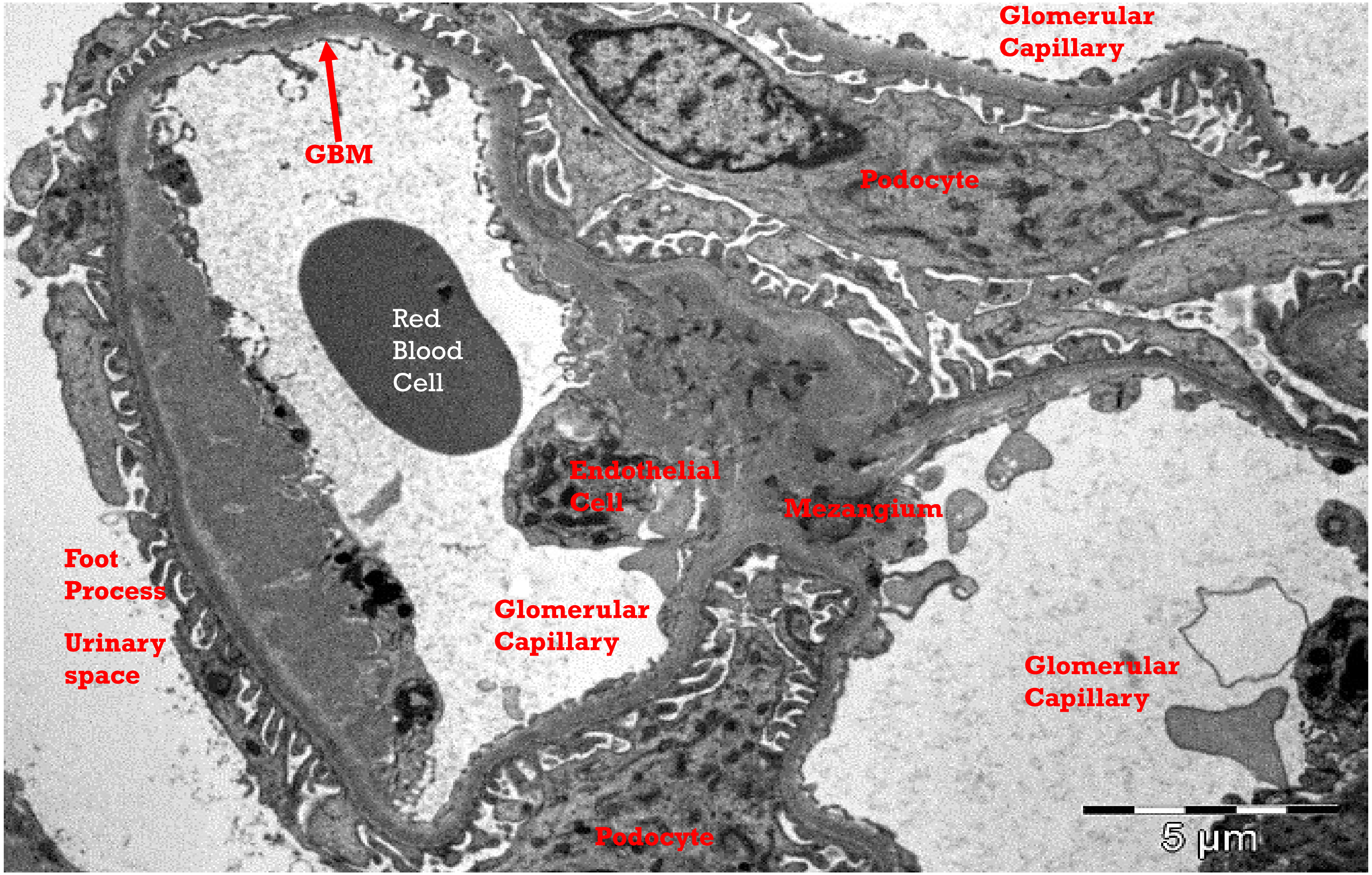
CLASS III – LUPUS NEPHRITIS



CLASS III – LUPUS NEPHRITIS



IgA – intense + granular in the mesangium and MBG
IgG – intense + granular in mesangium, MBG, focal in MBT and vessels
IgM – intense + granular in the mesangium C1q – intense + granular in the mesangium and MBG
C3c – intense + granular in mesangium and MBG, focal in MBT and in vessels


Glomerular
Capillary
GBM
Podocyte
Red
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Endothelial
Cell
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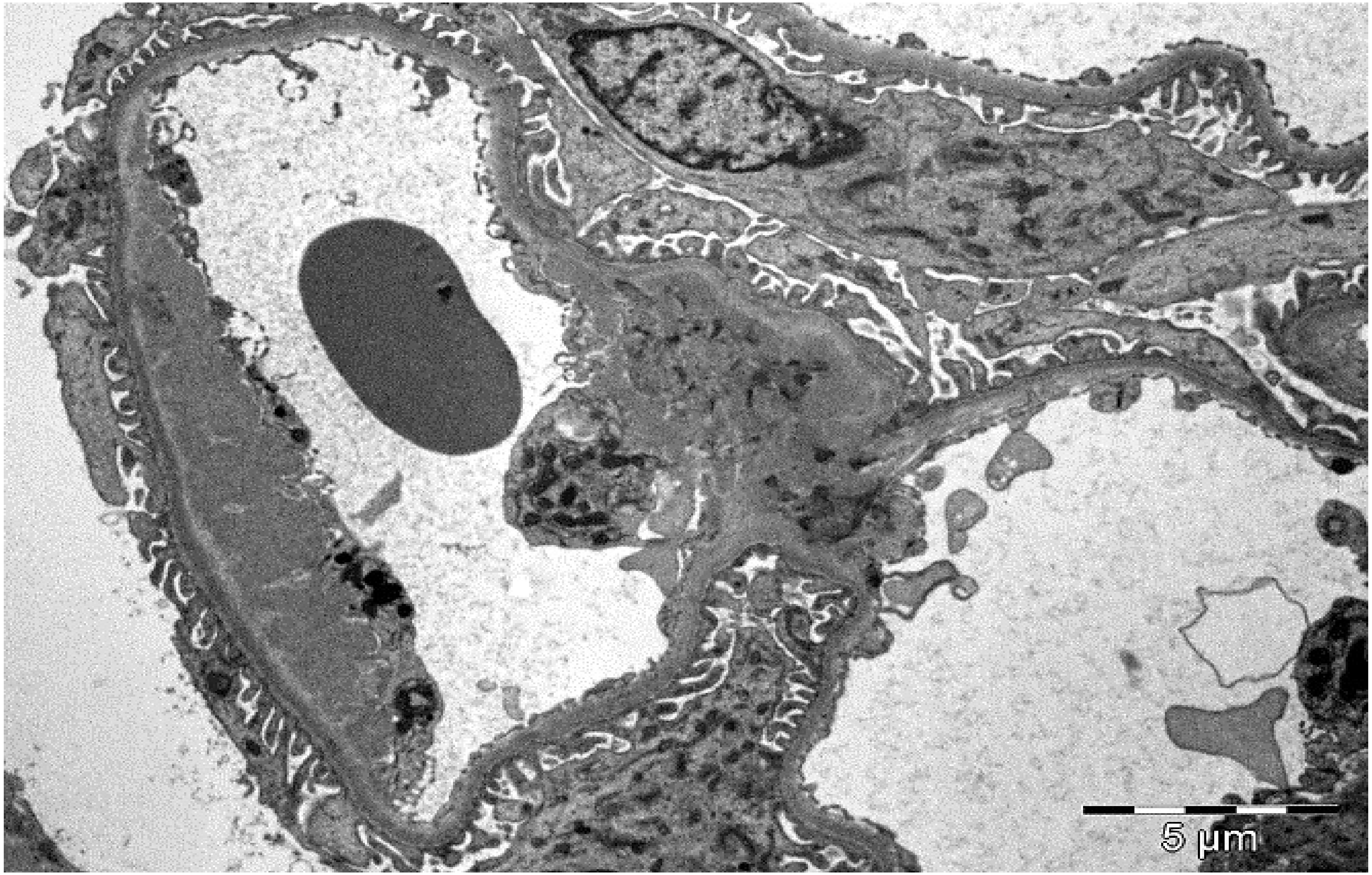
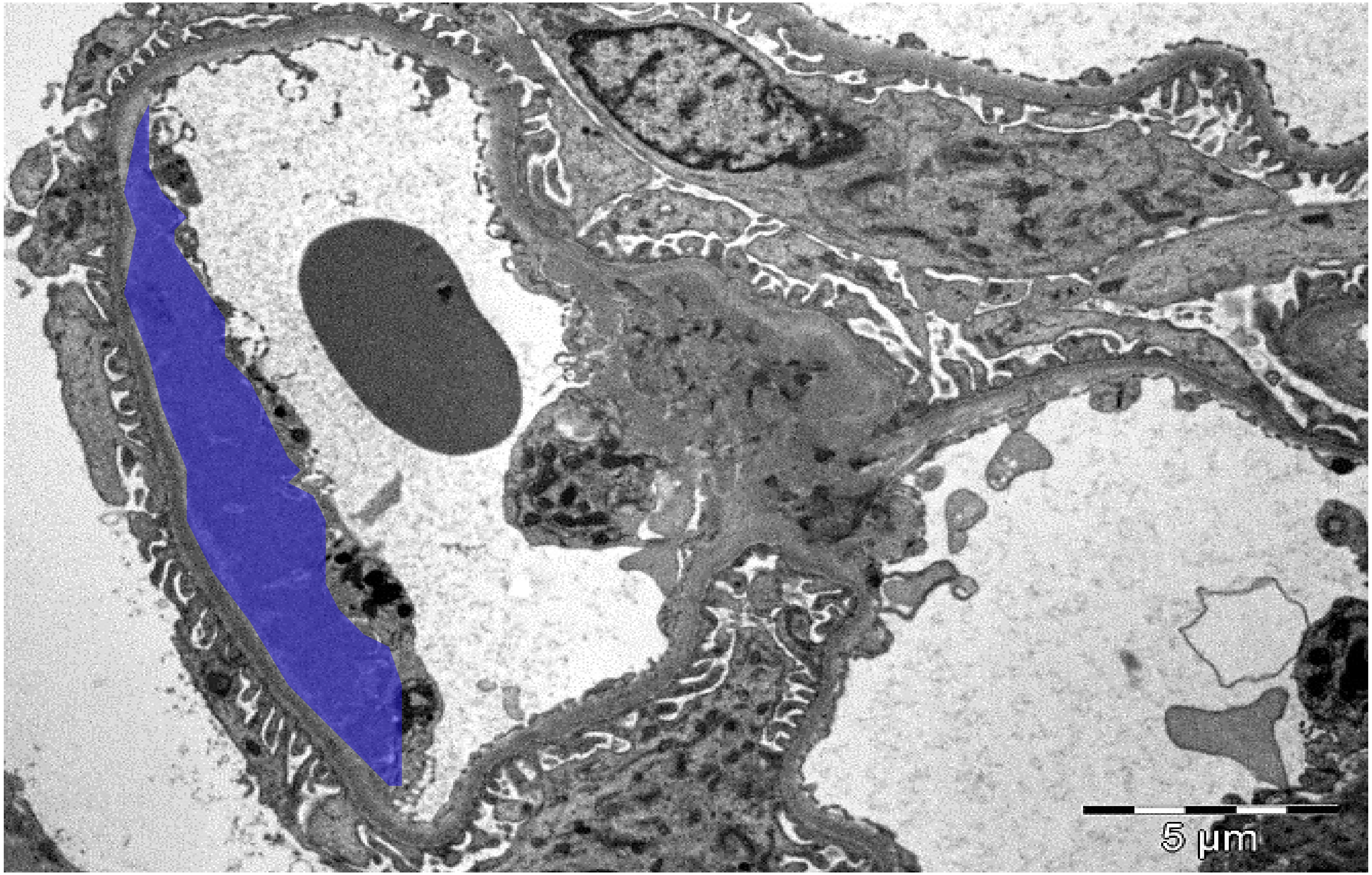
Capillary
Glomerular
Capillary
Podocyte
5 µm

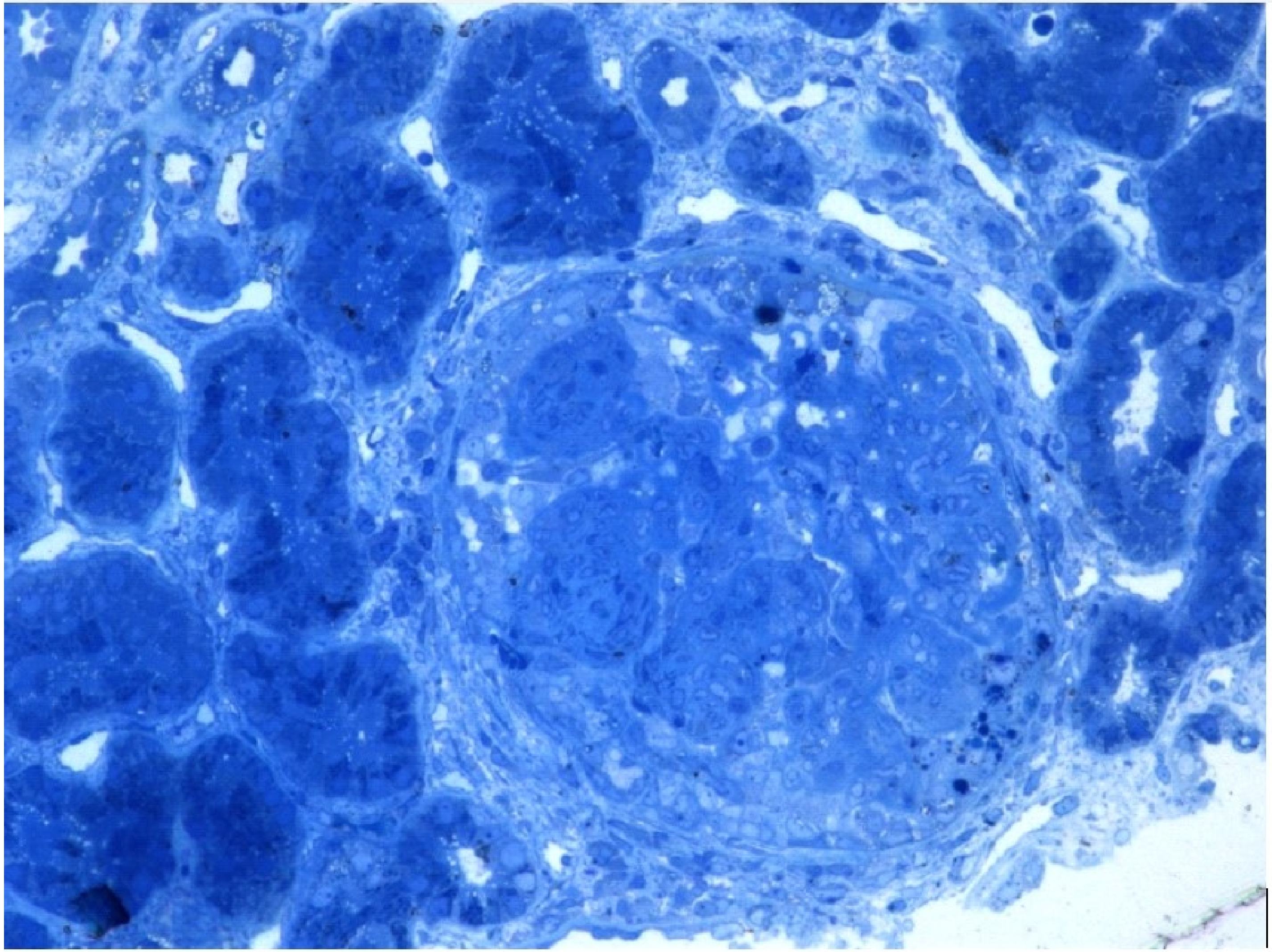
CLASS III – LUPUS NEPHRITIS



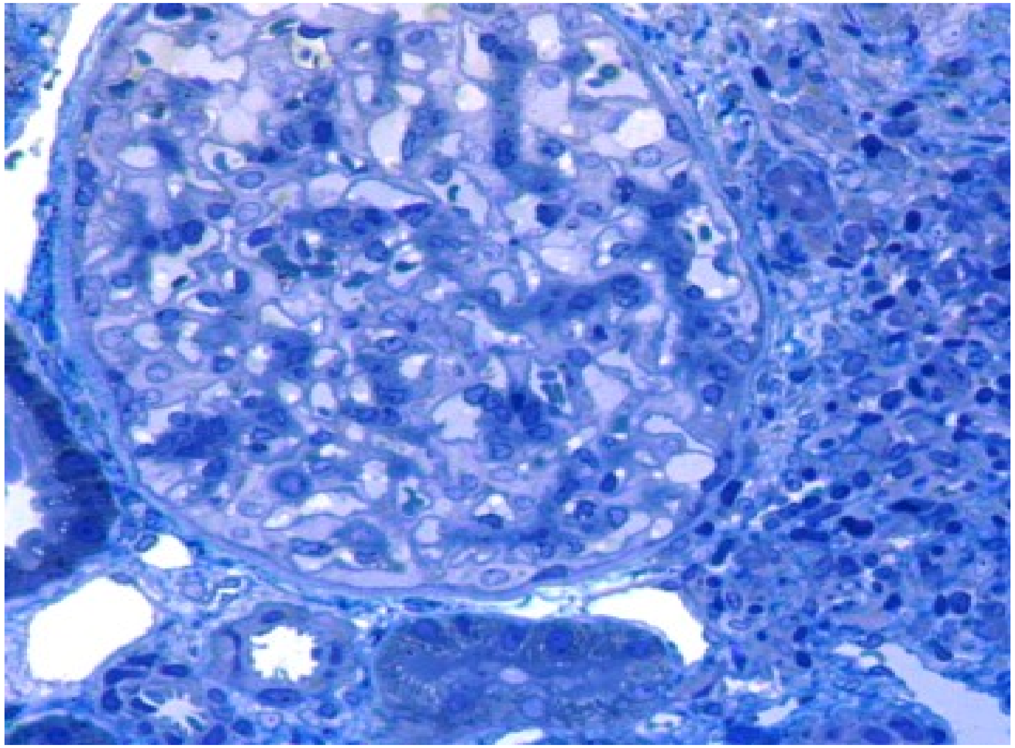
CLASS III – LUPUS NEPHRITIS

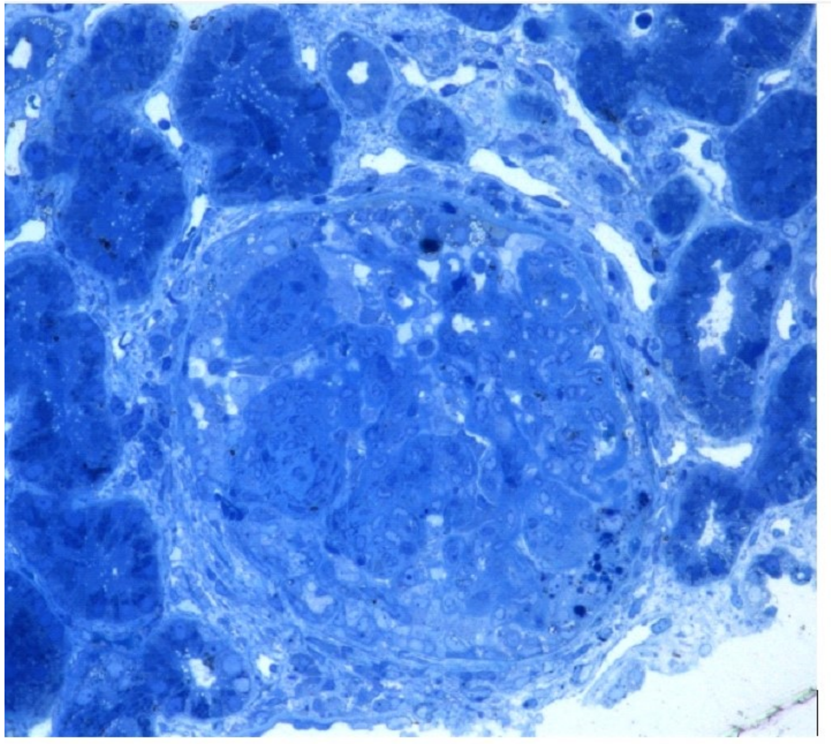


SECOND BIOPSY
CLASS IV – LUPUS NEPHRITIS



SECOND BIOPSY
CLASS IV – LUPUS NEPHRITIS





SECOND BIOPSY
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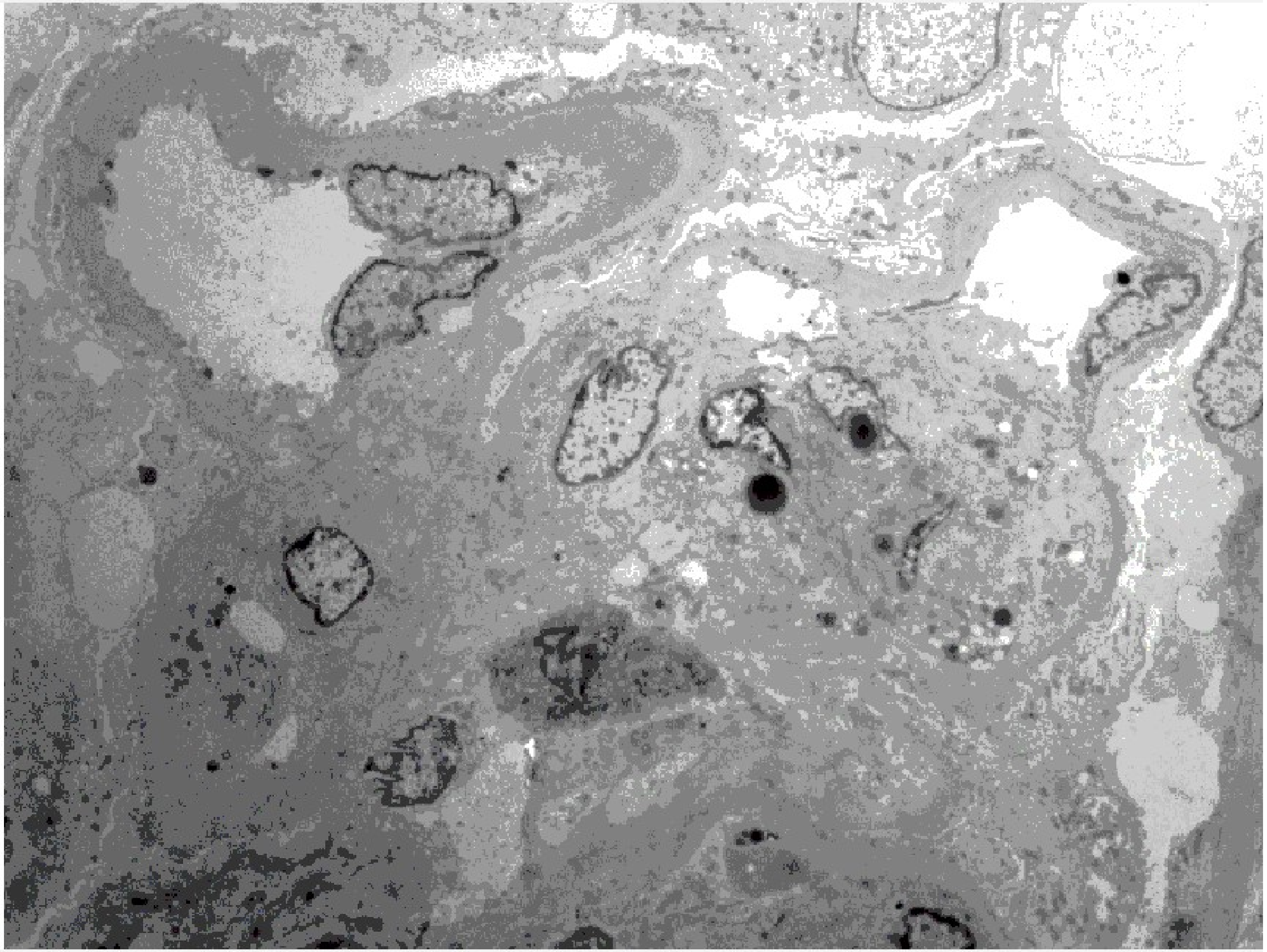
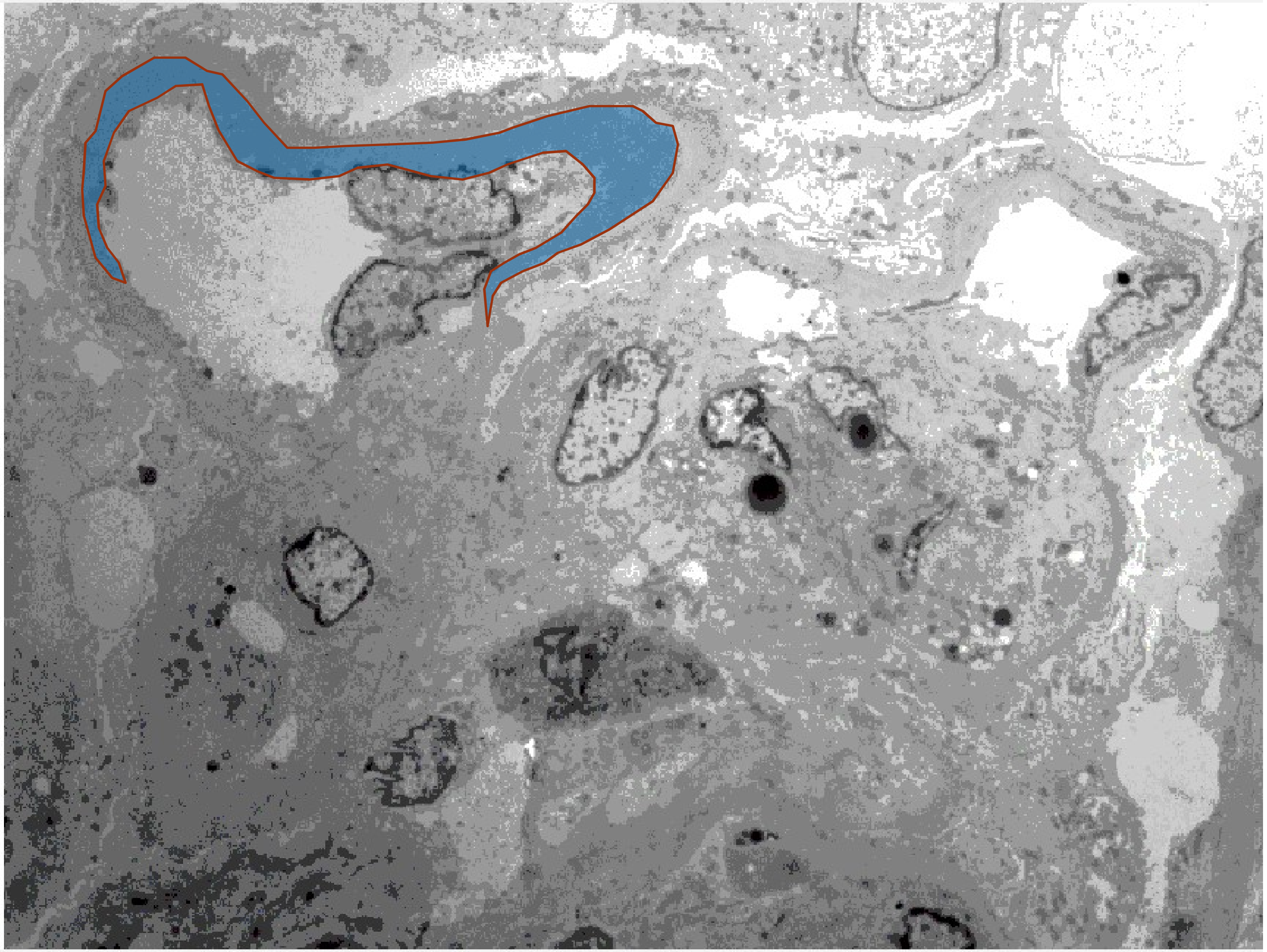


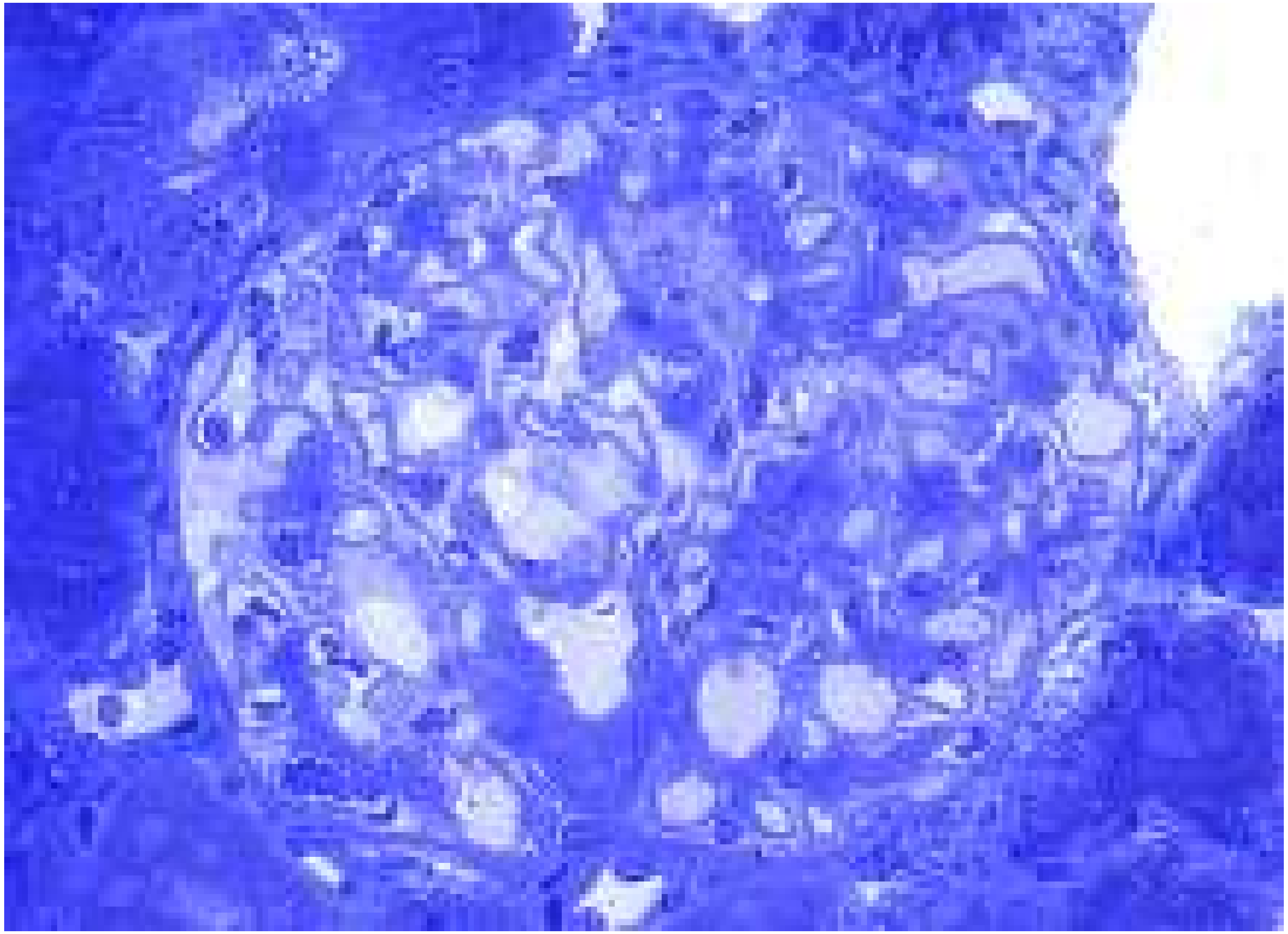
SECOND BIOPSY
CLASS IV – LUPUS NEPHRITIS



CASE 5

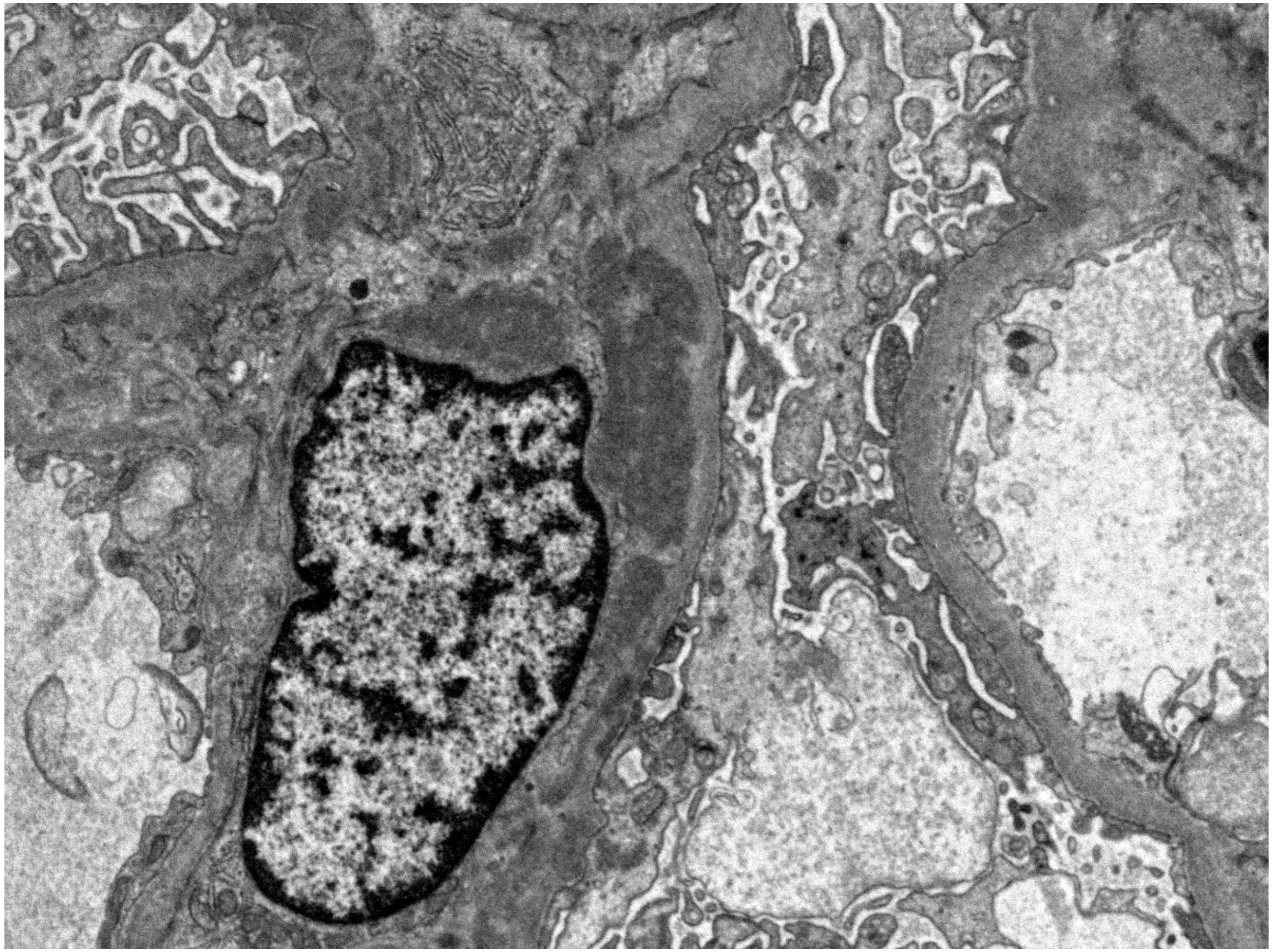
ION

CASE 5 – BLUNT URINE SEDIMENT



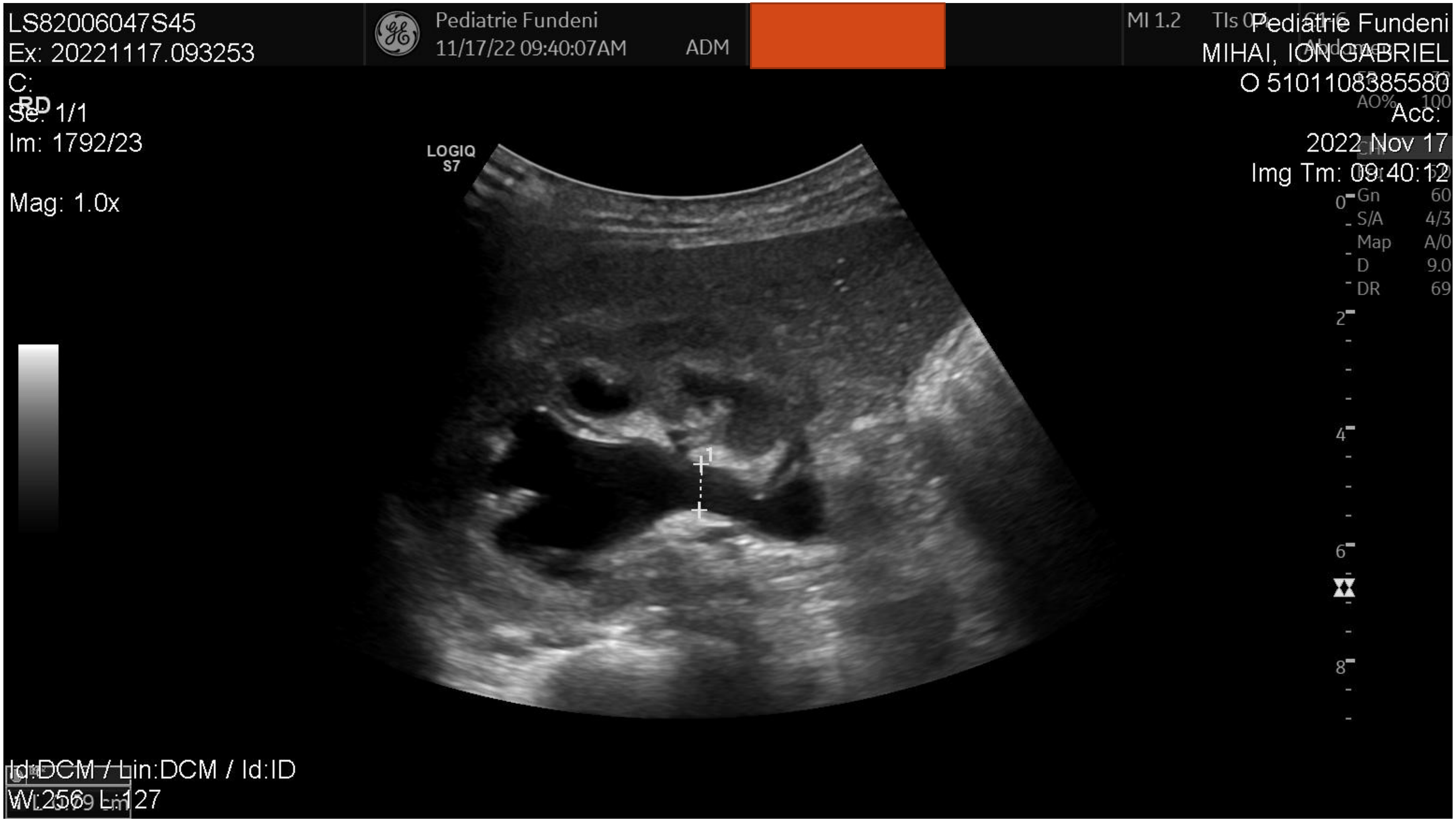
Class II

CASE 5



CASE 5

CASE 5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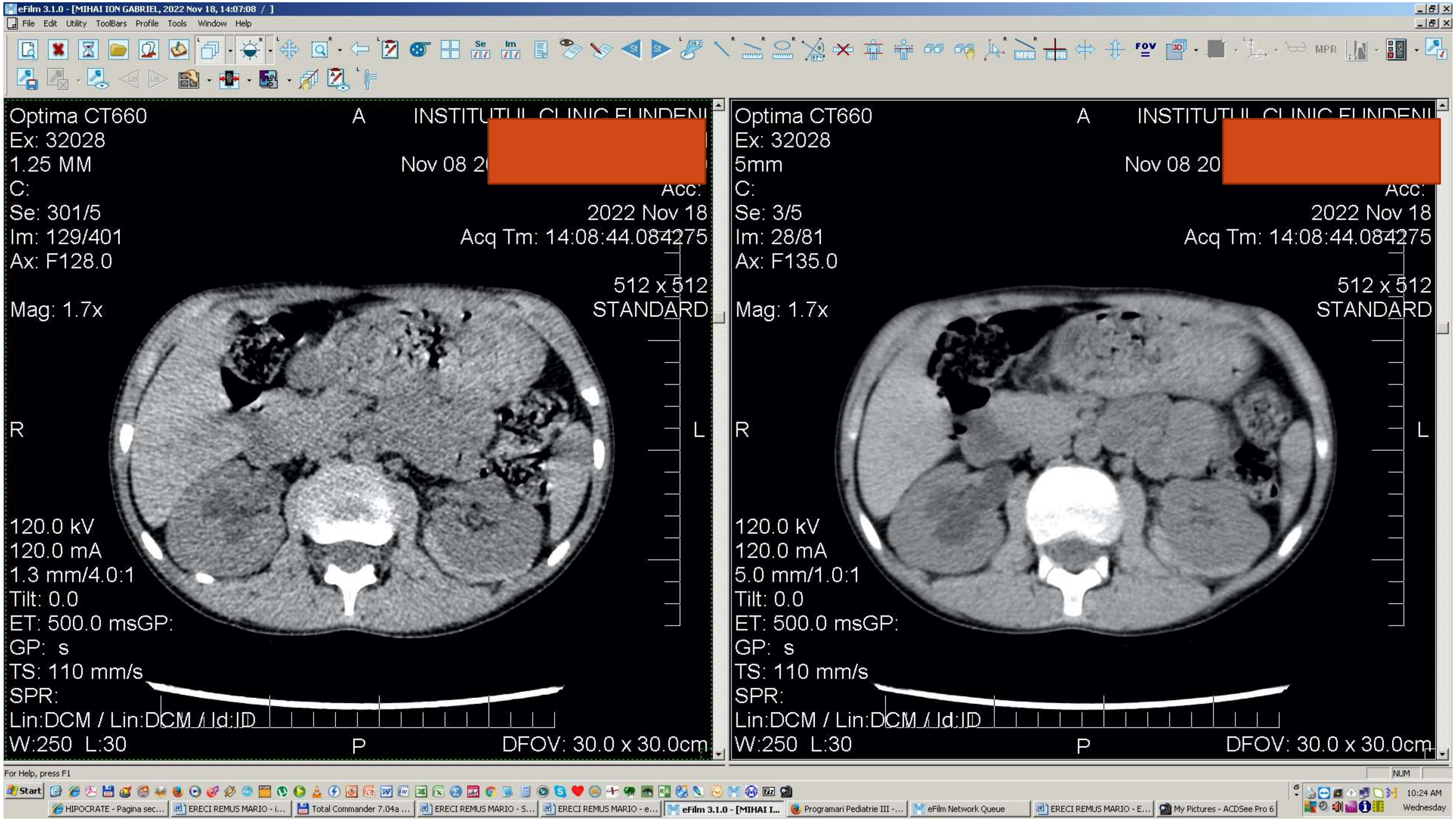
CASE 5



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CASE 5
GENETICS

GENE **IRF8**	**TRANSCRIPT** NM_002163.4	**NOMENCLATURE** c.474G>A, p.(Met158Ile)	**GENOTYPE** HET	**CONSEQUENCE** missense_variant	**INHERITANCE** AD,AR	**CLASSIFICATION** **Variant of uncertain significance**
	ID	**ASSEMBLY** GRCh37/hg19	**POS** 16:85946763	**REF/ALT** G/A		
	gnomAD AC/AN 0/0	**POLYPHEN** benign	**SIFT** tolerated	**MUTTASTER** polymorphism	**PHENOTYPE** Immunodeficiency 32A (CD11C-positive/CD1C-positive dendritic cell deficiency), Immunodeficiency 32B (monocyte and dendritic cell deficiency)	

IRF8 c.474G>A, p.(Met158Ile)

This variant is absent in gnomAD, a large reference population database (n>120,000 exomes and >15,000 genomes) which aims to exclude individuals with severe pediatric disease.

The *IRF8* c.474G>A p.(Met158Ile) variant is predicted to be deleterious by all in silico tools utilized. The alternate amino acid is present at this position in multiple mammals (UCSC Genome Browser), which suggests that this amino acid change may be tolerated.

To the best of our knowledge, this variant has not been reported in the medical literature or on disease-related variation databases.

CASE 5
GENETICS

IRF8

IRF8 gene (MIM *601565) encodes inferferon regulatory factor 8. This plays a role as a transcriptional activator or repressor and specifically binds to the upstream regulatory region of type I IFN and IFN-inducible MHC class I genes. It has a negative regulatory role in cells of the immune system (UniProtKB - Q02556).

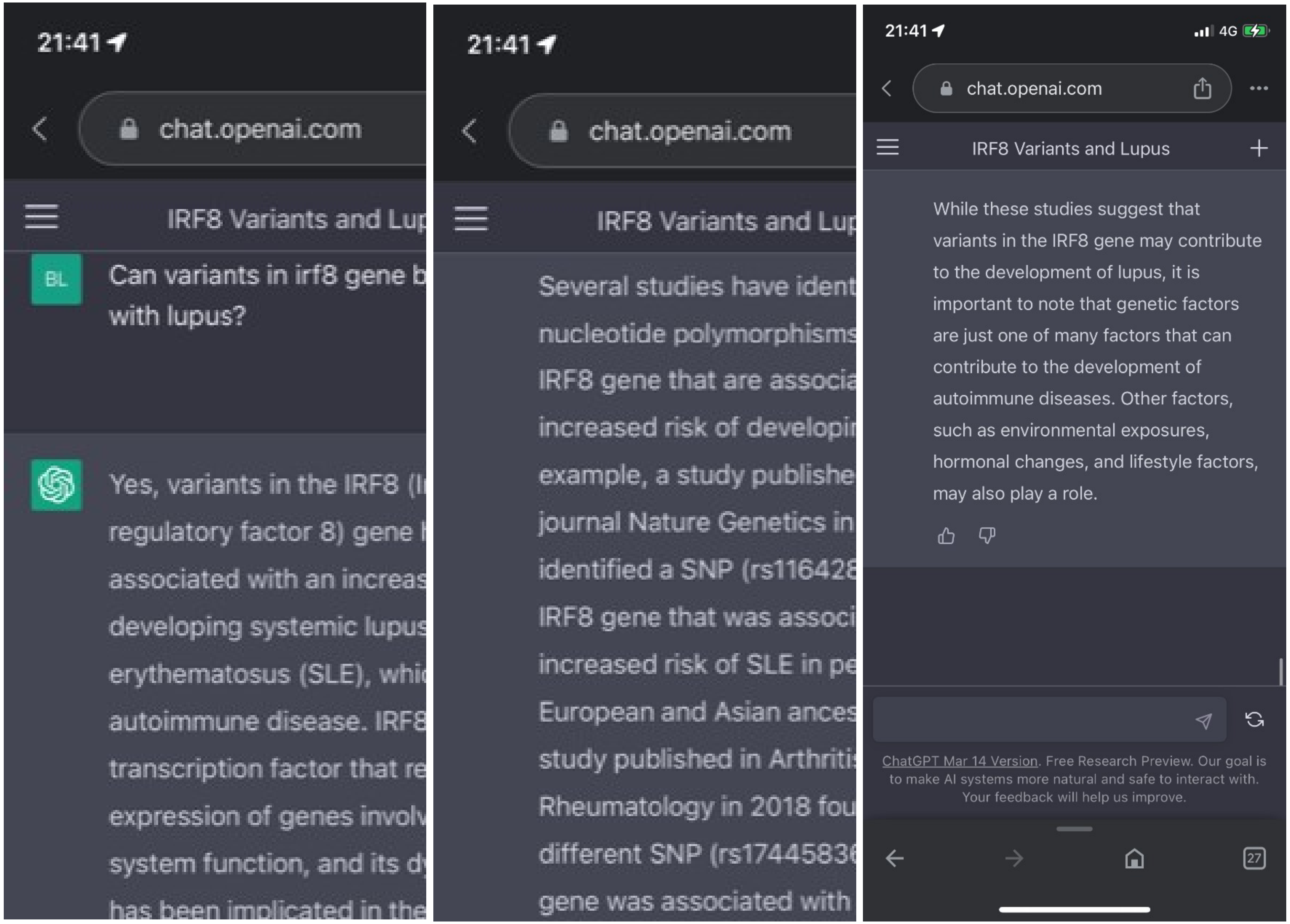
Pathogenic, heterozygous variants in *IRF8* cause immunodeficiency 32A, mycobacteriosis that is inherited in a dominant manner (IMD32A, MIM #614893), while biallelic pathogenic variants cause immunodeficiency 32B, monocyte and dendritic cell deficiency, that is inherited in a recessive manner (IMD32B, MIM #226990).

Dominantly inherited IMD32A causes an abnormal peripheral blood myeloid phenotype with a marked loss of CD11c-positive/CD1c dendritic cells, resulting in selective susceptibility to mycobacterial infection (PMID 21524210). Patients suffering from recessively inherited IMD32B have particular susceptibility to viral diseases. The IMD32B disease was originally reported by Fleisher *et al.* already in 1982 (PMID 6279813). Several related patients suffered from markedly deficient NK cell activity and all but one of them were deceased due to this disease during later follow-up of this family (PMID 27893462).

There are <10 disease-causing variants of *IRF8* reported in the HGMD Professional database (March 2020). These are all missense variants. The pLI value (probability for loss-of-function intolerance) for the gene is 0.95, indicating that it tolerates loss-of-function variation poorly. There are only 3 loss-of-function variants in the gnomAD reference population cohort, while 22.5 such variants are expected based on gene length and sequence.

Mutation nomenclature is based on GenBank accession NM_002163.4 (*IRF8*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CASE 5
CHAT GPT



CASE 5

AJHG

CellPress

Volume 90, Issue 4, 6 April 2012, Pages 648-660

Article

Identification of *IRF8*, *TMEM39A*, and *IKZF3-ZPBP2* as Susceptibility Loci for Systemic Lupus Erythematosus in a Large-Scale Multiracial Replication Study

Christopher J. Lessard [1 2], Indra Adrianto [1], John A. Ice [1], Graham B. Wiley [1], Jennifer A. Kelly [1], Stuart B. Glenn [1], Adam J. Adler [1], He Li [1 2], Astrid Rasmussen [1], Adrienne H. Williams [3], Julie Ziegler [3], Mary E. Comeau [3], Miranda Marion [3], Benjamin E. Wakeland [4], Chaoying Liang [4], Paula S. Ramos [5], Kiely M. Grundahl [1], Caroline J. Gallant [6], Marta E. Alarcón-Riquelme for the BIOLUPUS and GENLES Networks [1 7], Graciela S. Alarcón [8]...Kathy L. Moser [1 2]

› Int J Immunogenet. 2014 Apr;41(2):112-8. doi: 10.1111/iji.12087. Epub 2013 Sep 3.

Single-nucleotide polymorphisms of IRF8 gene are associated with systemic lupus erythematosus in Chinese Han population

S-W Li [1], Y He, Z-H Zheng, D-W Liu, Z-S Liu

Affiliations + expand

PMID: 24034601 DOI: 10.1111/iji.12087

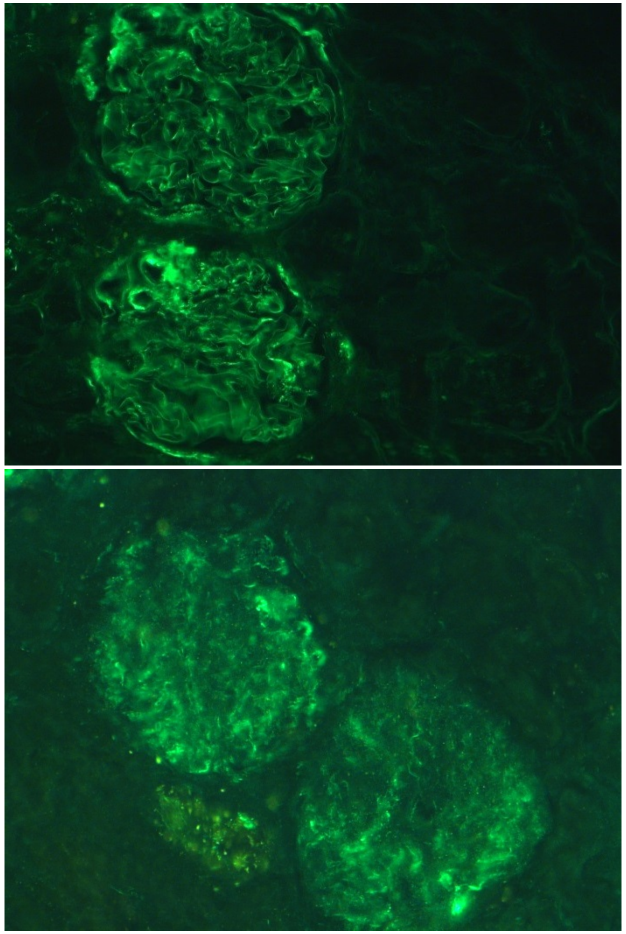
Abstract

Interferon regulatory factor 8 (IRF8) has been shown to have diverse roles in the regulation of the immune system. Two recent studies had revealed the association between the single-nucleotide polymorphisms (SNPs; rs11644034 and rs2280381) of IRF8 and systemic lupus erythematosus (SLE) in a multiethnic population. The purpose of this study was to evaluate whether the association could be replicated in a Chinese Han population. Genotypes were determined by a multiplex polymerase chain reaction-ligase detection reaction (PCR-LDR) in 358 patients and 357 geographically matched healthy controls. Significant differences in genotype frequency were found between SLE and control individuals (rs11644034: AA vs. GG, P = 0.014, odds ratio (OR) = 0.980, 95% confidence internal (CI): 0.964-0.996; rs2280381: CC vs. TT, P = 0.005, OR = 0.150, 95% CI: 0.033-0.676). Conditional logistic regression analysis showed that the association of rs2280381 remained significant (P adjusted = 0.028) after adjustment for rs11644034, but not vice versa (P adjusted = 0.361).When stratifying patients with SLE according to clinical subtypes, SNP rs2280381 was found to be associated with low complement in patients with SLE. However, SNP rs11644034 was not found to be associated with SLE clinical subgroups. Analysis of the haplotypes revealed that haplotype G-T and G-C were also significantly associated with SLE (P = 0.002 and P = 0.012, respectively). Our study indicated that the IRF8 gene polymorphisms might be associated with susceptibility to SLE and with disease-related clinical manifestations in Chinese Han population.

CASE 6

MIRCEA

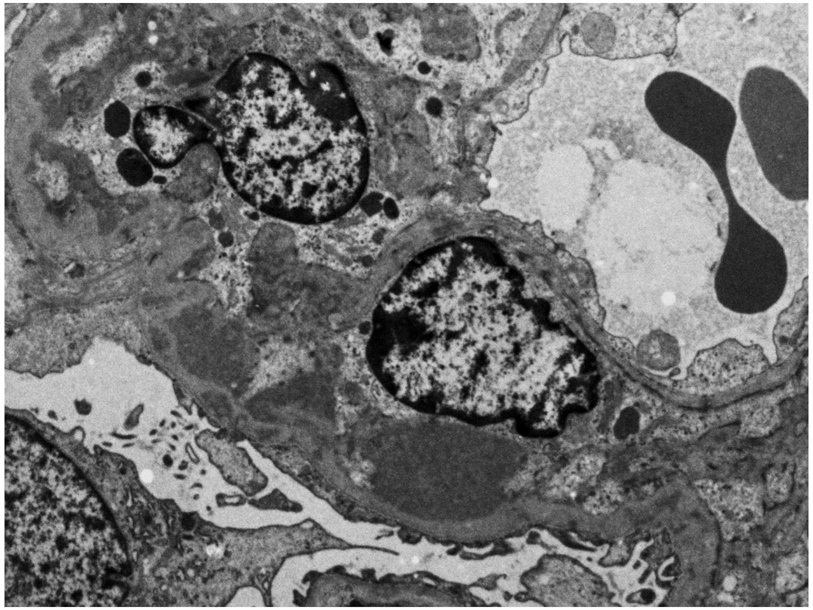
CASE 6
MIRCEA - NORMAL URINE SEDIMENT



IgA – moderate + granular, coarse in GBM
IgG – intense + granular mesangial, weak + in GBM
IgM – moderate + coarse granular mesangial and in GBM
C1q – weak + granular in GBM
C3c – intense + granular, coarse mesangial, in GBM, TBM, arterioles and arteries

Class III

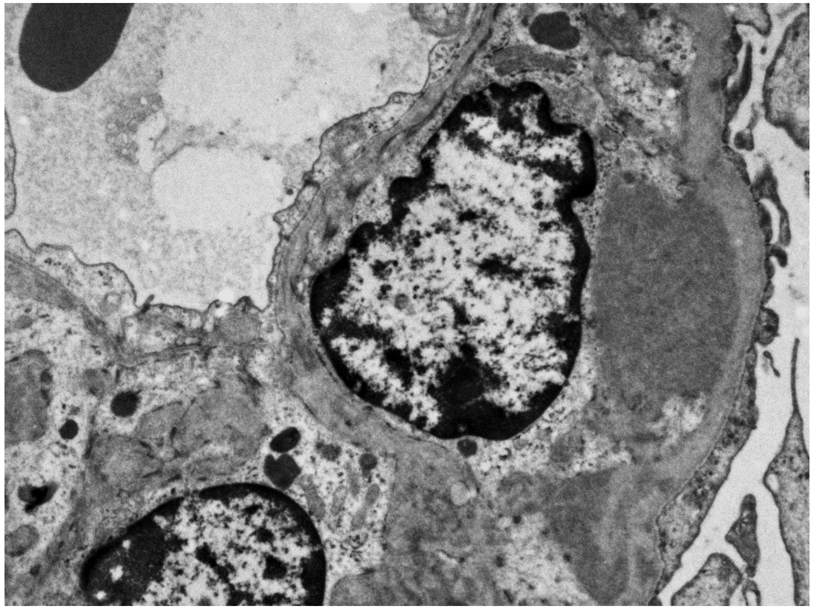
CASE 6

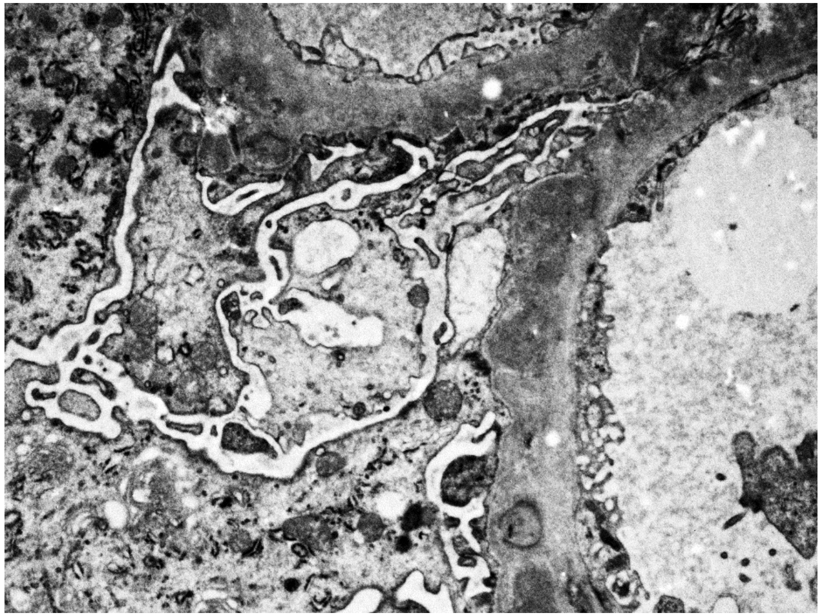


13 Glomeruly shows segmental cell mesangial proliferation (approx. 25% from the glomerulus). One glomerulus with perihilar sclerosis and 3 glomeruli with sclerosis segmental.

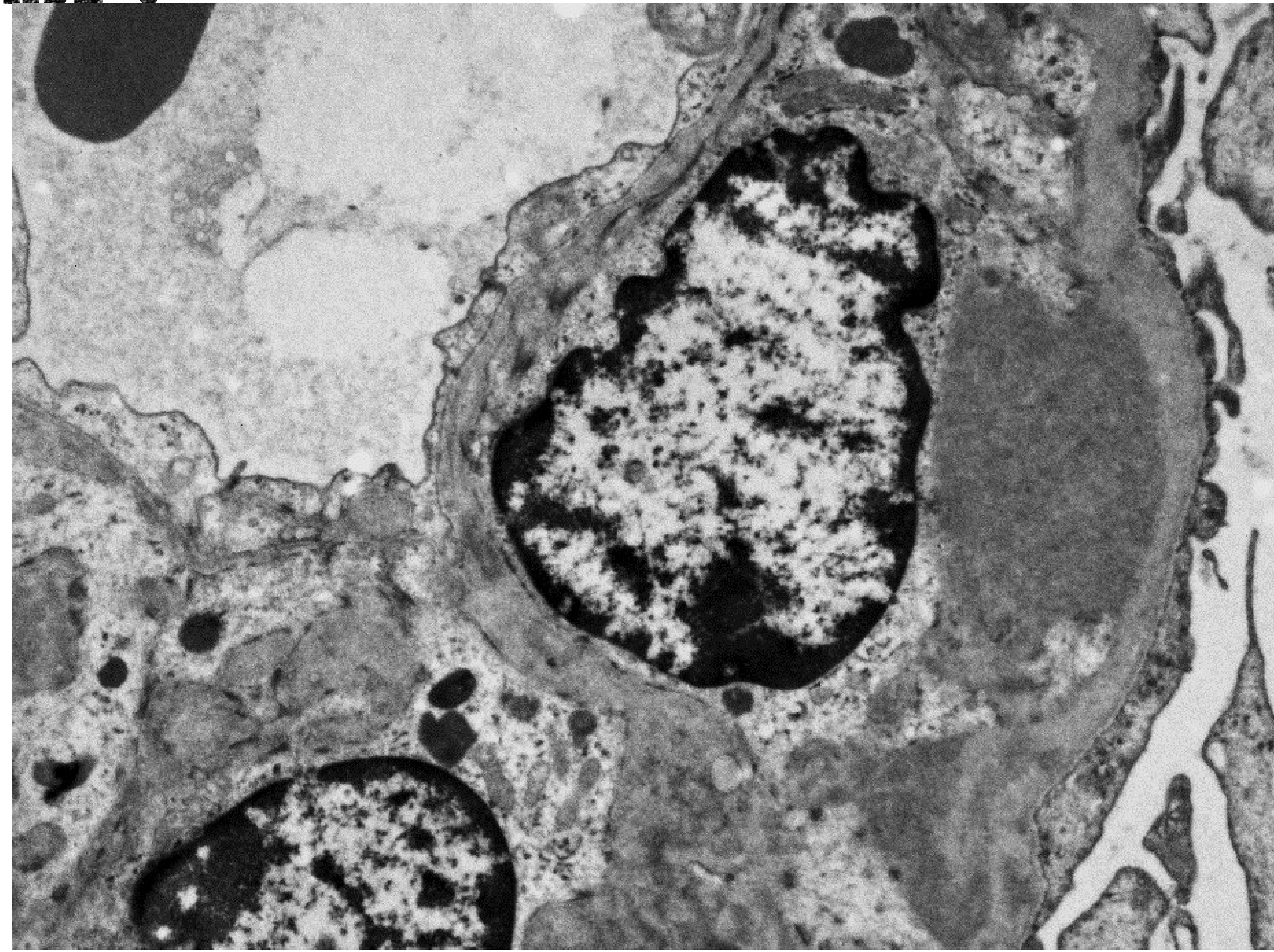
Dense mesangial, subendothelial deposits and rare subepithelial deposits of various sizes, segmental. Rare apoptotic cells. Focal, capillaries with MBG thin with disorganized architecture and ruptures. Pedicels partially obliterated (< 20%).

Class III Lupus Nephritis

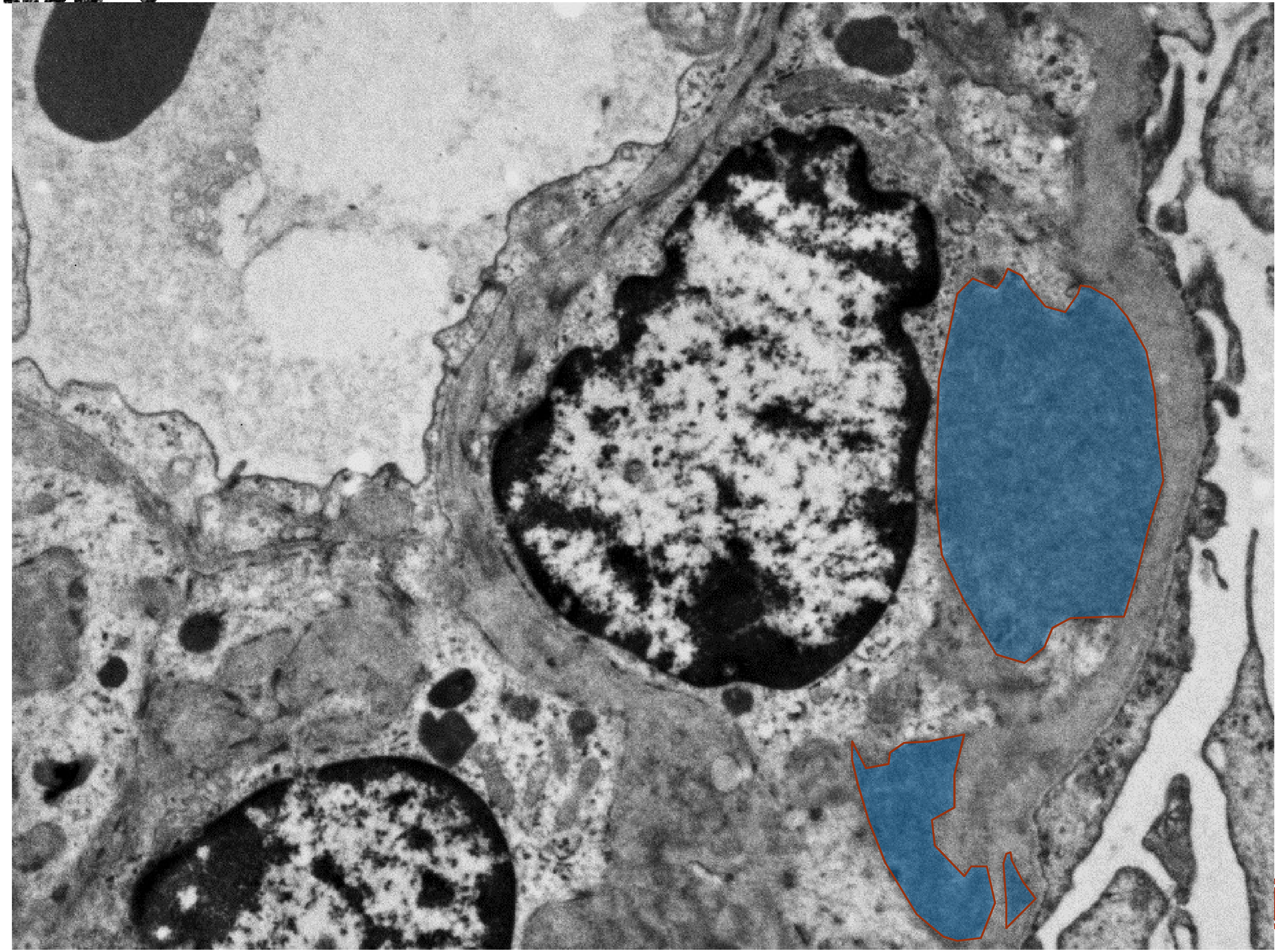




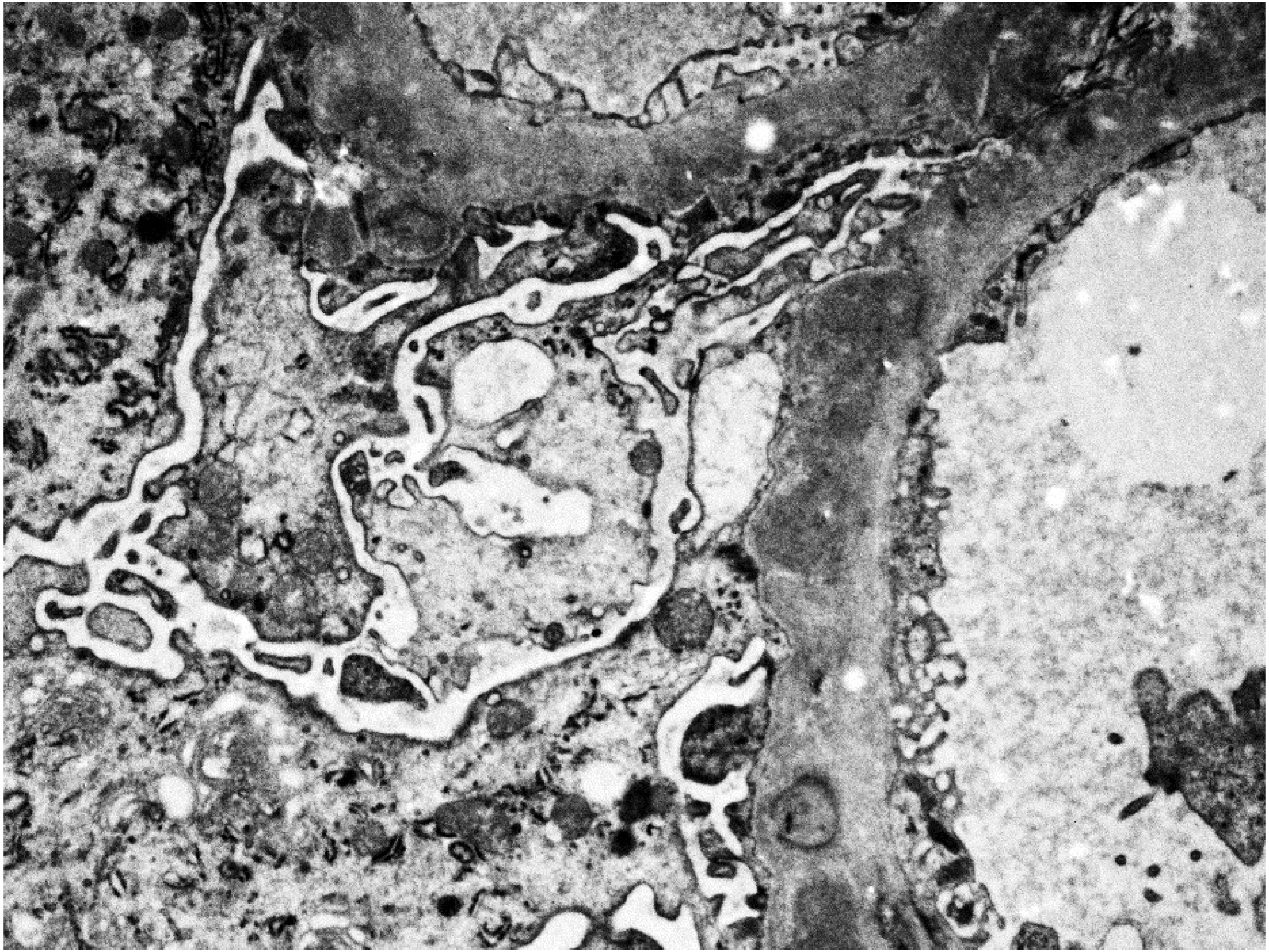
CASE 6



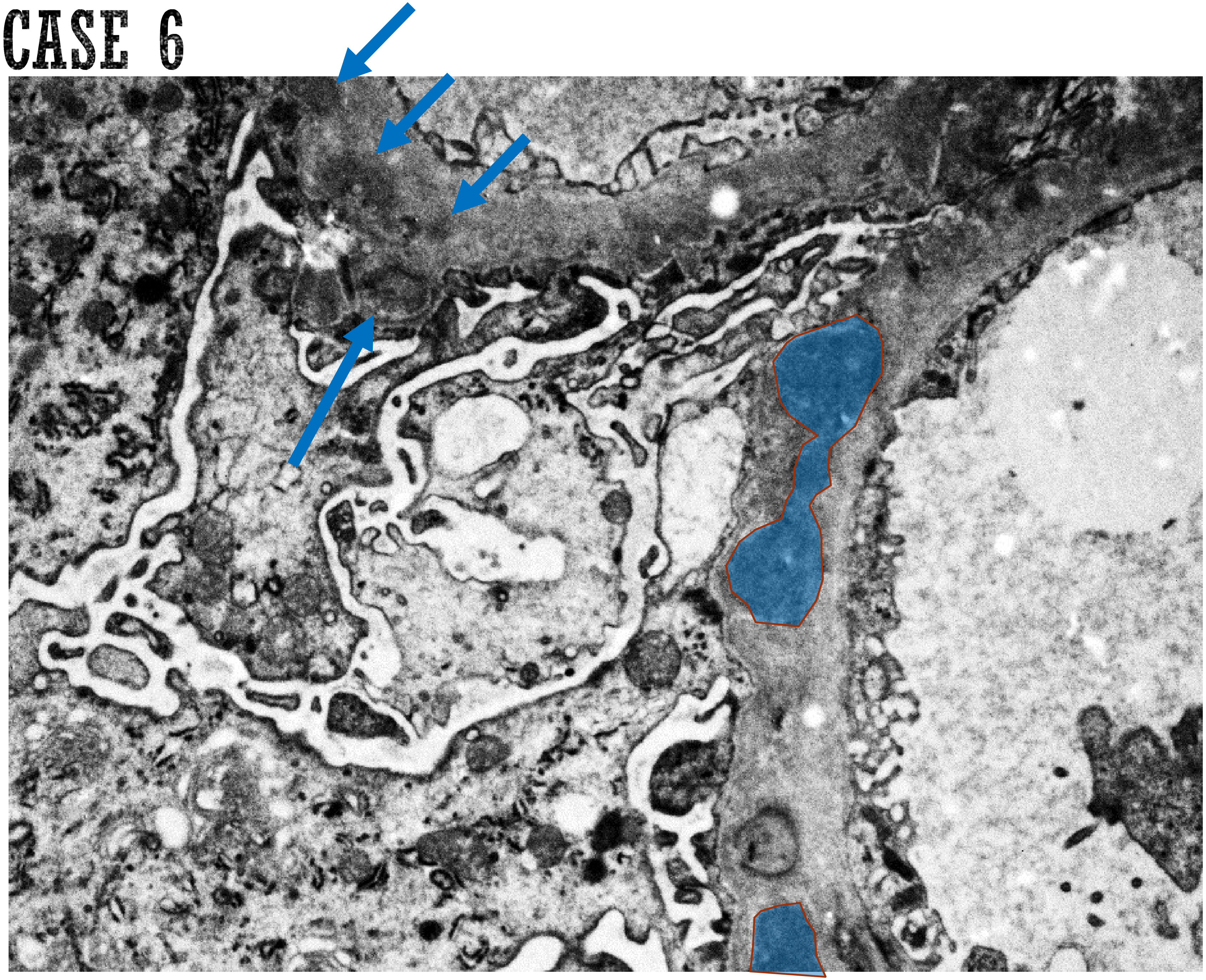
CASE 6



CASE 6



CASE 6



6

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2023, pp 1–14
DOI 10.1002/art.42416

CENTRE FOR PERSONALISED IMMUNOLOGY

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

De Novo *PACSIN1* Gene Variant Found in Childhood Lupus and a Role for PACSIN1/TRAF4 Complex in Toll-like Receptor 7 Activation

Chengmei Xie,[1] Haibo Zhou,[1] Vicki Athanasopoulos,[2] Qian Shen,[3] Yaoyuan Zhang,[2] Xiangpeng Meng,[2] Gaetan Burgio,[2] Todor Arsov,[4] Adrian C. Lungu,[5] Pingjing Zhang,[1] Yuting Qin,[1] Jiangyang Ma,[1] Xiaoqian Wu,[1] Xiaoyue Jiang,[1] Huihua Ding,[1] Yao Meng,[1] Nan Shen,[1] Yuke He,[1] and Carola G. Vinuesa[6]

Objective. Increased Toll-like receptor 7 (TLR-7) signaling leading to the production of type I interferon (IFN) is an important contributor to human systemic lupus erythematosus (SLE). Protein kinase C and casein kinase substrate in neurons 1 (PACSIN1), a molecule that regulates synaptic vesicle recycling, has been linked to TLR-7/TLR-9–mediated type I IFN production in humans and mice, but the underlying mechanism is unknown. We undertook this study to explore the pathogenicity and underlying mechanism of a de novo *PACSIN1* missense variant identified in a child with SLE.

Methods. *PACSIN1* Q59K de novo and null variants were introduced into a human plasmacytoid dendritic cell line and into mice using CRISPR/Cas9 editing. The effects of the variants on TLR-7/TLR-9 signaling in human and mouse cells, as well as *PACSIN1* messenger RNA and IFN signature in SLE patients, were assessed using real-time polymerase chain reaction and flow cytometry. Mechanisms were investigated using luciferase reporter assays, RNA interference, coimmunoprecipitation, and immunofluorescence.

Results. We established that PACSIN1 forms a trimolecular complex with tumor necrosis factor receptor–associated factor 4 (TRAF4) and TRAF6 that is important for the regulation of type I IFN. The Q59K mutation in PACSIN1 augments binding to neural Wiskott-Aldrich syndrome protein while it decreases binding to TRAF4, leading to unrestrained TRAF6-mediated activation of type I IFN. Intriguingly, PACSIN1 Q59K increased TLR-7 but not TLR-9 signaling in human cells, leading to elevated expression of IFNβ and IFN-inducible genes. Untreated SLE patients had high PACSIN1 expression in peripheral blood cells that correlated positively with IFN-related genes. Introduction of the *Pacsin1* Q59K mutation into mice caused increased surface TLR-7 and TRAIL expression in B cells.

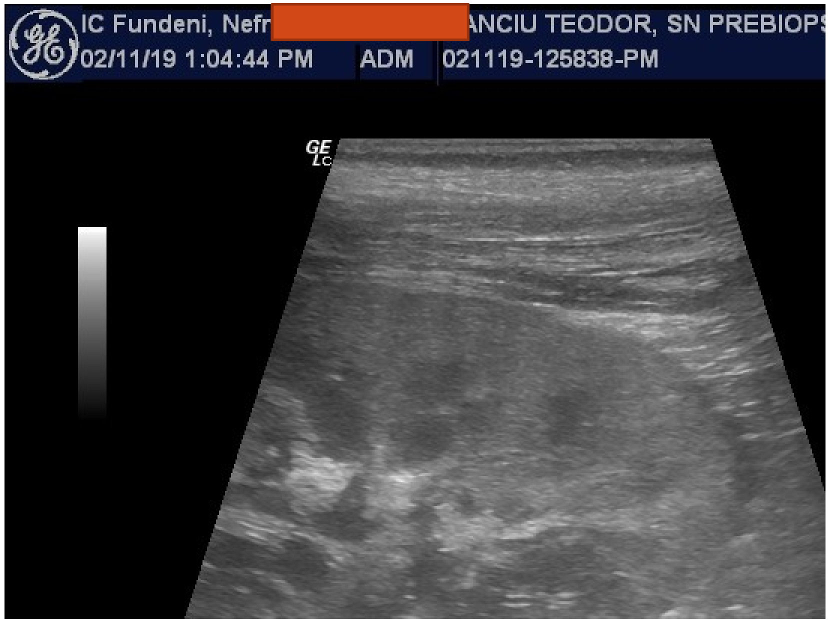
Conclusion. PACSIN1 Q59K increases IFNβ activity through the impairment of TRAF4-mediated inhibition of TLR-7 signaling, possibly contributing to SLE risk.

COMPLICATIONS OF KIDNEY BIOPSY

COMPLICATIONS OF KIDNEY BIOPSY

Kidney Biopsy 12.02.2019

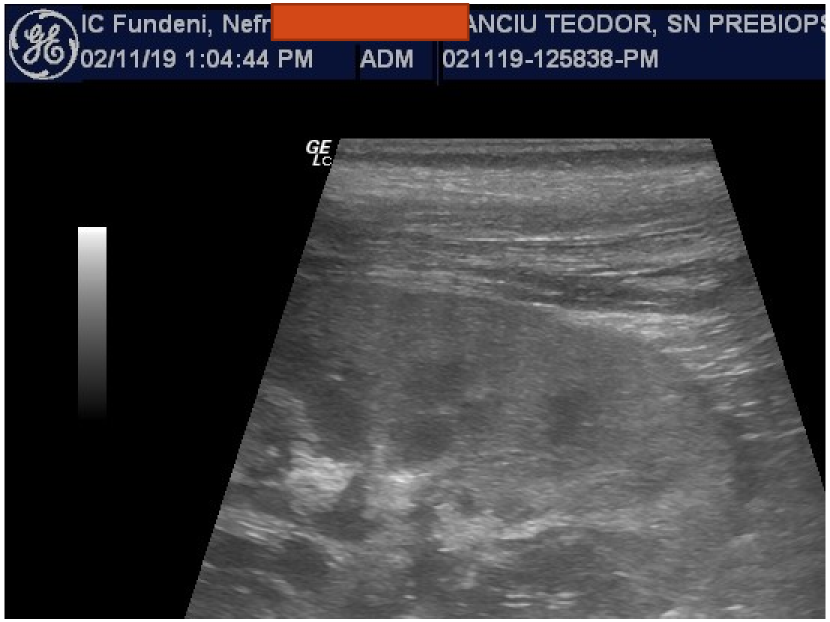
2 H after Kidney Biopsy

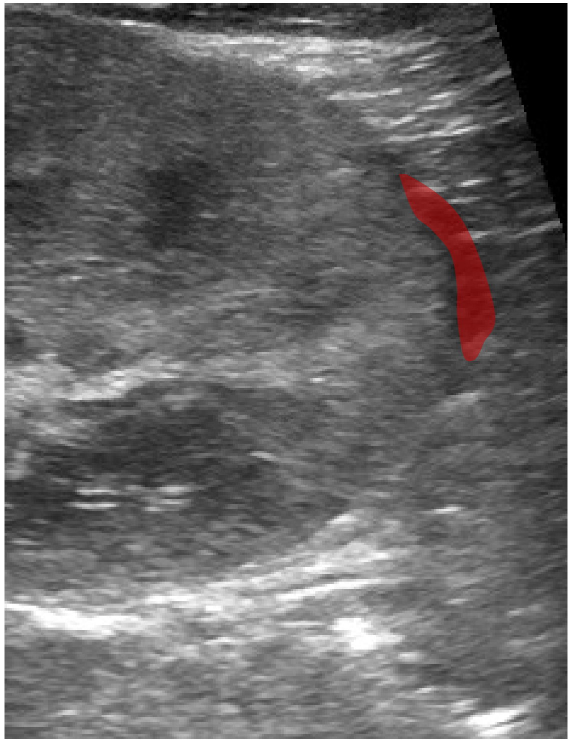


COMPLICATIONS OF KIDNEY BIOPSY

Kidney Biopsy 12.02.2019

2 H

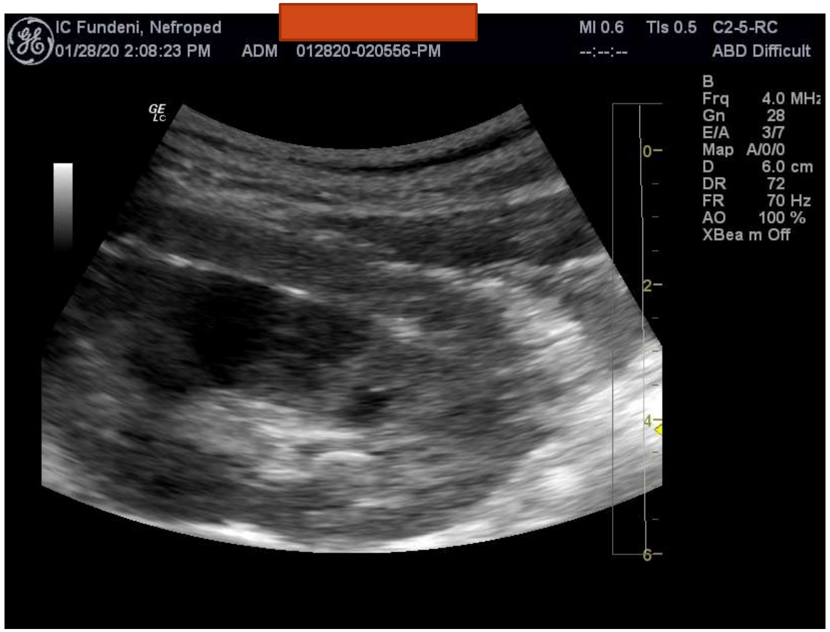


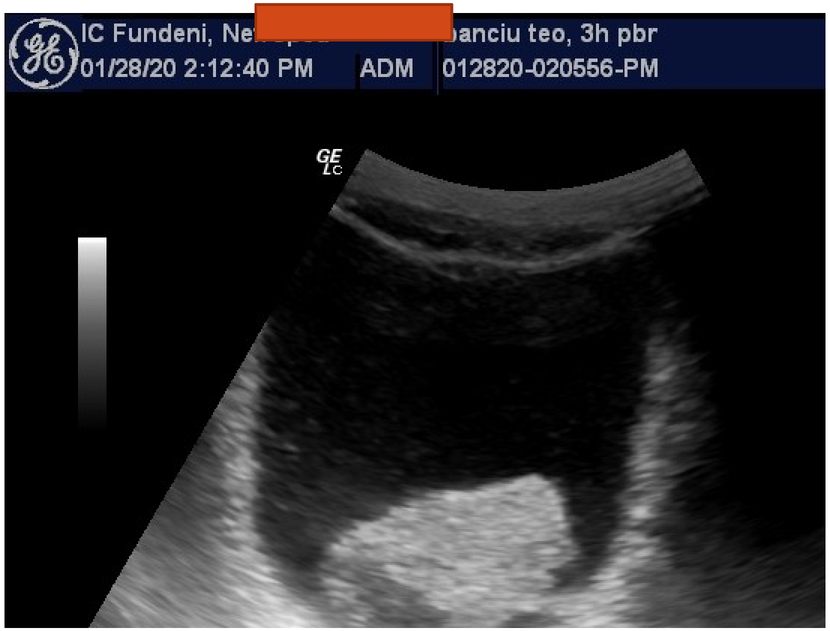


COMPLICATIONS OF KIDNEY BIOPSY

POST BIOPSY BLEEDING

Kidney Biopsy 28.01.2020 – 2 H

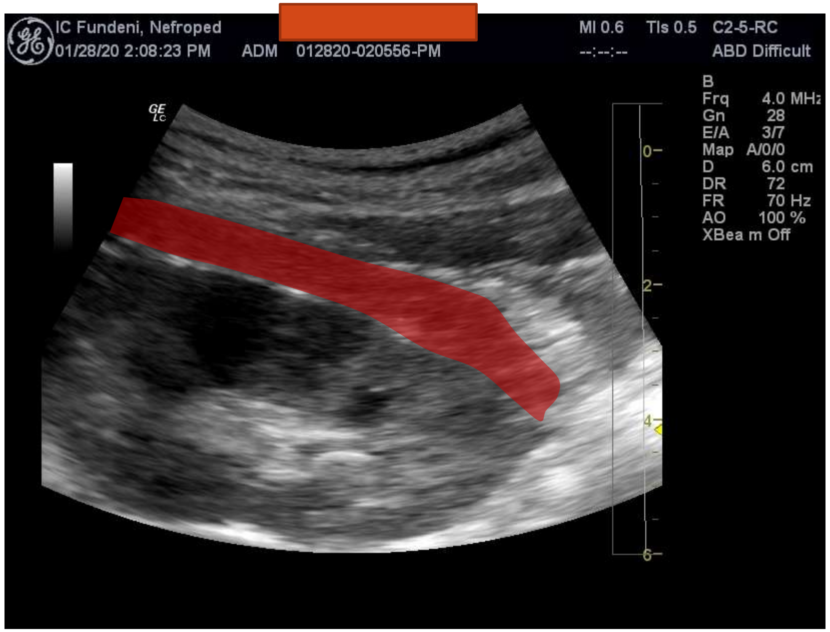


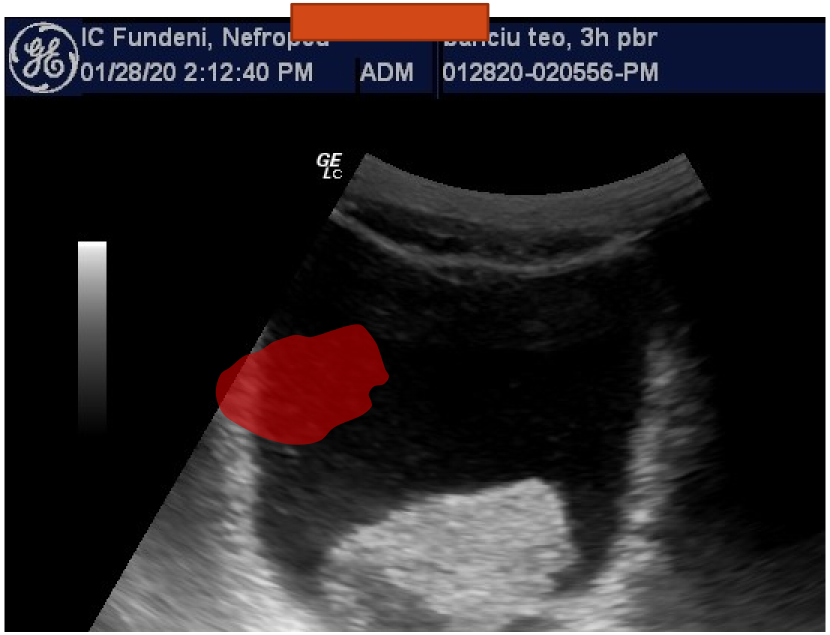


COMPLICATIONS OF KIDNEY BIOPSY

POST BIOPSY BLEEDING

Kidney Biopsy 28.01.2020 – 2 H

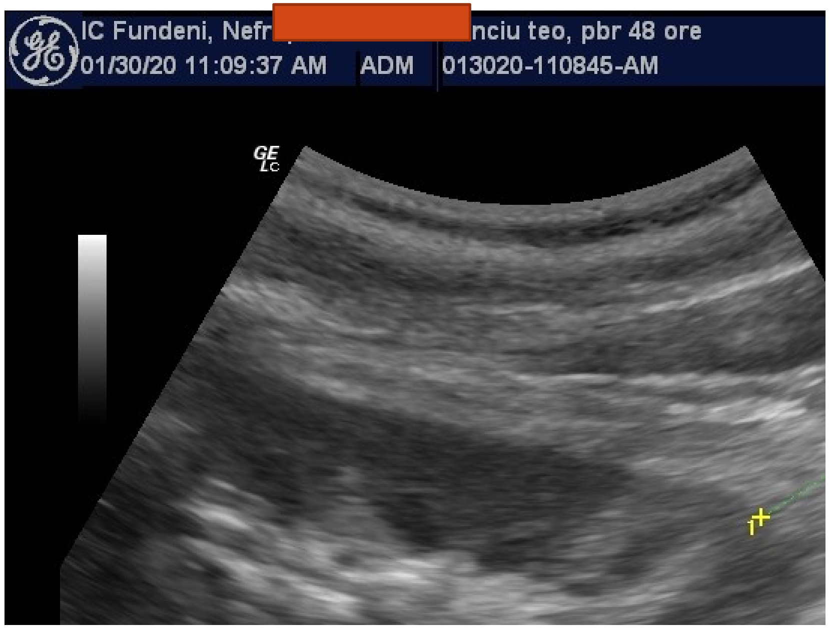


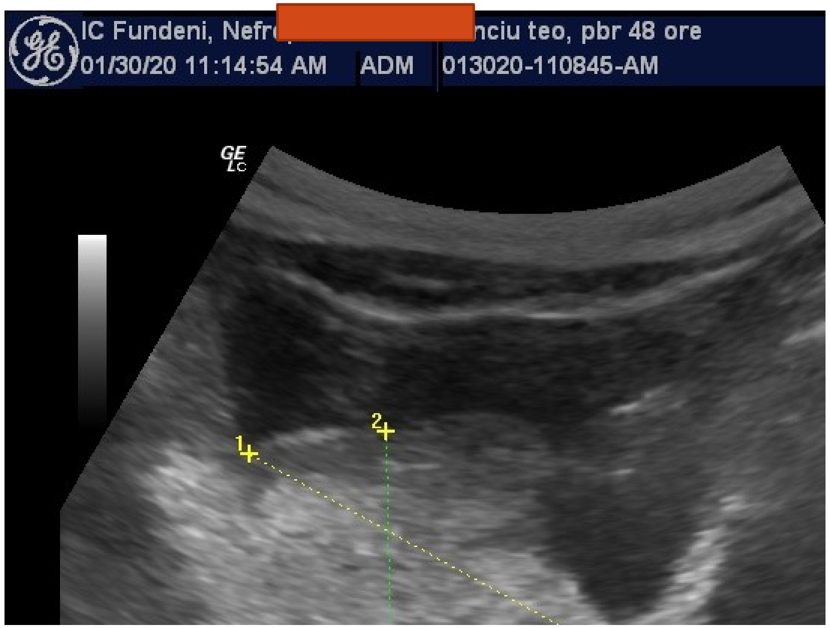


COMPLICATIONS OF KIDNEY BIOPSY

POST BIOPSY BLEEDING

Kidney Biopsy 28.01.2020 – 48 H

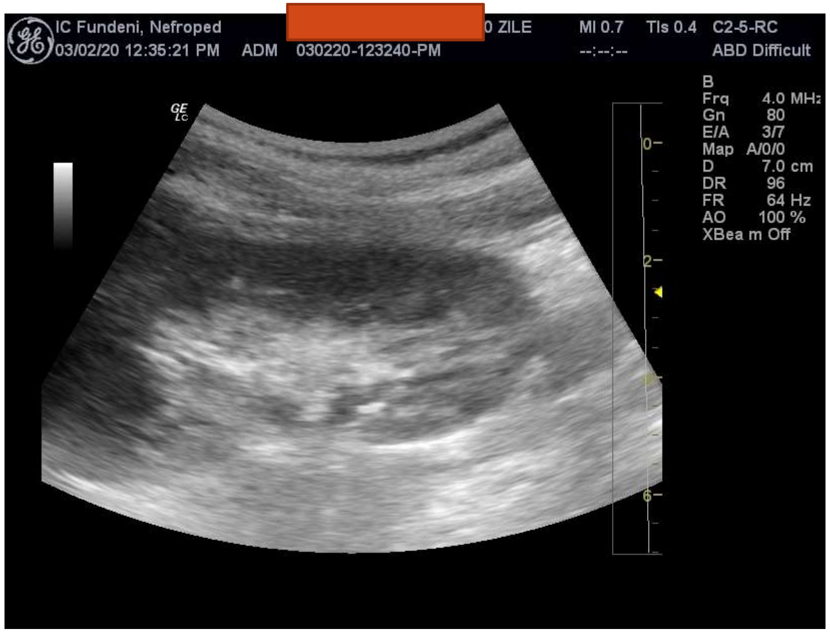


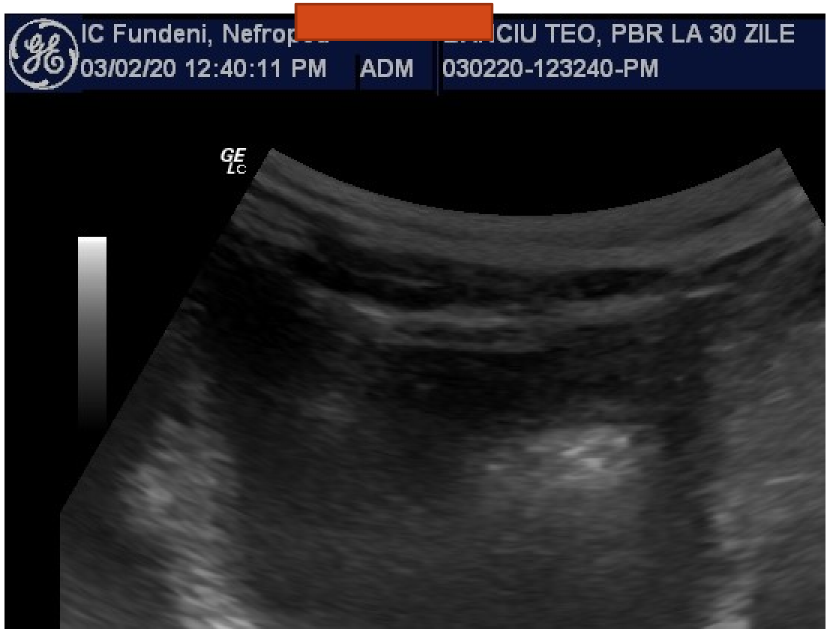


COMPLICATIONS OF KIDNEY BIOPSY

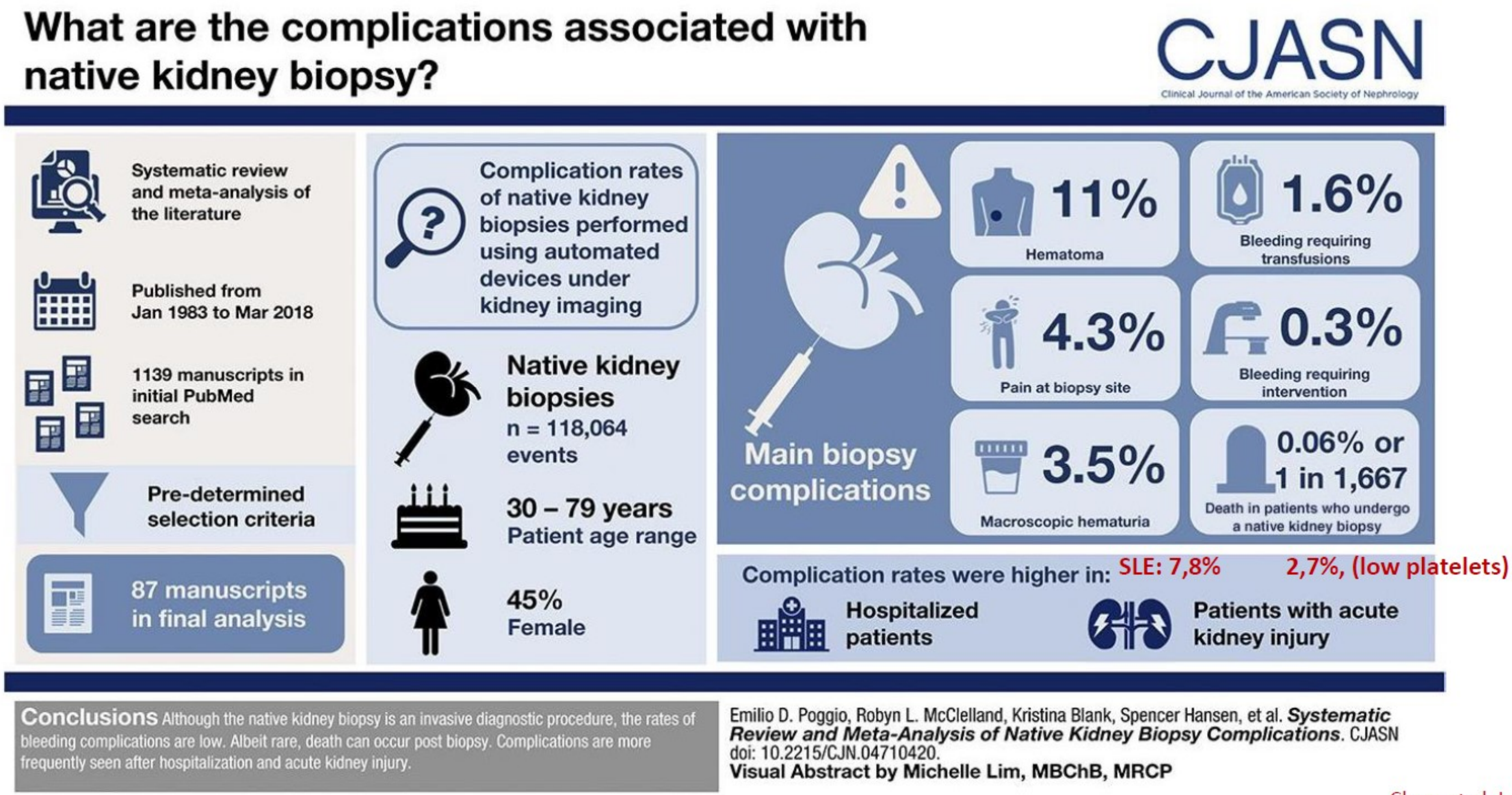
POST BIOPSY BLEEDING

Kidney Biopsy 28.01.2020 – 30 days





COMPLICATIONS OF KIDNEY BIOPSY



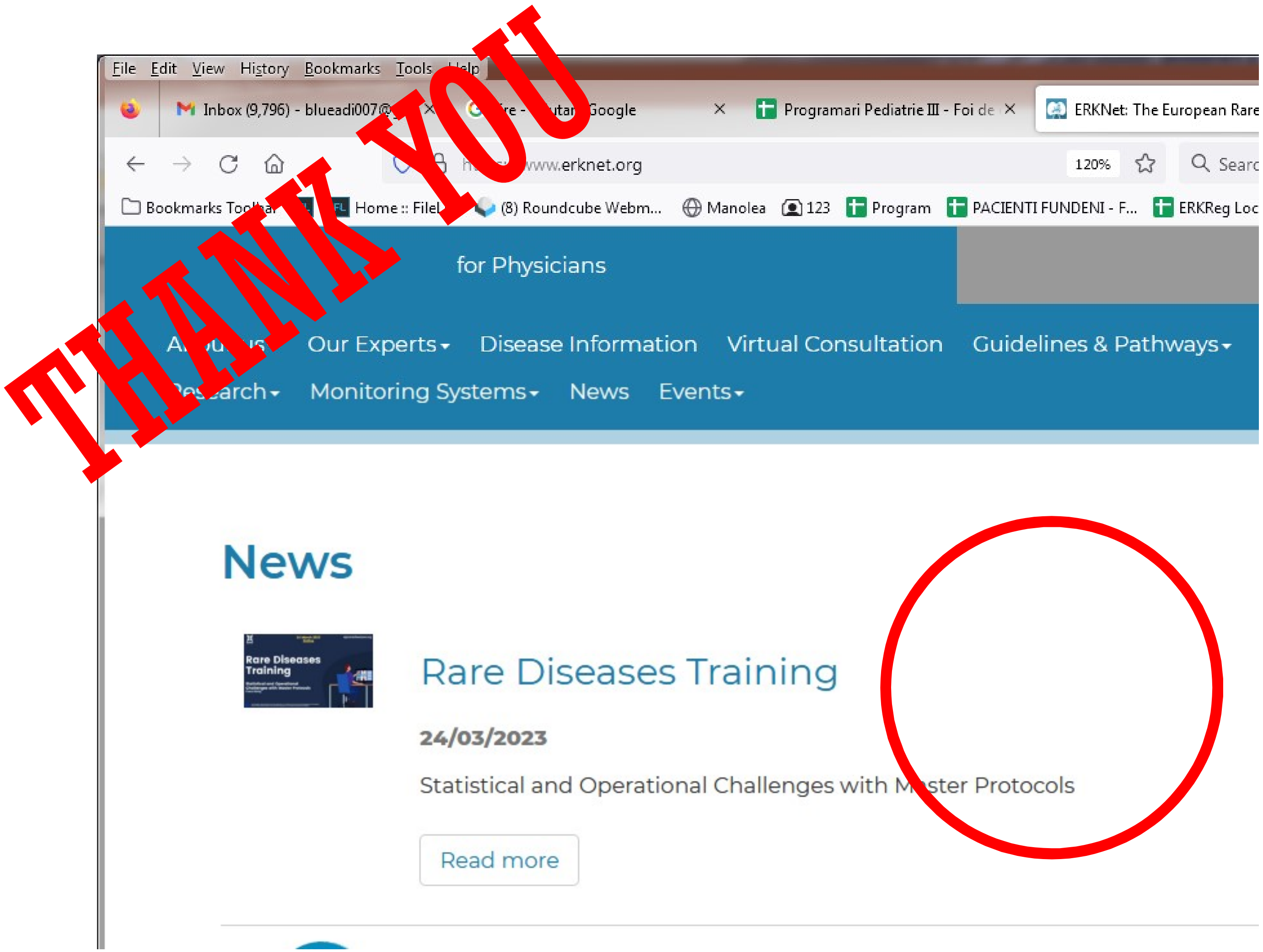
Chen, et al. Lupus 2012

ERKNet
The European Rare Kidney Disease Reference Network

European Reference Networks

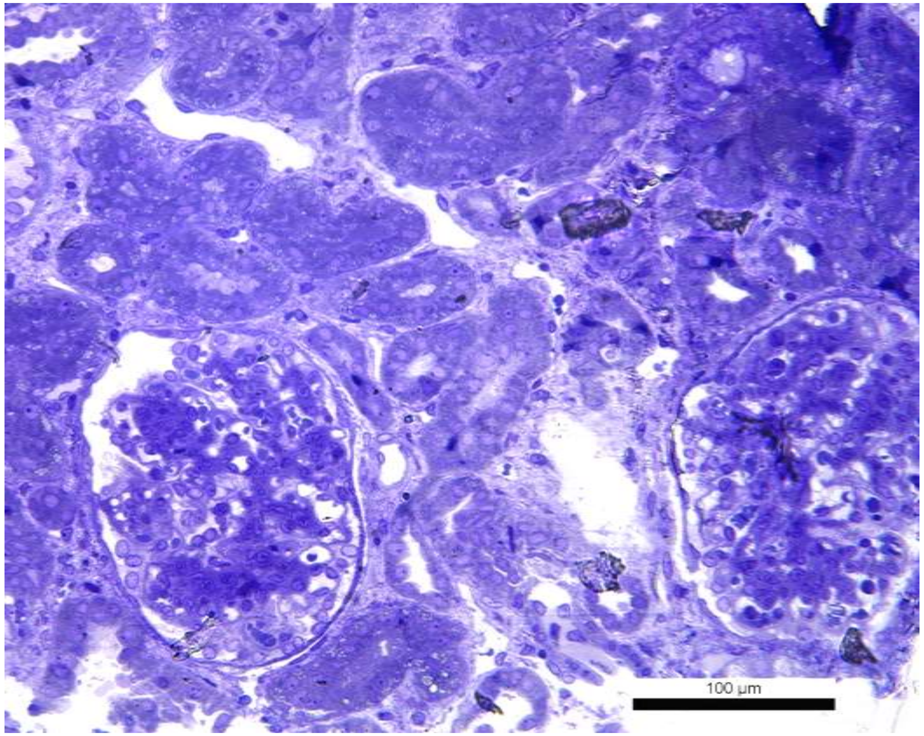
Funded by the European Union

- https://www.erknet.org/



TEO

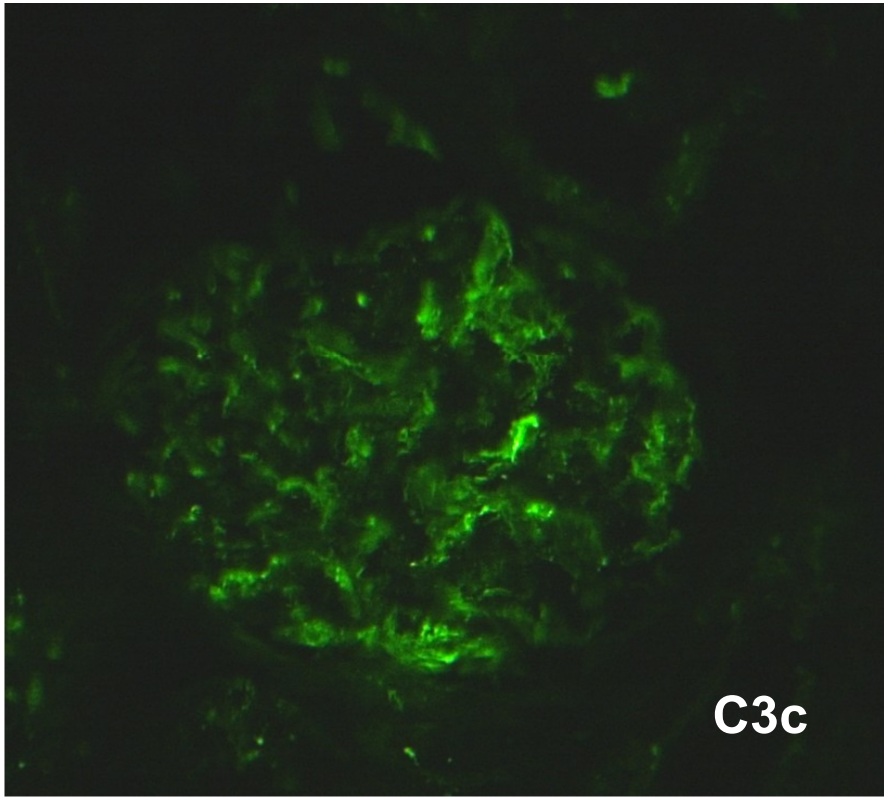
Kidney Biopsy 12.02.2019	Kidney Biopsy 28.01.2020

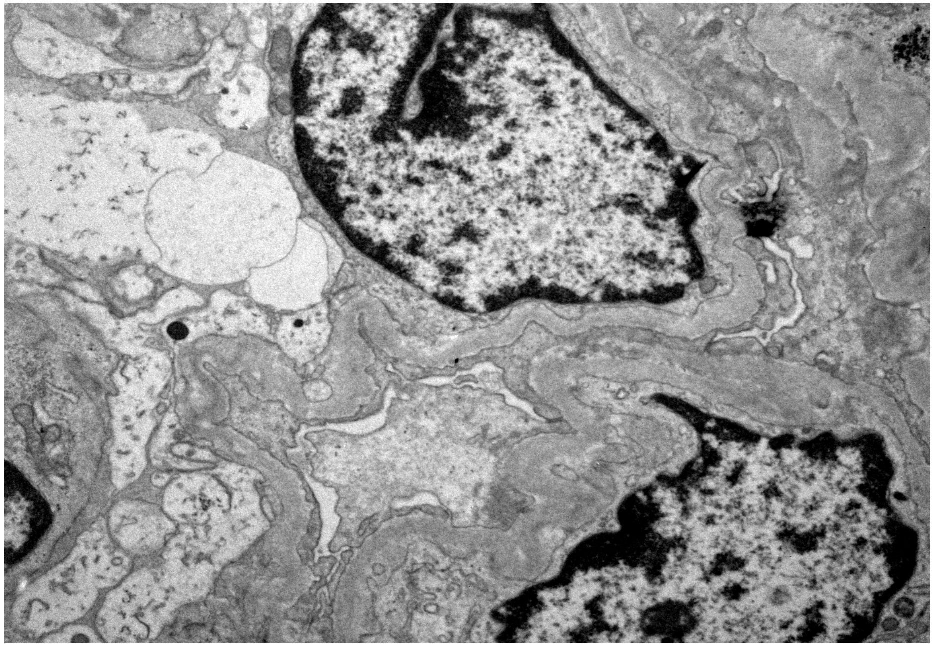


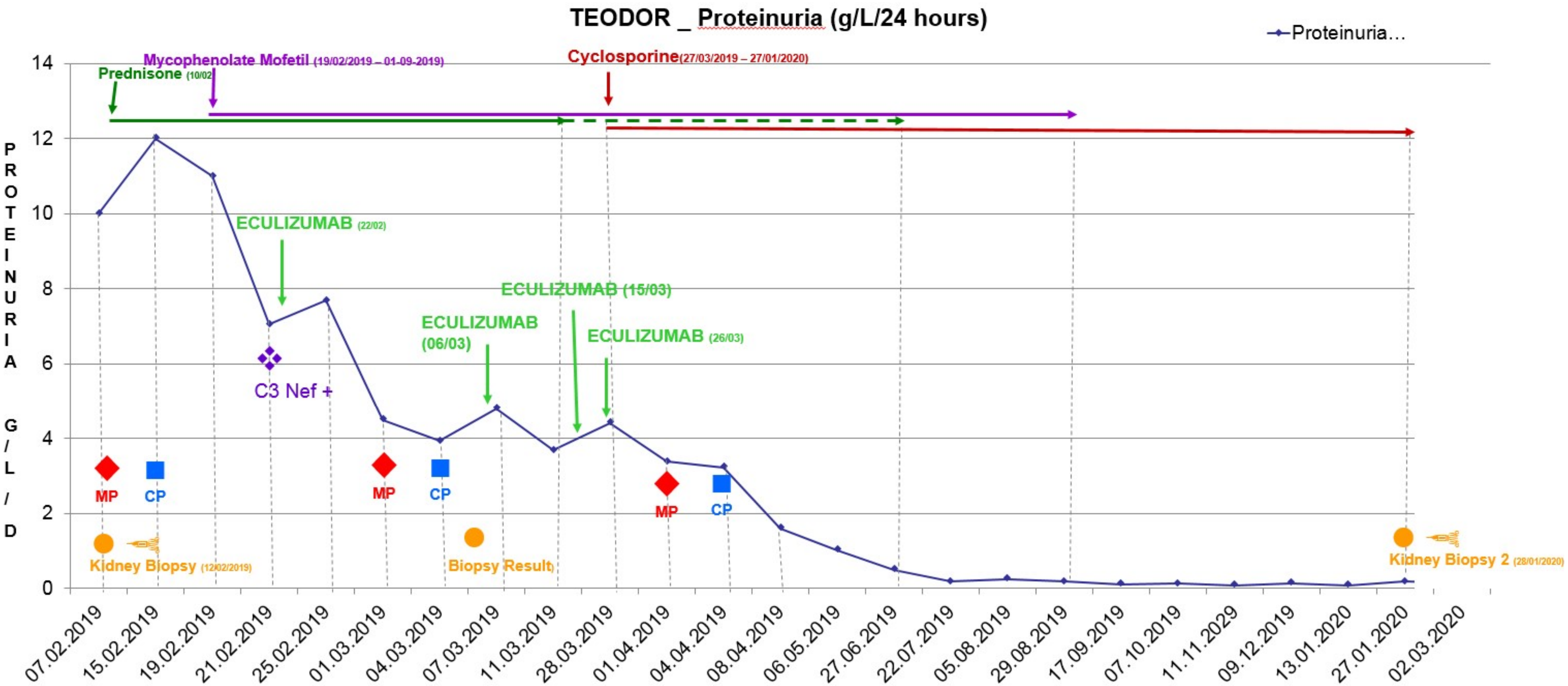
TEO

- Hematuria
- Nephrotic Proteinuria
- ANA +
- Anti DNA +
- C3 = 37
- C4=14
- HPT=0.03

Lupus Podocitopathy + TMA

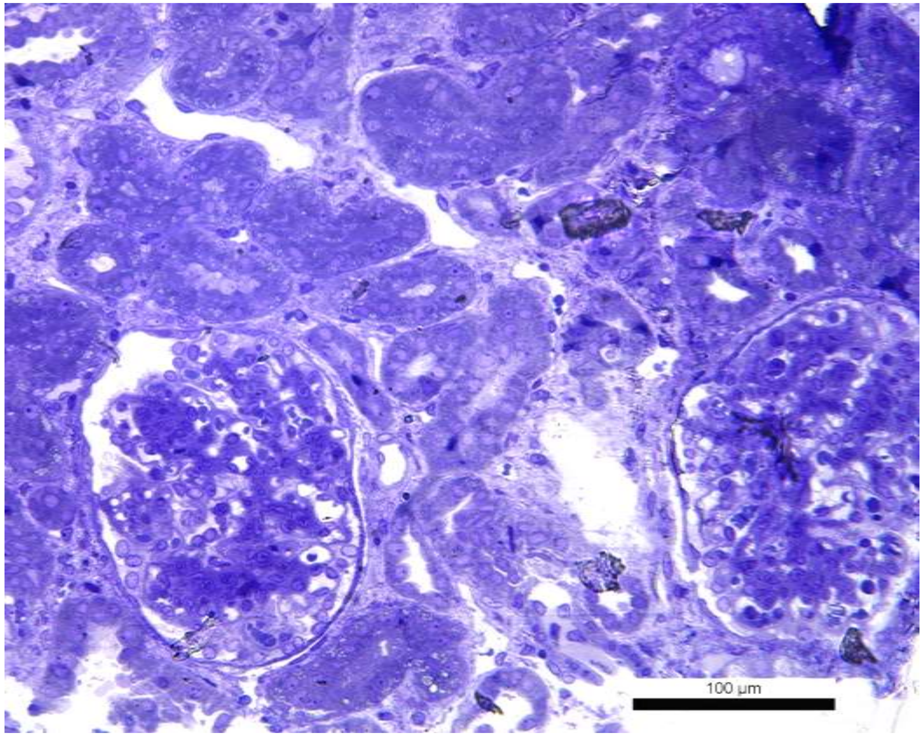
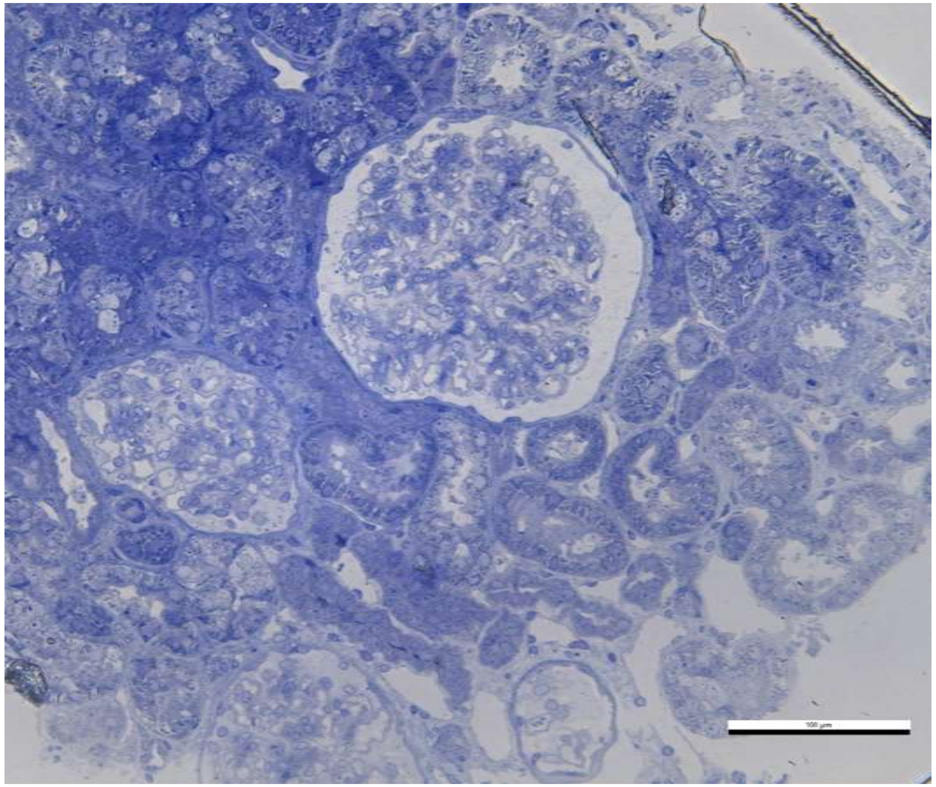
Kidney Biopsy 12.02.2019	Kidney Biopsy 28.01.2020
	

Kidney Biopsy 12.02.2019	Kidney Biopsy 28.01.2020
	

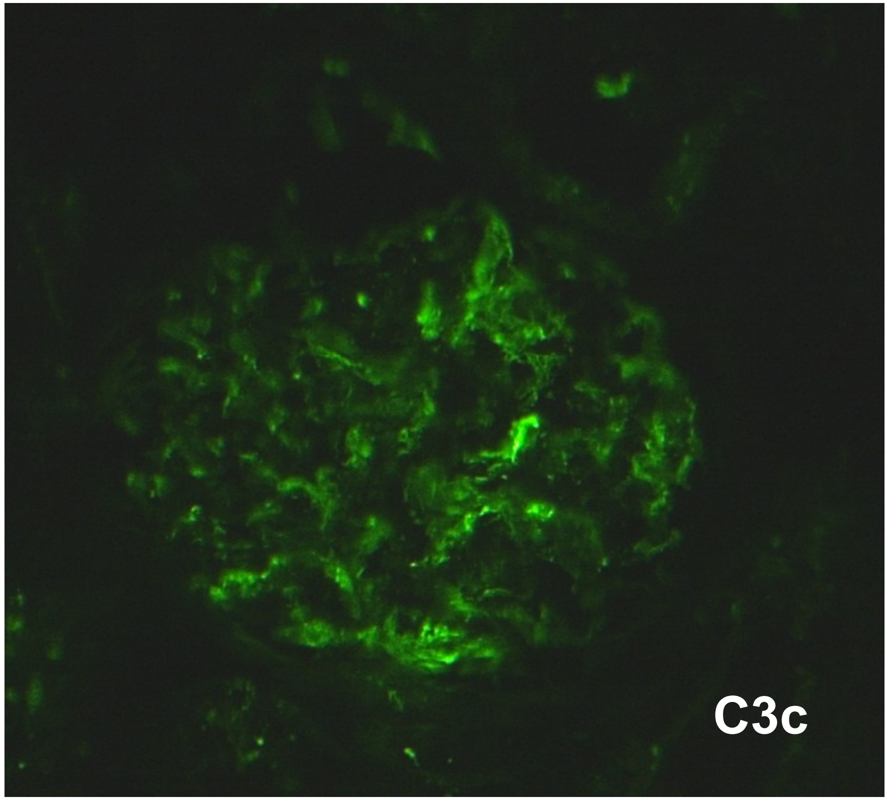


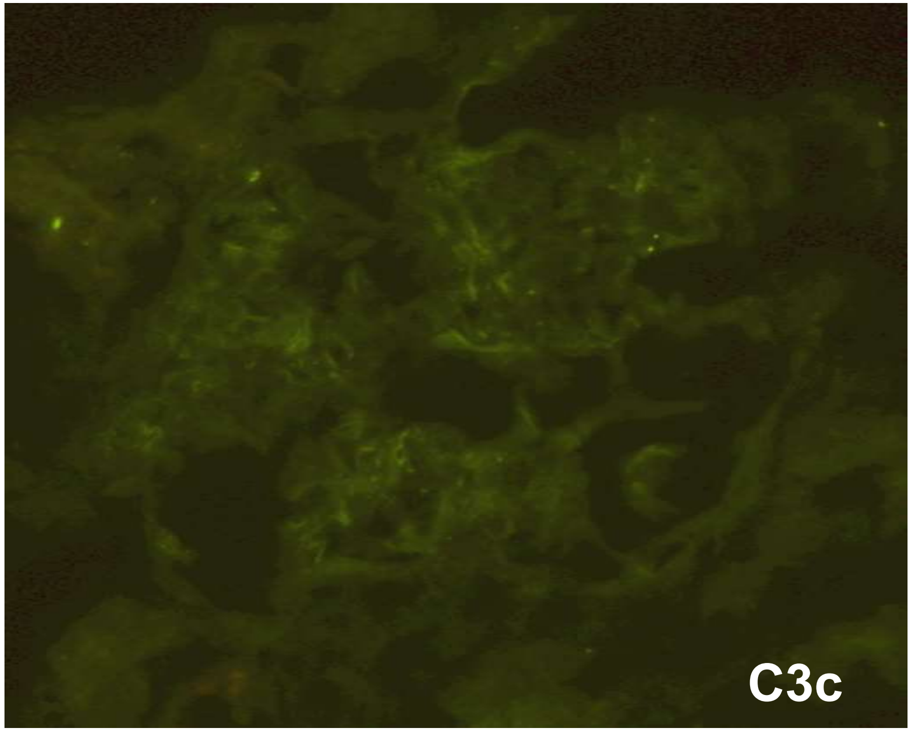
TEODOR _ Proteinuria (g/L/24 hours)
Proteinuria…
PROTEINURIA G/L/D
Prednisone (10/02
Mycophenolate Mofetil (19/02/2019 – 01-09-2019)
Cyclosporine(27/03/2019 – 27/01/2020)
ECULIZUMAB (22/02)
ECULIZUMAB (06/03)
ECULIZUMAB (15/03)
ECULIZUMAB (26/03)
C3 Nef +
MP
CP
MP
CP
MP
CP
Kidney Biopsy (12/02/2019)
Biopsy Result
Kidney Biopsy 2 (28/01/2020)
0
2
4
6
8
10
12
14
07.02.2019
15.02.2019
19.02.2019
21.02.2019
25.02.2019
01.03.2019
04.03.2019
07.03.2019
11.03.2019
28.03.2019
01.04.2019
04.04.2019
08.04.2019
06.05.2019
27.06.2019
22.07.2019
05.08.2019
29.08.2019
17.09.2019
07.10.2019
11.11.2029
09.12.2019
13.01.2020
27.01.2020
02.03.2020

Caz clinic
TEO

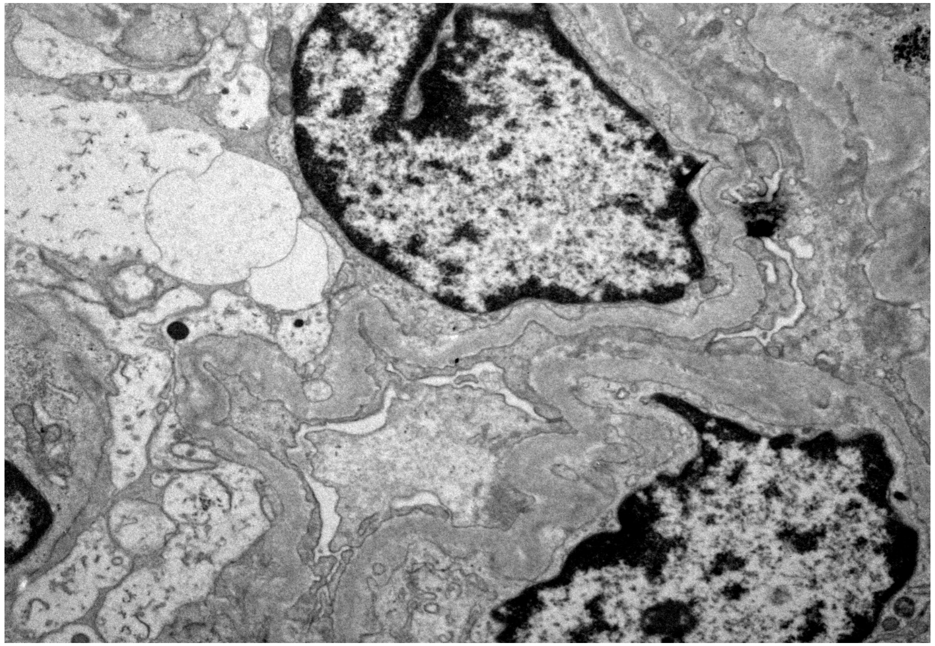
Kidney Biopsy 12.02.2019	Kidney Biopsy 28.01.2020
	

Kidney Biopsy 12.02.2019	Kidney Biopsy 28.01.2020

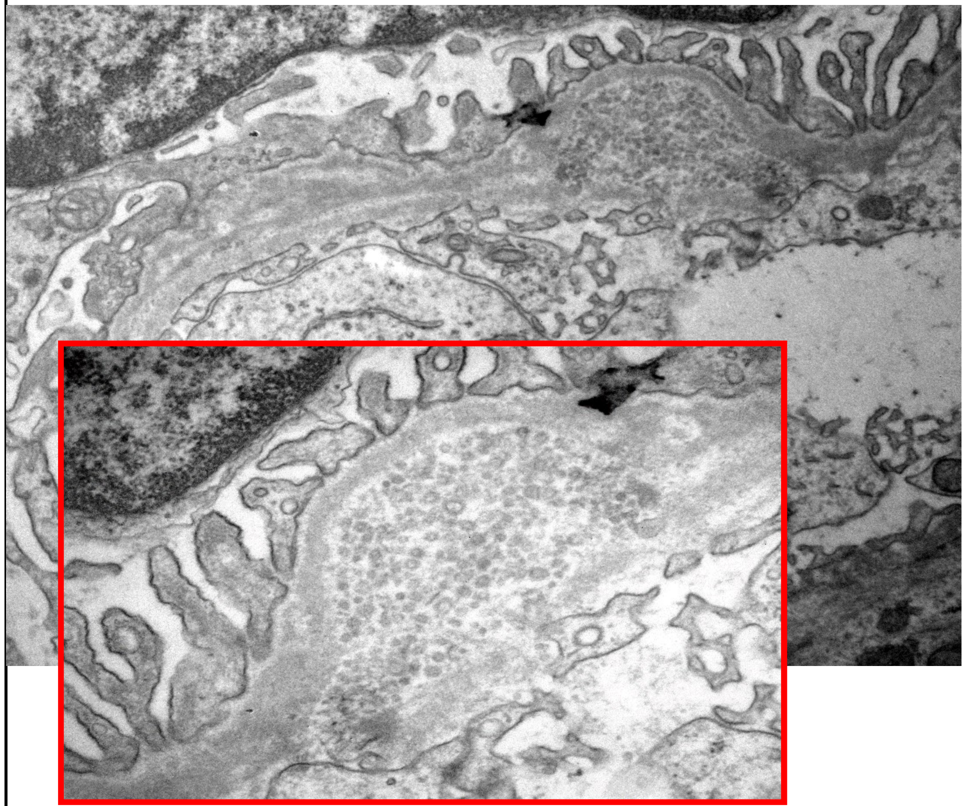




Kidney Biopsy 12.02.2019



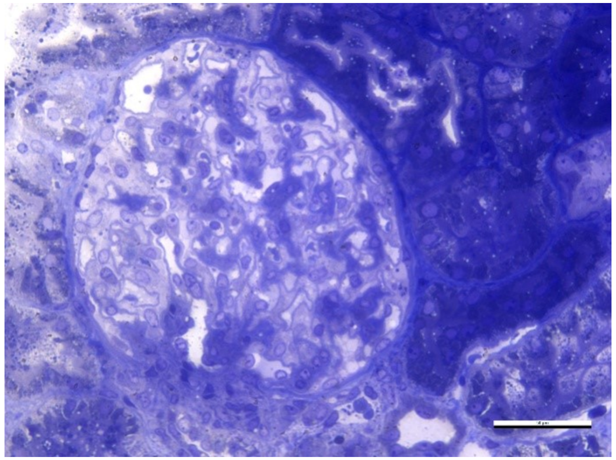
Kidney Biopsy 28.01.2020

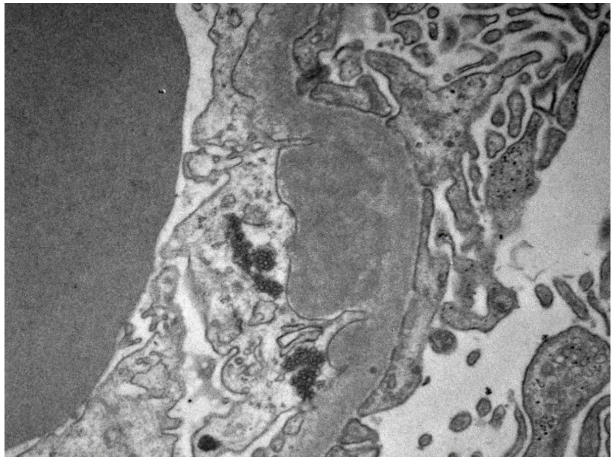


CASE 2

IULIANA

CASE 2
FIRST KIDNEY BIOPSY



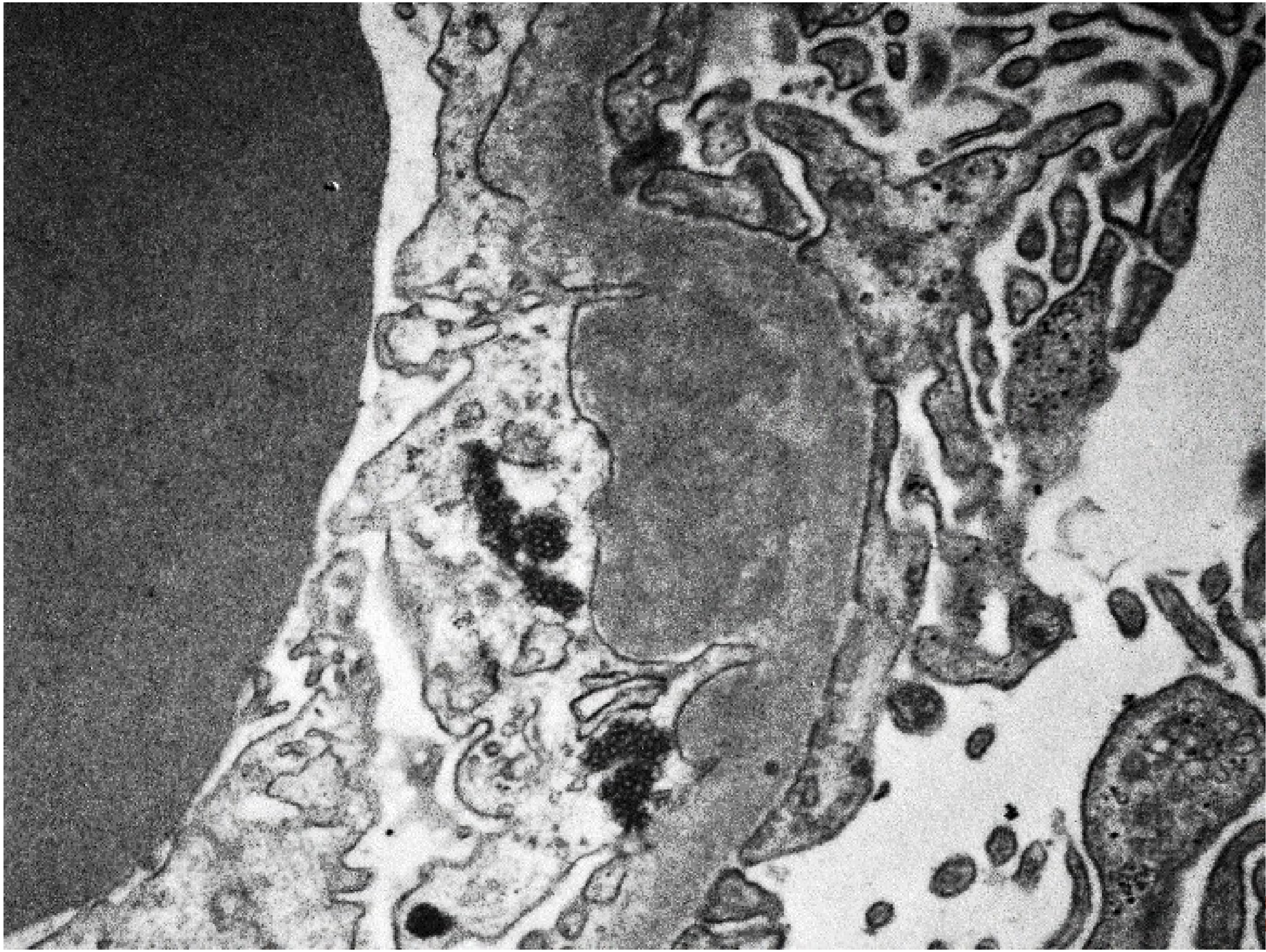


Class II Lupus Nephritis

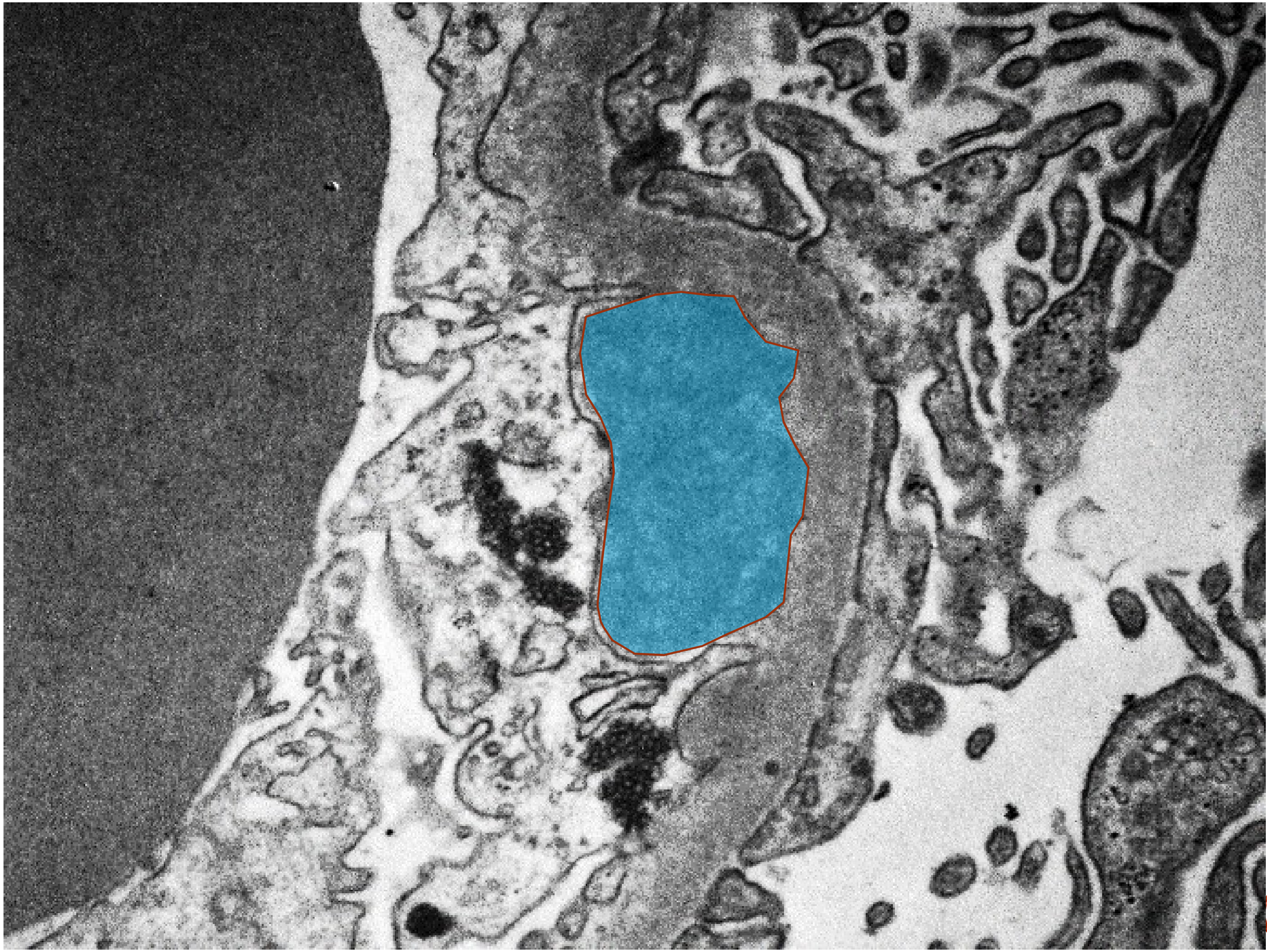
IgA – intense + granular mesangial and in MBG
IgG – intense + granular in MBG and nuclear (ANA+)
IgM – moderate + granular in the glomerulus
C1q – moderate + granular in the glomerulus
C3c – intense + granular in the glomerulus

Numerous dense mesangial deposits, rare subendothelial and subepithelial.

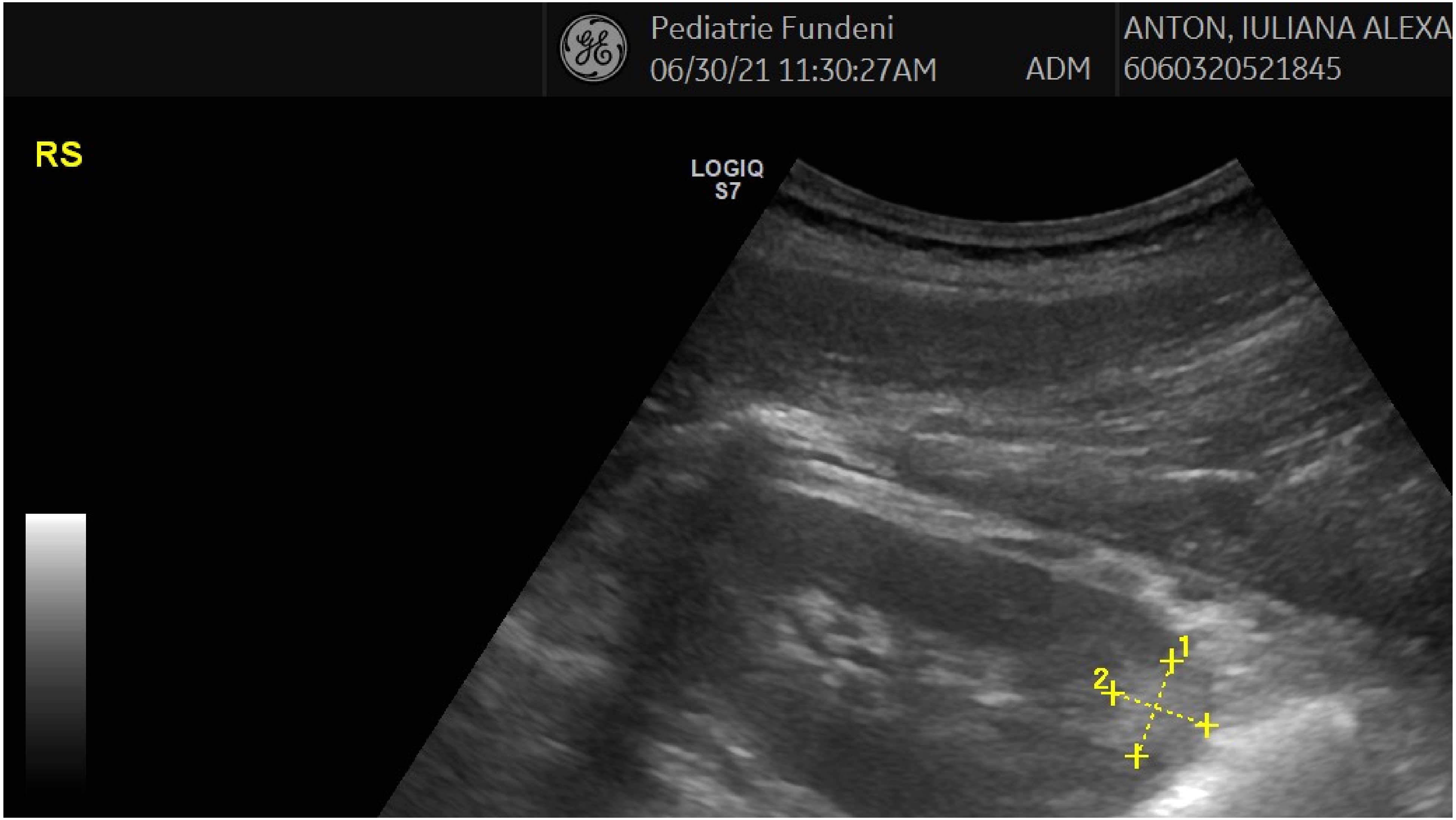
CASE 2



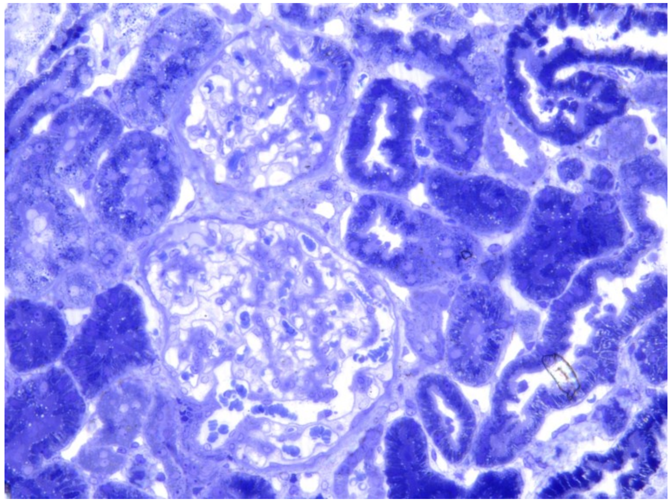
CASE 2



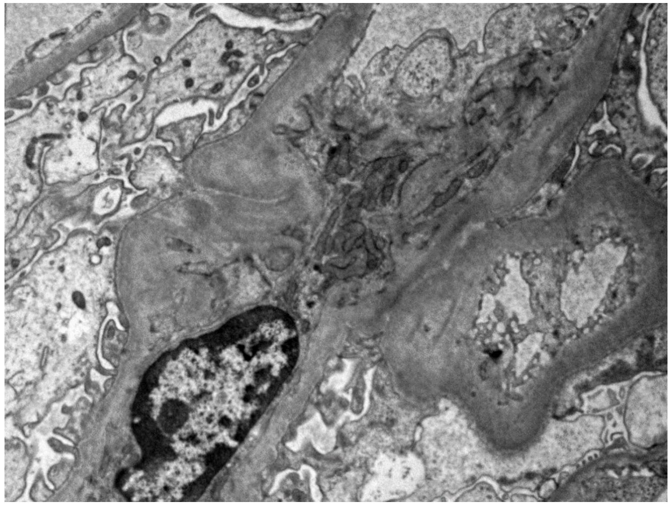
CASE 2


Pediatrie Fundeni
06/30/21 11:30:27AM
ADM
ANTON, IULIANA ALEXA
6060320521845
RS
LOGIQ
S7
1
2

CASE 2
SECOND KIDNEY BIOPSY



IgA – negative
IgG – rare deposits +
IgM – rare deposits +
C1q – negative
C3c – negative
K – negative
λ – negative
Lbumine – 3 glomeruli
Fb – negative

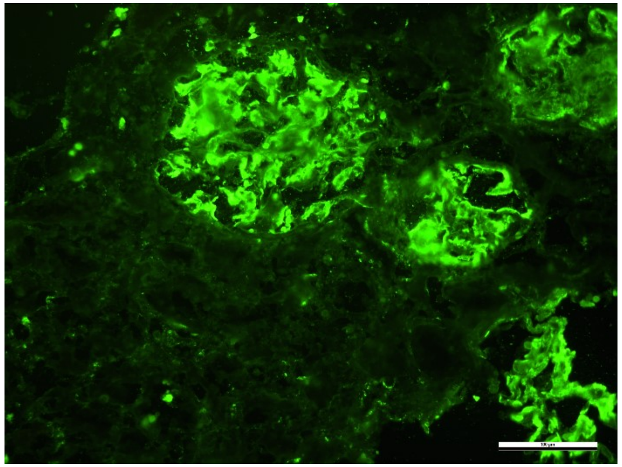


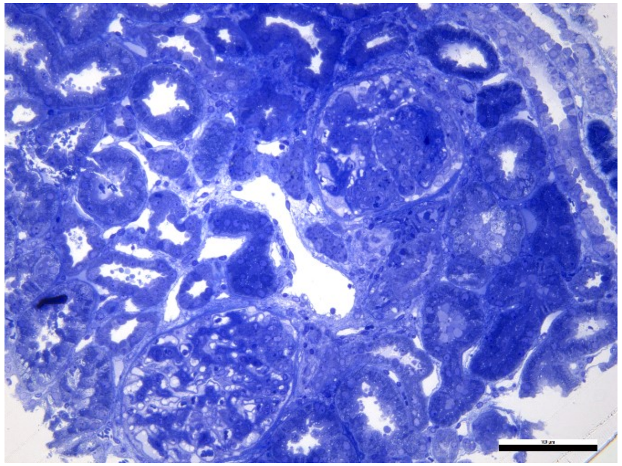
Small, rare intramembranous and mesangial deposits.

CASE 3

VIVIEN

CASE 3
FIRST KIDNEY BIOPSY





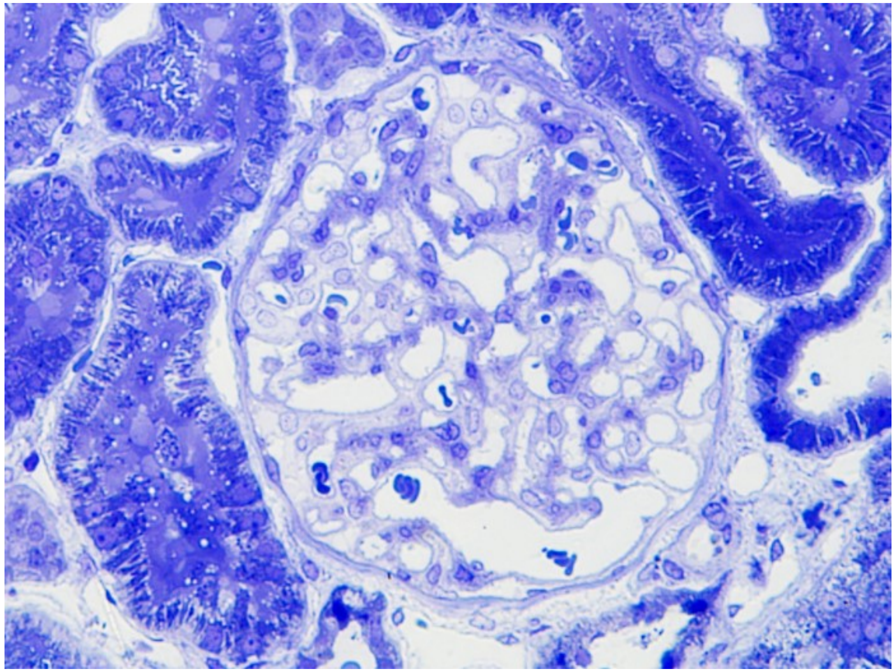
class IV

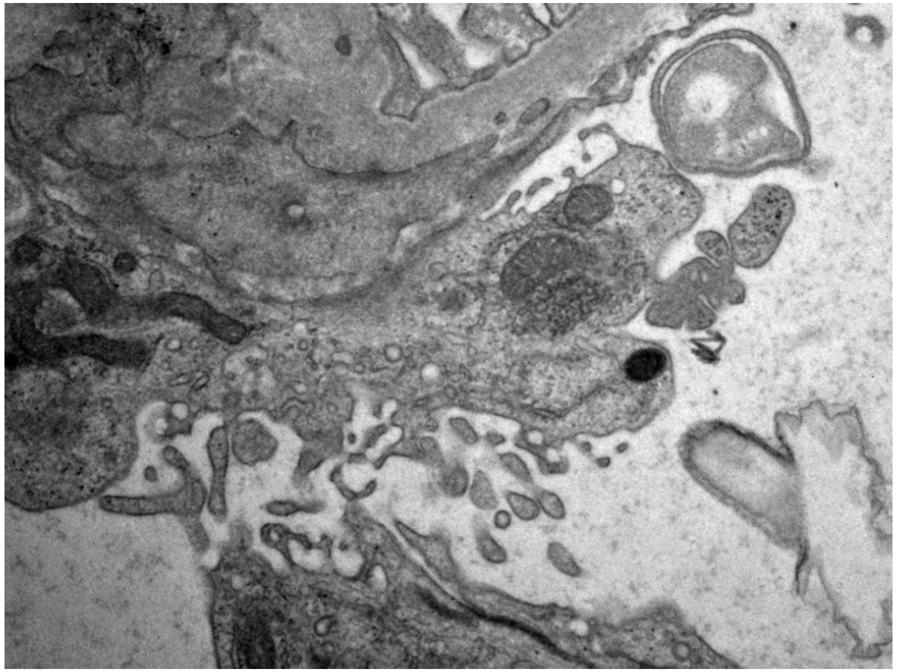
IgA – intense + granular at the glomerular level (mesangial and in the capillary wall) IgG – very intense + granular at the glomerular level; + in the nuclei of some epithelial cells – homogeneous pattern - ANA+)
IgM – moderate + granular at the glomerular level
C1q – intense + granular at the glomerular level
C3c – intense + granular at the glomerular level

3 glomeruli with segmental endocapillary proliferation and "wire loop" type lesions; 2 with global endocapillary proliferation; 1 glomerulus with segmental endocapillary proliferation, "wire loop" deposits, fibrinoid necrosis and cellular crescent.

Numerous dense mesangial and subendothelial deposits, of various sizes, some form "wire loops" and intraluminal pseudothrombi.

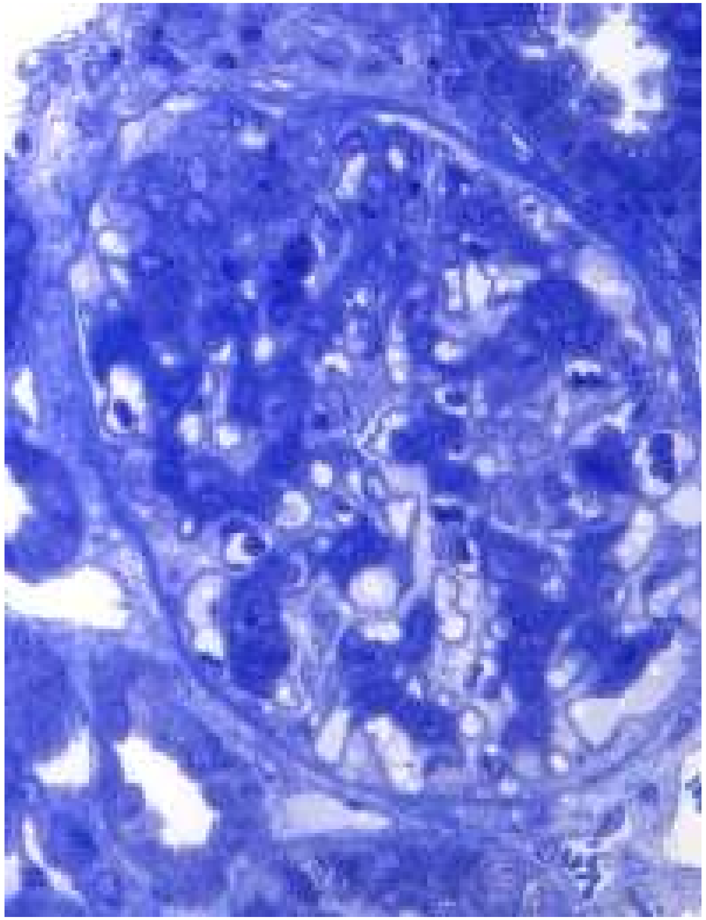
CASE 3
SECOND KIDNEY BIOPSY

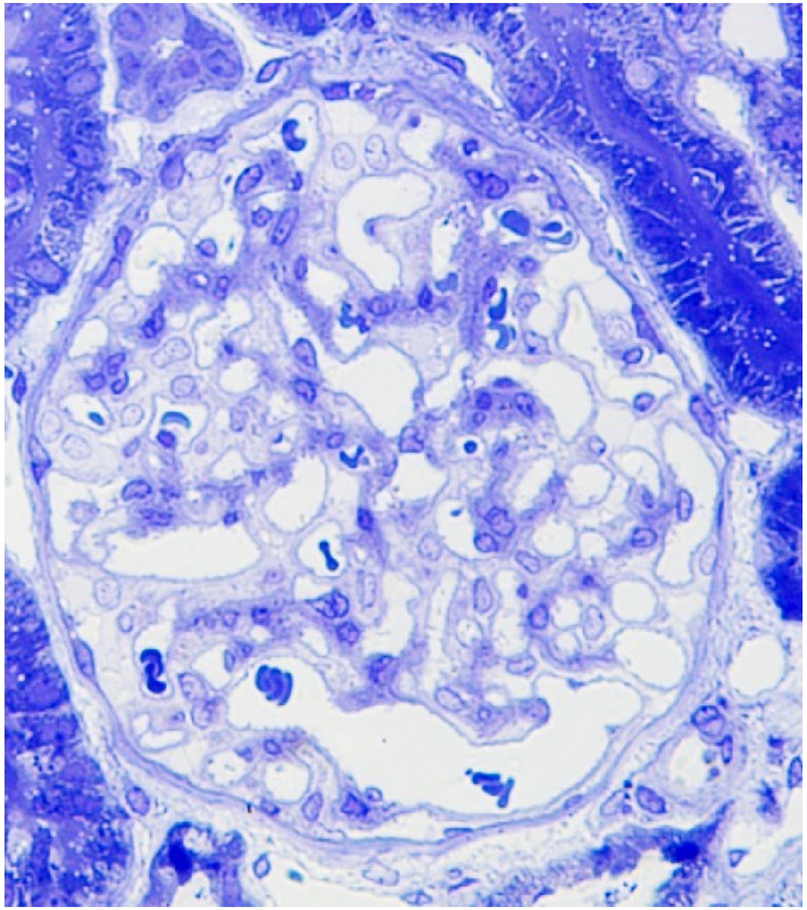




Class II

CASE 3
COMPARISON





Lupus Nephritis and Conventional Treatment

Prof. Dr. Rezan Topaloglu

Ankara, Turkey

X SEPNWG MEETING AND IPNA Sponsored TEACHING COURSE 2023

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

Nothing to Disclose

Outline presentation

- Lupus classification and current standard-of-care
- New treatment options for lupus nephritis will be given by Dr.Roussinov

Systemic Lupus Erythematosus in Children(cSLE)

- SLE is a chronic autoimmune disease predominantly affects women
- cSLE is onset of disease before 18 years of age
- Approximately 15-20% of SLE cases begin before age 18
- Incidence and prevalence rates vary by ethnicity
- US administrative database showed higher in Asians followed by African Americans, Native Americans & Hispanic children
- The prevalence in White children is lowest
- Incidence of childhood onset SLE 6-30/100.000 children/year
- The mean age at diagnosis is 12-13 years
- F/M ratio increases from 2:1 in prepubertal children to 4.5:1 in adolescents
- İn late 1950s death from SLE within the first 2 y after diagnosis was common

Arthritis Rheum 2012;64:2669-2676
Curr Opin Rheumatol 2013;25:616-622
Pediatric Research 2017;81:406-414

SLE and kidney

- Kidney involvement is the most important predictor of morbidity and mortality
- SLE patients have 25-80 %kidney involvement either as an initial presentation or later in the disease course
- Lupus nephritis (LN) typically occurs in the early stages of the disease (often in the first 6-36 months)
- Risk > young age, male gender
- Mortality was significantly higher in those with LN
- 10-30% of patients progress to ESKD and need RRT in adult series

Similarities in cSLE and adult SLE

- Same autoimmune processes
- Same ISN/RPS classification criteria
- Same disease markers
- Same drugs

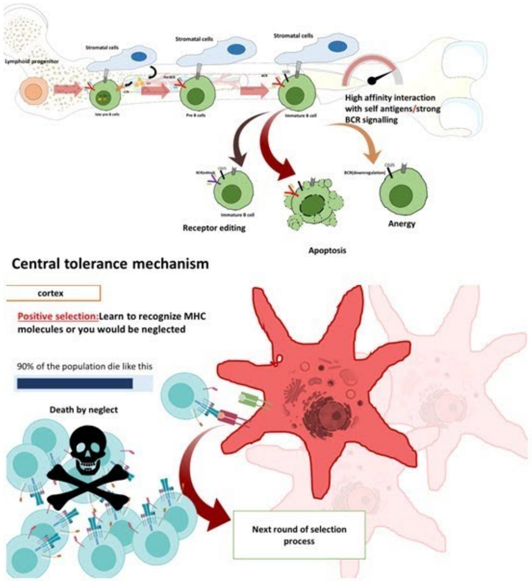
Lupus Nephritis in children versus adults

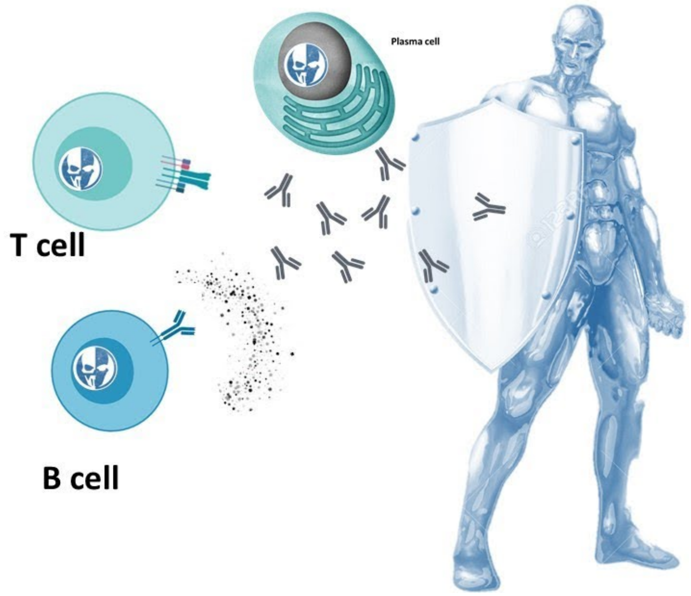
- Greater risk of kidney involvement
- More tendency to active disease
- Longer duration immunosuppressive therapy
- More damage
- Increased drug toxicity

- Diagnostics, management and monitoring based on limited, non-randomized evidence in children so mostly based on adult series

Etiopathogenesis

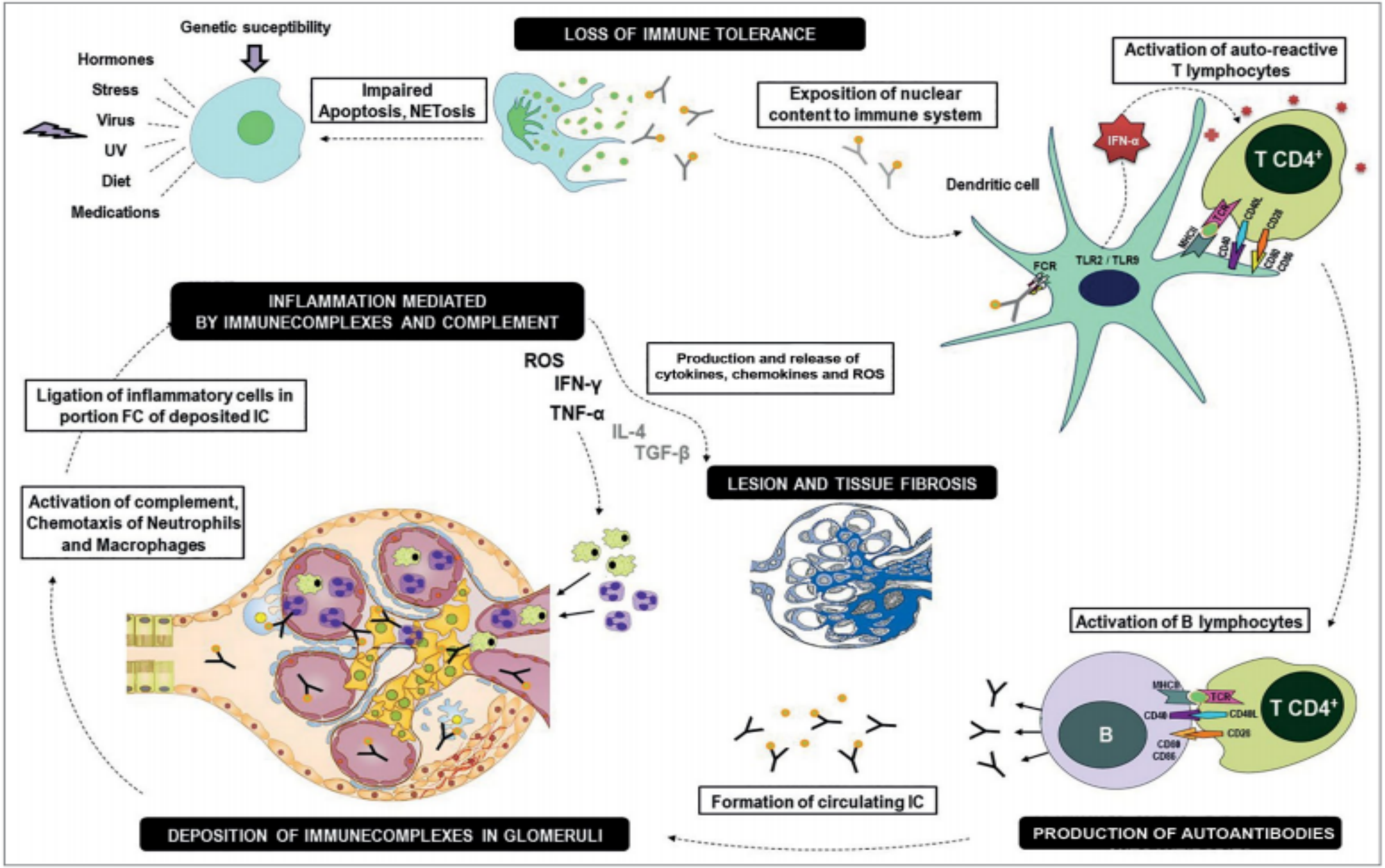
- İmmun tolerans systems
    - Clearence of nuclear self antigens
        - Apoptozis
        - «Neutrophil extracellular traps» (NETosis)





Pinheiro SVB, et al. J Bras Nephrol 2019; 41: 252-265

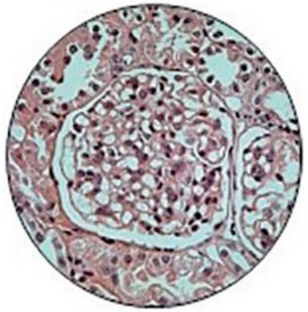
Figure 1. Schematic representation of the pathogenesis of lupus nephritis.



Pinheiro SVB, et al. J Bras Nephrol 2019; 41: 252-265

CLASS I

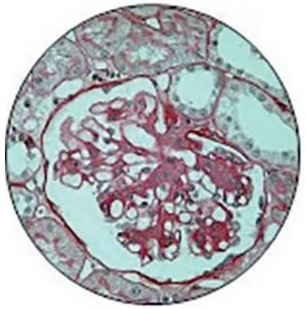
Minimal mesengial



Normal glomeruli by LM, but mesangial immune deposits by IF or EM

CLASS II

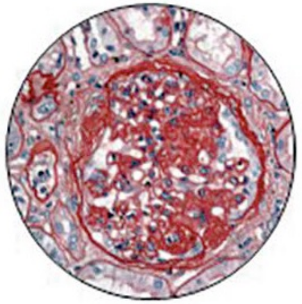
Mesengial



Purely mesangial hypercellularity of any degree or mesangial matrix expansion by LM, with mesangial immune deposits.

CLASS III

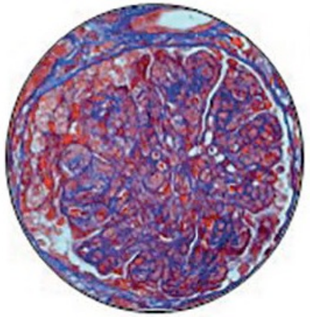
Focal Proliferative



Focal Active or chronic , segmental or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli

CLASS IV

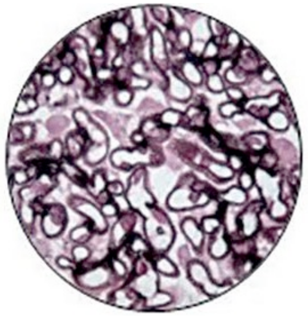
Diffuse Proliferative



Diffuse Active or chronic Segmental or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli

CLASS V

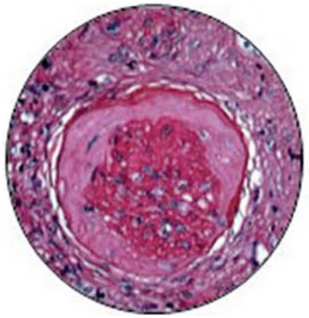
Membranous



Global or segmental subepithelial immune deposits or their morphological sequelae by LM and by IF or EM, with or without mesangial alterations.

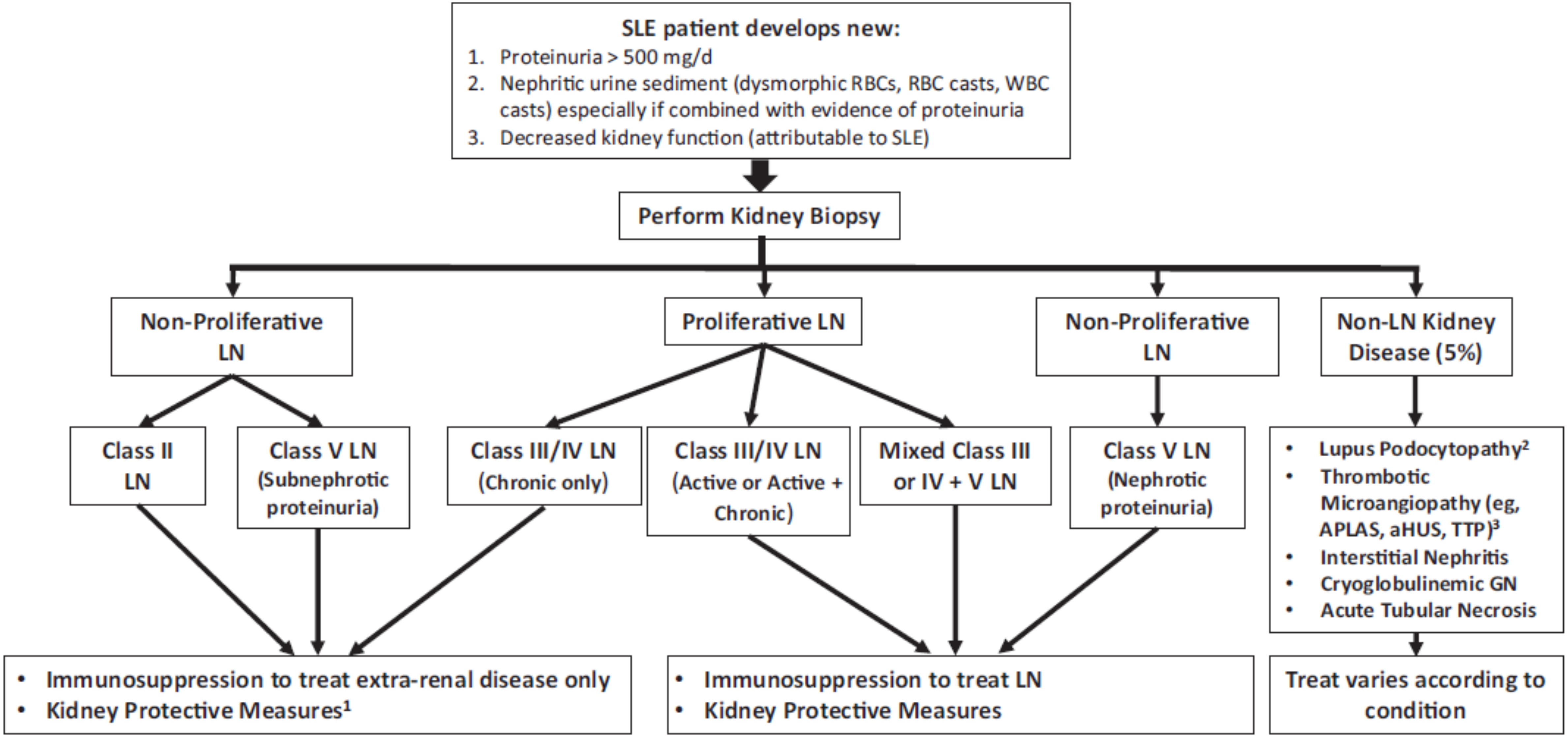
CLASS VI

Sclerotic



≥90% of glomeruli globally sclerosed without residual activity

ISN/RPS 2003 classification



Am J Kidney Dis. 2020 Aug;76(2):265-281.

Treatment Decisions in Lupus Nephritis

- **Treatment strategies mostly based on adult trials**
- **Treatment decision based on *all* of the following**
  - Renal histology
  - Extent of clinical renal disease
  - Extrarenal lupus
  - Serology
  - Previous treatment
- **Goals of Treatment**
  - Long term preservation of renal function
  - Prevention of flares
  - Avoidance of treatment related coplications
  - Improved quality of life and survival

Guidelines in LN

- American College of Rheumatology Guidelines for screening, treatment and management of lupus nephritis (**ACR 2012**)
- Joint European League Against Rheumatism and European Renal Association (**EULAR/ERA-EDTA**) Recommendations for the management of adult and pediatric lupus nephritis, **2012**
- **KDIGO** (Kidney Disease Improving Global Outcomes) Clinical Practice Guideline for Glomerulonephritis, **2012**
- Consensus Treatment Plans for Induction Therapy of Newly Diagnosed proliferative lupus nephritis in children, **CARRA 2012**
- Treat to Target in SLE **(T2T/SLE) 2014** recommendations
- European evidence-based recommendations for the diagnosis and treatment of Childhood onset lupus nephritis: **The Share Initiative 2017**
- **2019** update of the **EULAR-ERA EDTA** recommendations for the management of systemic lupus erythematosus
- **2021 KDIGO LN update in glomerular diseases**

KDIGO CLINICAL PRACTICE GUIDELINE
ON GLOMERULAR DISEASES

Practice Point 10.3.3.1. Treat pediatric LN patients with immunosuppression similar to regimens used in adults but consider issues relevant to this population, such as dose adjustment, growth, fertility, and psychosocial aspects when designing the therapy plan.

Initial therapy of childhood-onset proliferative lupus nephritis

Childhood Arthritis and Rheumatology Research Alliance (CARRA) 2012	
Initial regimen (pick one)	
Cyclophosphamide IV q 4 weeks × 24 weeks 500 mg/m^2 body surface area titrated up to 1500 mg/dose based on white blood cell (WBC) nadir	**Mycophenolate mofetil** 600 mg/m^2/dose twice per day × 24 weeks (Max 3000 mg/d)

Steroid regimen (pick one)

	Oral steroid regimen		**IV steroid regimen**		**Mixed regimen**	
	Initial dose	Taper goal	Initial dose	Taper goal	Initial dose	Taper goal
Weight > 30 kg	60–80 mg/d	20 mg/d	Initial pulse then 20 mg every 1–4 weeks	10 mg monthly	Mixed oral and IV dosing regiment	
Weight < 30 kg	2 mg/kg/d	0.5 mg/kg/d	Initial pulse then 10 mg every 1–4 weeks	5 mg monthly	Mixed oral and IV dosing regiment	

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Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) 2017

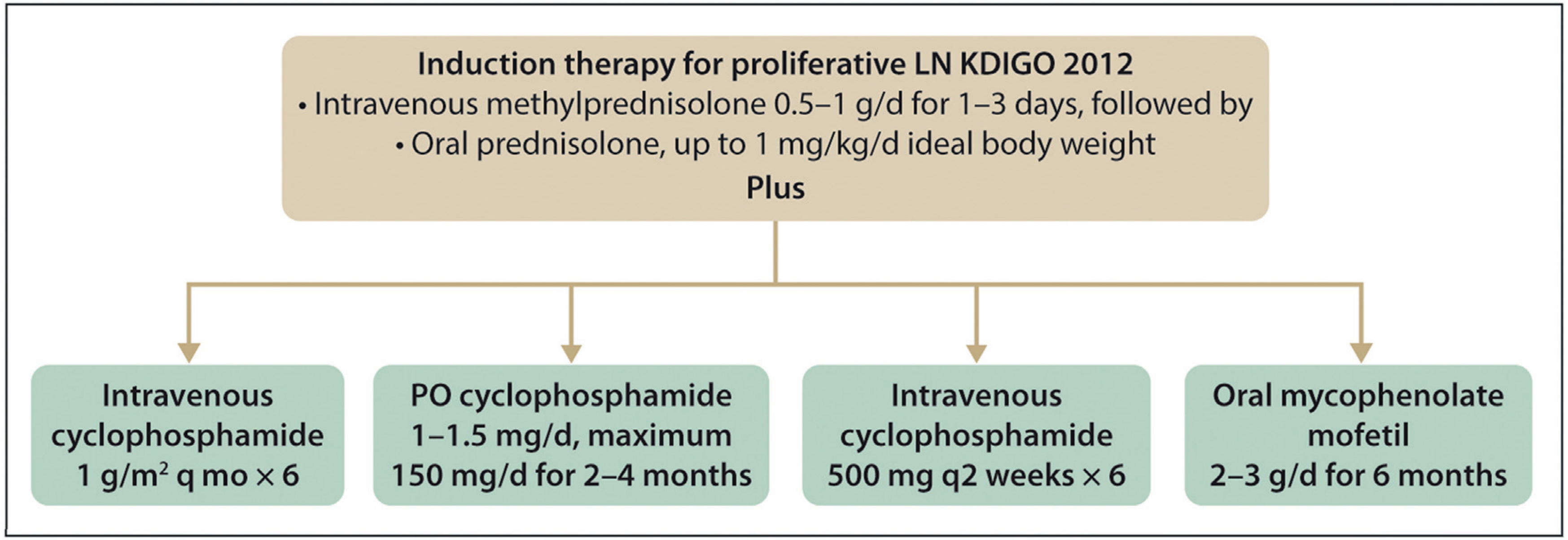
Initial regimen (pick one)

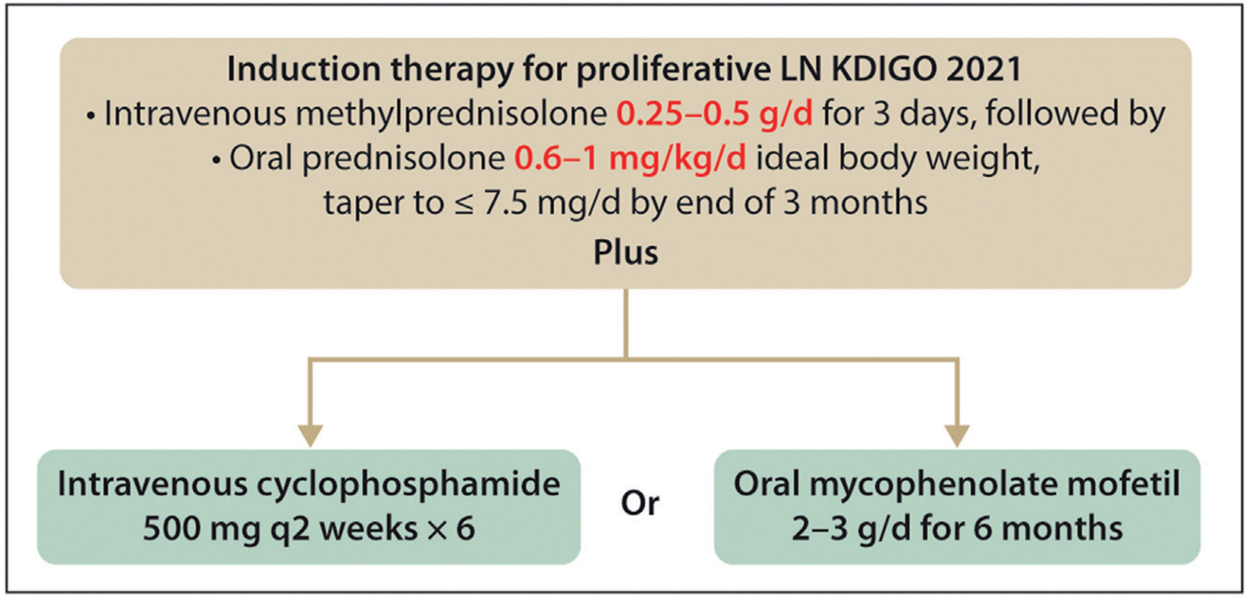
- High-dose IV Cyclophosphamide:
  500 mg/m^2 if tolerated increase to 750 mg/m^2/dose (Max 1000–2000 mg/dose), 6 monthly doses
  OR
  Low-dose IV Cyclophosphamide:
  500 mg/pulse (in adults) q 2 weeks × 6 pulses
- Mycophenolate mofetil 1200 mg/m^2 × 24 weeks (Max 2000 mg/day)
  When poor response, option to increase to 1800 mg/m^2/day (Max 3000 mg/day)

Steroid regimen

High dose prednisone:
1–2 mg/kg/day (Max 60 mg/day)

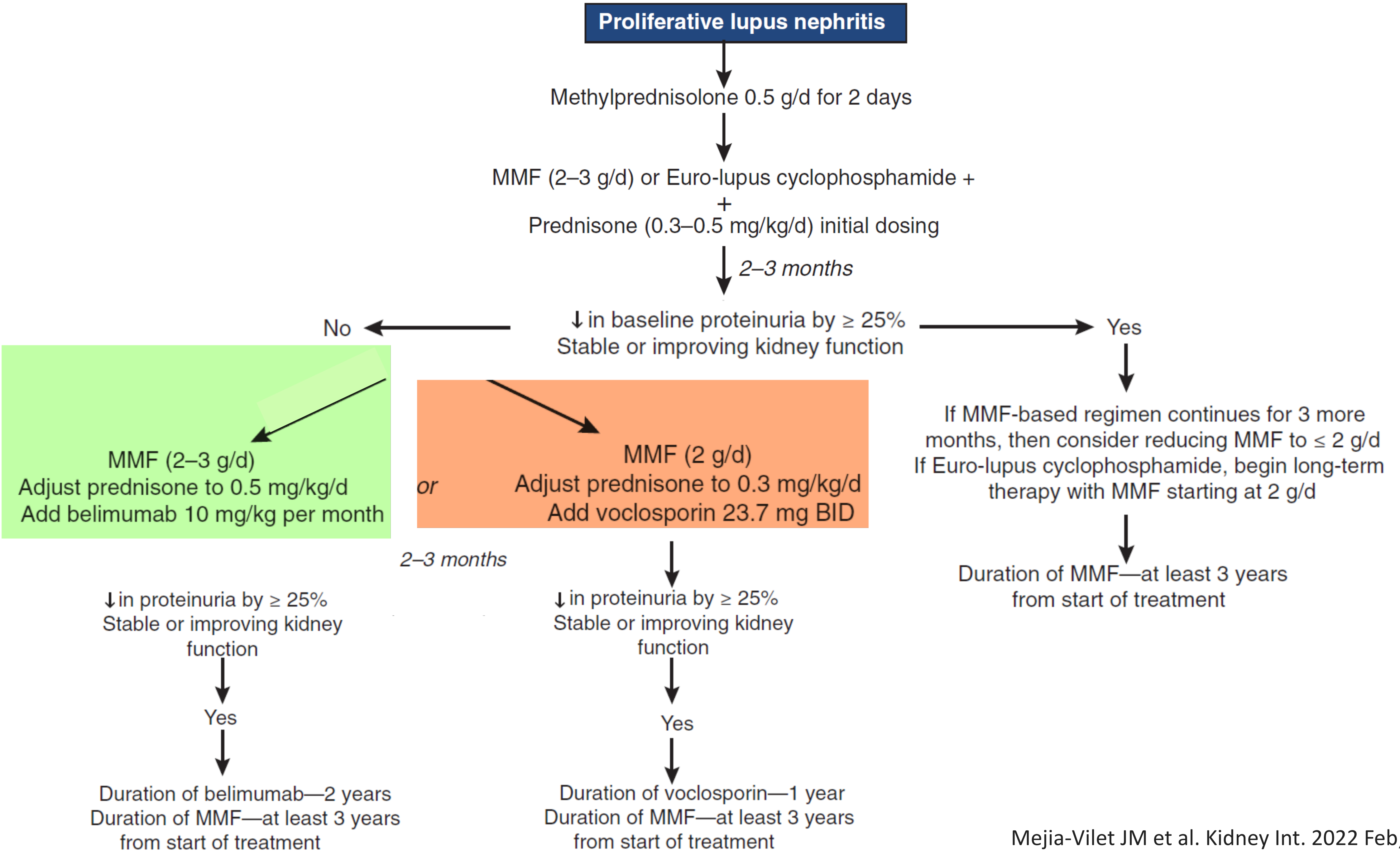
Proliferative LN INDUCTION Treatment Standard of Care





Rovin BH et al. Kidney International (2021) 100, 753–779

	EULAR/ERA-EDTA 2019	KDIGO 2021
Induction therapy active class III/IV (±V), steroids	**IV pulses MPZ** (total dose 0.5–2.5 g, depending on disease severity) followed by **Oral prednisone** (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3–6 months	• Initial **IV MPZ** 0.25-0.5 g/day for 1–3 days • **Oral prednisolone** at start 0.6–1 mg/kg (max. 80 mg) tapering to <5–7.5 mg/day over a few months • If satisfactory improvement in kidney AND extrarenal disease to initial therapy**, Oral steroids** **moderate-dose* (0.6–0.7 mg/kg to <5 mg after week >25) OR **reduced-dose* (0.5–0.6 mg/kg to <2.5 mg after week >25) can be considered
Induction therapy active class III/IV (±V)	**MMF** (2–3 g/day, or MPA at equivalent dose) or **low-dose IV CYC** (6× 0.5 g every 2 weeks)	• **MMF** (2–3 g/day) or **MPA** (1.44–2.16 g/day) for >6 months • **Low-dose CYC IV** (0.5 g/2 weeks for 6 doses) (efficacy data in mainly in Caucasians) • ***MMF/MPA preferred*** → *in patients at risk of infertility, Asian, Hispanic, African ancestry or prior exposure to CYC* • ***CYC preferred*** → *if suboptimal adherence is anticipated*
Induction therapy active class III/IV (±V), alternatives	In patients at **high risk for kidney failure consider high-dose IV CYC** (0.5–0.75 g/m^2 monthly for 6 months)	• **Pulse IV CYC** (0.5–1 g/m^2) for 6 months (efficacy data in different ethnicities) • **Oral CYC** 1–1.5 mg/kg/day max. 150 mg for 2–6 months (efficacy data in different ethnicities) • **Belimumab**: can be added to standard therapy • **RTX**: consider for repeated flares
Induction therapy active class III/IV (±V), CNI + reduced dose MMF	**MMF** (1–2 g/day) or MPA at equivalent dose) with a **CNI (especially TAC**), particularly in nephrotic-range proteinuria	*Only, in patients not tolerating MPA regimen or unfit for CYC or refuse CYC* • **Voclosporin** (23.7 mg ×2) can be added to MMF/MPA and steroids for 1 year in eGFR >45 mL/min/1.73 m^2

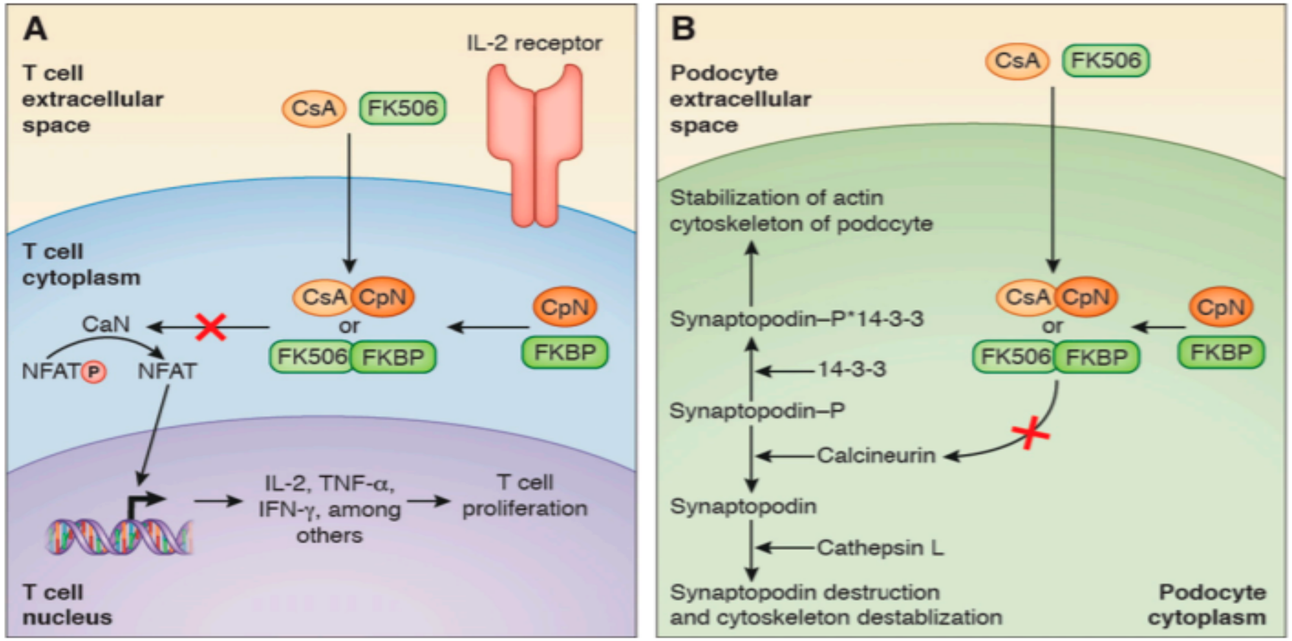


Mejia-Vilet JM et al. Kidney Int. 2022 Feb;101(2):242-255.

Calcineurin Inhibitors (cyclosporine, tacrolimus, voclosporin)

Both immunomodulatory and non-immune mediated
roles in treating SLE

They inhibit T-cell proliferation in addition to non-immunological effects that reduce proteinuria, including podocyte cytoskeleton stabilization and afferent arteriole vasoconstriction



- CNIs may be considered as second-line agents for induction or maintenance therapy mainly in membranous LN,
- Podocytopathy,
- or in proliferative disease with refractory nephrotic syndrome, despite standard-of-care within 3–6 months

Voclosporin A novel CNI in LN

- Voclosporin is a calcineurin inhibitor (CNI) modified from the cyclosporine backbone that is more potent than cyclosporine

- seems to cause less hypertension and hyperlipidemia than cyclosporine, seems to cause less diabetes than tacrolimus, and, at least in experimental animals, does not cause CNI nephrotoxicity.

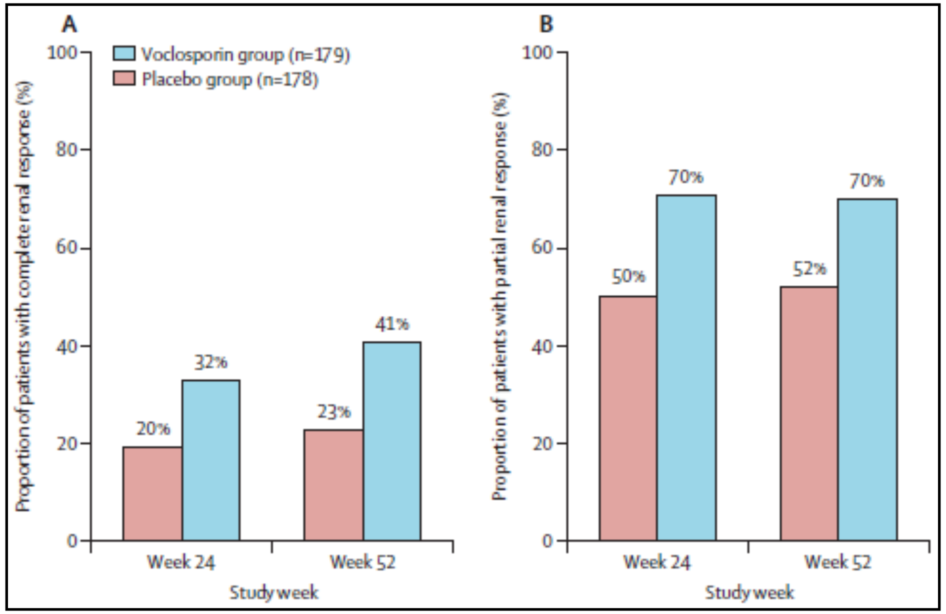
- However, voclosporin has not been compared directly with cyclosporine or tacrolimus for the treatment of LN, so no conclusions can be drawn regarding superior safety or efficacy.

Kidney International (2022) 101, 242–255

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Patients were randomly assigned (1:1) to oral voclosporin (23·7 mg twice daily) or placebo, on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids

	Voclosporin group (n=179)	Placebo group (n=178)	OR or HR (95% CI)	p value
Primary endpoint*				
Complete renal response at 52 weeks	73 (41%)	40 (23%)	OR 2·65 (1·64–4·27)	<0·0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2·23 (1·34–3·72)	0·002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	OR 2·43 (1·56–3·79)	<0·001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2·26 (1·45–3·51)	<0·001
Time to UPCR ≤0·5 mg/mg, days	169 (141–214)	372 (295–NC)	HR 2·02 (1·51–2·70)	<0·001
Time to 50% reduction in UPCR, days	29 (29–32)	63 (57–87)	HR 2·05 (1·62–2·60)	<0·001

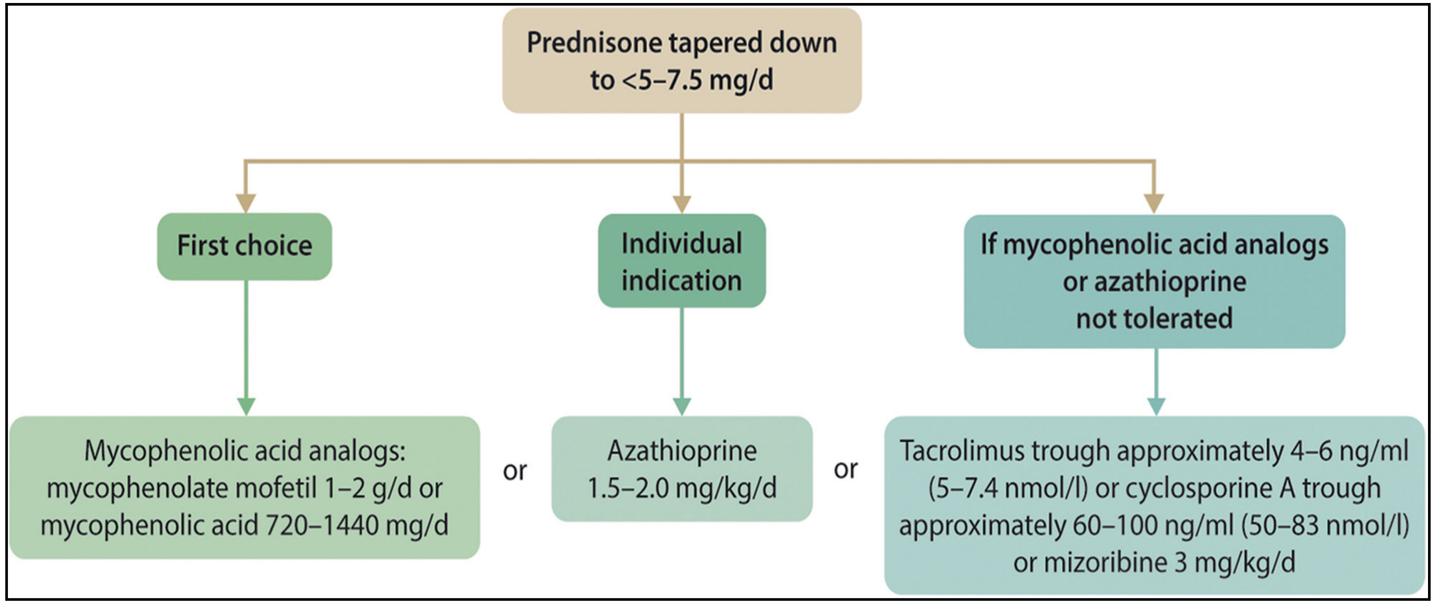


- **Voclosporin in combination with MMF and low-dose steroids led to a clinically and statistically superior complete renal response rate versus MMF and low-dose steroids alone, with a comparable safety profile.**
- **The most frequent serious adverse event involving infection was pneumonia, occurring in 7 (4%) patients in the voclosporin group and in 8 (4%) patients in the placebo group.**

Rovin B et al. Lancet 2021; 397: 2070–80

Proliferative LN Maintenance therapy

- First choice → MMF
- Alternative → AZA
- Optimal duration?
  - At least 12-18 months after clinical response
  - Most renal exacerbations are within the first 5-6 years



- CNIs
  - target have been based on the transplant literature
  - Dosing – titrate to obtain the desired effect on proteinuria balancing dose escalation against serum creatinine
  - Discontinue if serum creatinine level does not fall after dose reduction

Rovin BH et al. Kidney International (2021) 100, 753–779

Class V LN

	EULAR/ERA-EDTA 2019	KDIGO 2021
Induction therapy pure class V: first line	**Initial IV methylprednisolone** 0.5–2.5 g followed by **Oral prednisone** 20 mg tapered to ≤5 mg by 3 months plus **MMF** 2–3 g/day or MPA	**Low-level proteinuria:** •HCQ, RAAS inhibition (extrarenal SLE) **Nephrotic-range proteinuria:** (Combined immunosuppression) **Steroids** and **MMF/MPA (reasonable first choice)** or **CYC** (for <6 months) or **CNI** (if prior CYC or intolerant) or **RTX** (if prior CYC or intolerant) or **AZA** • HCQ, RAAS inhibition
Induction therapy pure class V: second line	• **CYC** • **CNI (especially TAC) monotherapy** • **CNI + MMF/MPA** in patients with nephrotic-range proteinuria	
Maintenance therapy pure class V	Continuation,switching to or addition of CNIs (especially TAC) can be considered at the lowest effective dose and after considering nephrotoxicity risks	

Refractory disease / Failure to achieve treatment goals

- One-third of patients are refractory to conventional therapy, with active urine sediment and deterioration of renal function.
- Medication nonadherence is a common contributor.

EULAR/ERA-EDTA 2019

- Evaluation of the possible causes (Drug-adherence and therapeutic drug monitoring)
- For active disease: ***switch to one of the alternative initial therapies*** or ***RTX (1 g on days 0 and 14)***
- Mentioned: *obinutuzumab, belimumab, IVIGs, plasma exchange (rarely indicated)*

KDIGO 2021

- Evaluate compliance and adequate dosing (drug levels)
- Repeat biopsy, if concern for chronicity/other diagnoses (TMA)
- ***Switch MMF/MPA to CYC, CYC to MMF/MPA***
- ***If refractory, combine MMF/MPA + CNI OR add RTX (or another biologic agent) OR extend IV CYC***
- Mentioned: *obinutuzumab, belimumab*

Plasma Exchange and Immunoadsorption

- Little evidence
- APS
- It can be considered in refractory disease, in which aggressive treatment is contraindicated.

Nephrol Dial Transplant (2022) 37: 1069–1077
doi: 10.1093/ndt/gfab152
Advance Access publication 7 April 2021

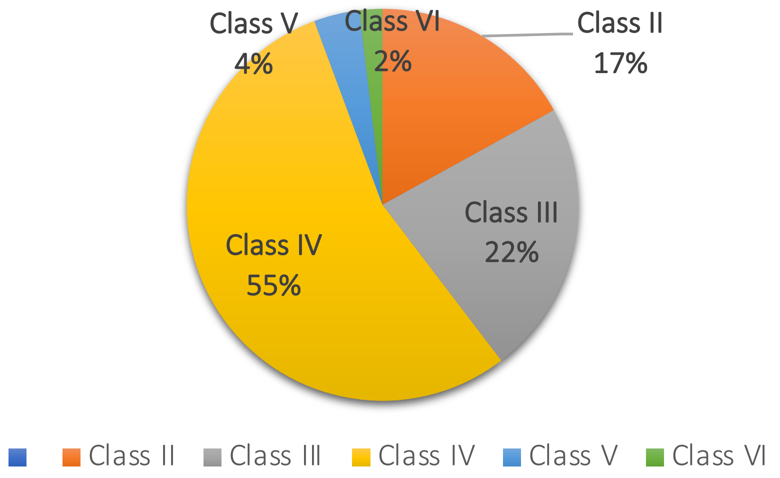
Long-term renal survival of paediatric patients with lupus nephritis

Selcan Demir [1,*], Bora Gülhan [2,*], Seza Özen [1], Kübra Çeleğen [2], Ezgi Deniz Batu [1], Nesrin Taş [2], Diclehan Orhan [3], Yelda Bilginer [1], Ali Düzova [2], Fatih Ozaltin [2,4] and Rezan Topaloğlu [2]

[1]Department of Pediatrics, Division of Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Department of Pediatrics, Division of Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [3]Department of Pediatric and Perinatal Pathology Research, Hacettepe University Faculty of Medicine, Ankara, Turkey and [4]Nephrogenetic Laboratory, Hacettepe University Faculty of Medicine, Ankara, Turkey

- **102 SLE patients**
- **The median age at onset of SLE → 13.3 years (IQR:10.4–15.8)**
- **The median follow-up duration → 43.1 months (IQR 24.3–69.3)**

- **Of the 102 SLE patients, 53 (52%) had LN**
- **The most frequent histopathological classes**
  Class IV LN (54.7%)
  Class III (22.6%)



Treatment		Proliferative LN (n = 41)			Non-proliferative LN (n = 12)		
		Class III ($n = 12$), n	Class IV ($n = 29$), n	Total ($n = 41$), n (%)	Class II ($n = 9$), n	Class V ($n = 2$), n	Total ($n = 11$), n (%)
Induction therapy	Pulse MPZ + CYC	2	20	22 (53.7)	–	–	–
	Pulse MPZ + MMF	7	3	10 (24.4)	1	–	1 (9)
	Pulse MPZ + AZA	1	–	1 (2.4)	3	2	5 (45.4)
	Pulse MPZ + oral CYC	2	3	5 (12.1)	1		1 (9)
	Pulse MPZ + RTX	–	3	3 (7.3)	4	–	4 (36.3)
	Prednisolone alone	3	–	3 (7.3)	–	–	–
Maintenance therapy	Prednisolone + AZA	4	9	13 (31.7)	3	2	5 (45.4)
	Prednisolone + MMF	6	16	22 (53.7)	2	–	2 (18.1)
	Prednisolone + CsA	0	1	1 (2.4)	–	–	–
	Prednisolone alone	2	1	3 (7.3)	4	–	4 (36.3)
	Lost to follow–up	0	2	2 (4.8)	–	–	–

Time to first relapse of LN patients who received MP+CYC or MP+MMF as induction treatment (0.681).

Either the complete or partial remission rates at all LN

77.3% at 6 months

73% at 12 months

Renal survival LN

5-year renal survival rate → 92%

10- year renal survival rate → 85.7%

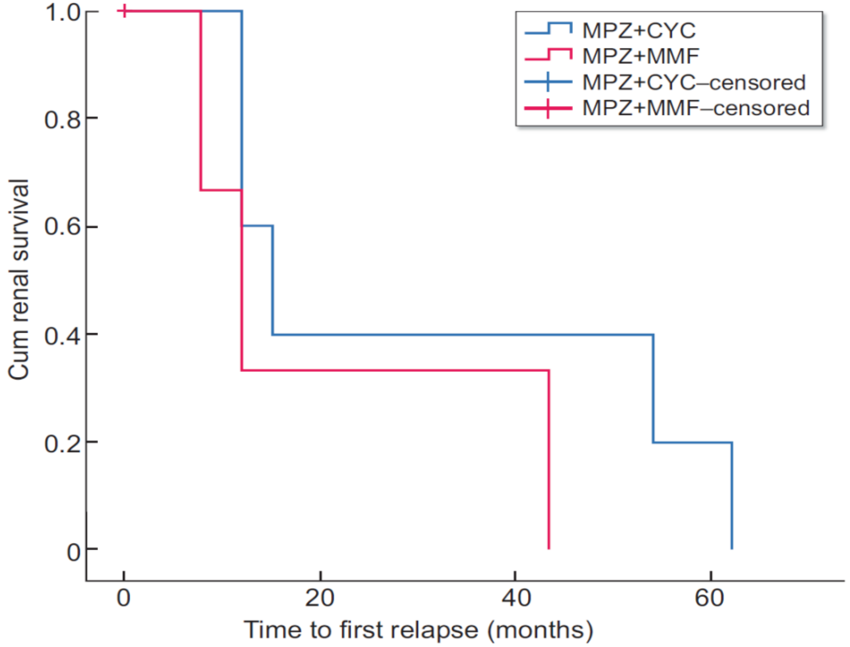
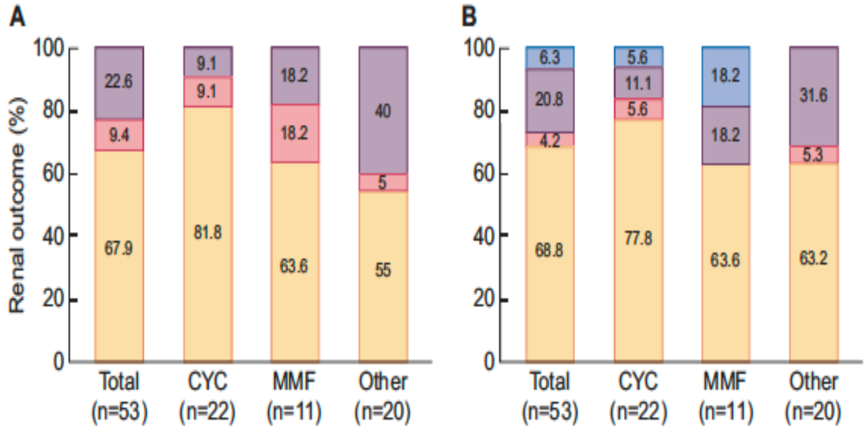
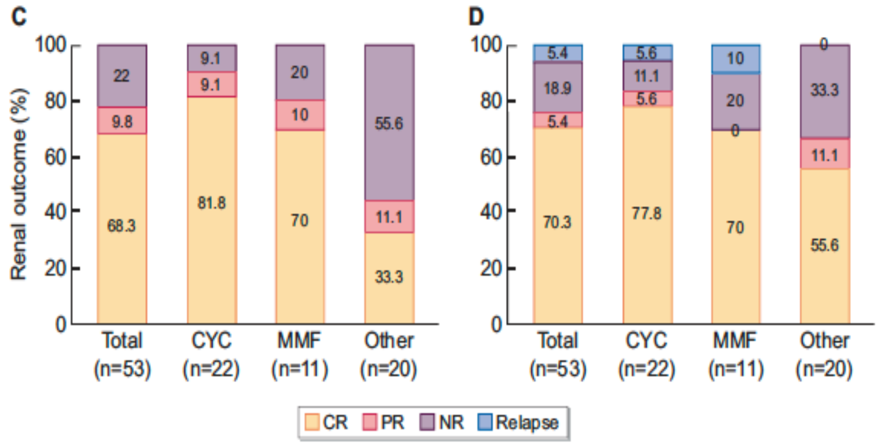


FIGURE 1: Renal outcomes of LN patients. (A) Renal outcome (%) at 6 months for all LN patients (P = 0.053). (B) Renal outcome (%) at 12 months for all LN patients (P = 0.71). (C) Renal outcome (%) at 6 months for LN patients with Classes III and IV. The remission rate at 6 months was significantly higher in the MMF- and CYC-treated groups than other combination therapies (P = 0.02). (D) Renal outcome (%) at 12 months for LN patients with Classes III and IV (P = 0.56). NR, non-response.

Renal outcome 6 months and 12 months in all LN patients



enal outcome 6 months and 12 months in LN patients with Class IV and III



Nephrol Dial Transplant 2022; 37: 1068-2007 doi:10.1093/ndt/gfab152
Advance Access publication 7 April 2021

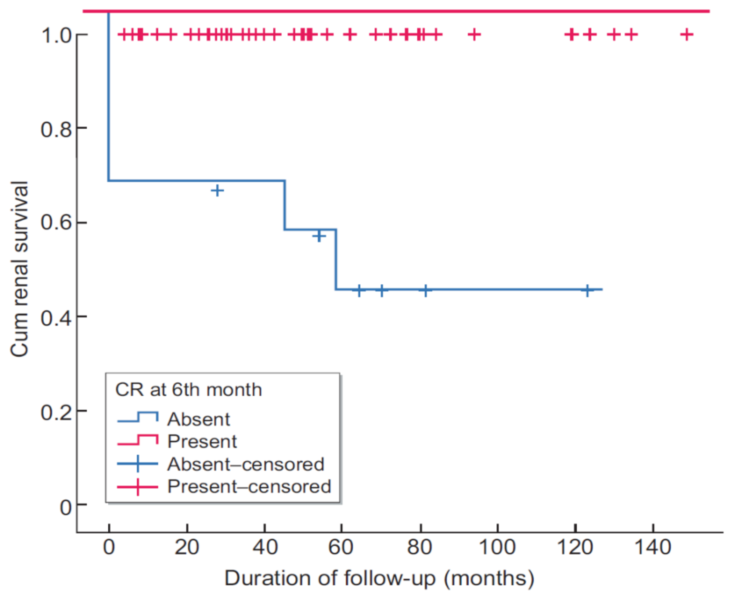
Table 4. Cox regression analysis for poor renal outcome among LN patients with Classes III and IV

Variables	HR (95% CI)	P-value
Male gender	8.41 (1.79–39.47)	**0.007**
SLE diagnosis before 12-year-old age	0.34 (0.10–1.13)	0.79
Serositis at the time of LN diadnosis	2.6 (0.47–14.32)	0.272
Neurological involvement at the time of LN diagnosis	1.18 (0.13–10.13)	0.874
GFR <60 mL/min at the time of LN diagnosis	0.15 (0.04–6.82)	0.337
Hypoalbuminaemia at the time of LN diagnosis	0.67 (0.18–2.47)	0.552
Dialysis at the time of LN diagnosis	6.48 (1.78–22.68)	**0.023**
Hypertension at the time of LN diagnosis	0.36 (0.09–1.44)	0.150
SLEDAI at the time of LN diagnosis	1.09 (0.99–1.19)	**0.054**
Anti-phospholipid positivity at the time of LN diagnosis	1.36 (0.40–4.61)	0.612
Increased creatinine at the time of LN diagnosis	1.94 (0.17–22.34)	0.592
Renal relapse	0.81 (0.20–3.34)	0.781
Thrombocytopenia at the time of LN diagnosis	3.56 (0.86–14.74)	0.079
No response at 6 months	8.6 (1.65–44.91)	**0.010**
No response at 12th months	13.82 (1.68–113.49)	**0.014**

Statistically sugnificant values are presented in bold.

Poor Prognosis

- male gender
- requiring dialysis at the time of LN diagnosis
- failure to achieve remission at 6 and 12 months

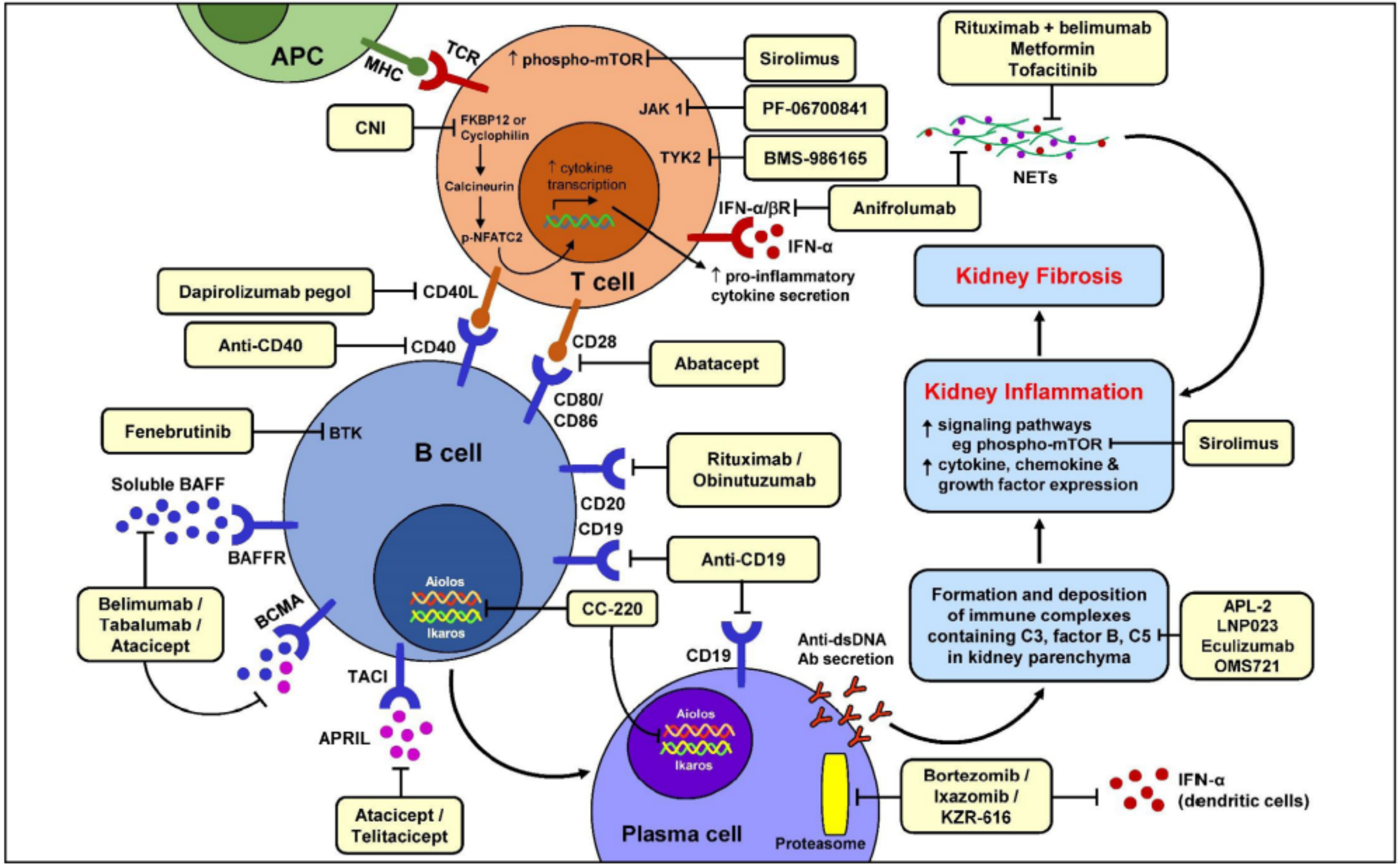


Conclusions

- Convential treatment is widely used

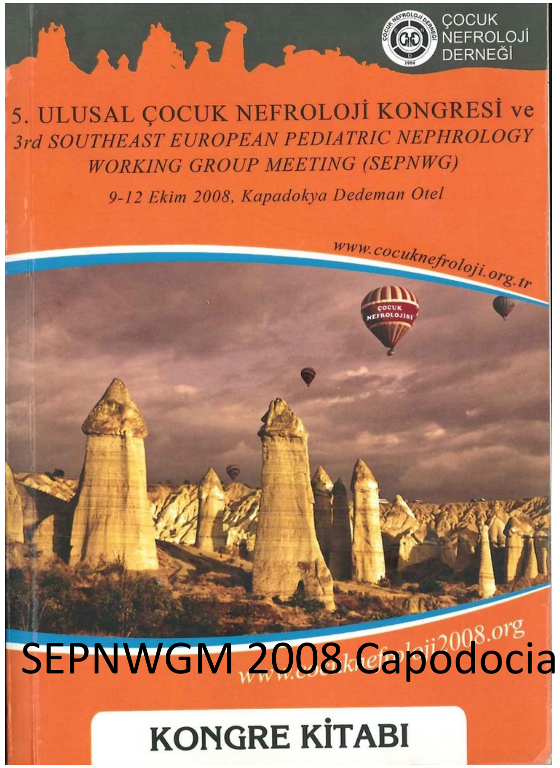
- Recognition that cSLE is a potentially aggressive disease with high morbidity and mortality rates is an essential step towards the development of safer and more efficacious treatments.

Immunopathogenic pathways leading to kidney damage in lupus nephritis and emerging novel therapies



Yung S, et al. F1000Research 2020, 9(Faculty Rev):905
https://doi.org/10.12688/f1000research.22438.1


SEPNWGM 2001 Istanbul



SEPNWGM 2008 Capodocia


SEPNWGM 2012 Ohrid


SEPNWGM 2015 Sarajevo


SEPNWGM 2019 Belgrade


SEPNWGM 2021 Crotia

Thank you