OUTWITTING THE GREAT MIMICKER
How to Spot Systemic Lupus Erythematosus

KEEPING KIDS ACTIVE
Juvenile Rheumatoid Arthritis Treatments

WHEN LYME DISEASE LINGERS
Special Therapy for Advanced Cases

Rheumatologic Disease Facts at Your Fingertips
I introduce this issue of Pediatric Perspective with the good news that Philip Ozuah, MD, PhD, has been appointed as Chairman of the Department of Pediatrics at Montefiore and the Albert Einstein College of Medicine and as Physician-in-Chief of The Children’s Hospital at Montefiore. Dr. Ozuah previously served as Interim Chairman of Pediatrics and before that was Vice Chairman for Clinical and Educational Affairs and Chief of the Section of Social Pediatrics. He has been a member of the Montefiore-Einstein faculty since 1992 and is a remarkable clinician, educator and administrator, who emerged from our national search as the hands-down choice to lead the department and the Children’s Hospital at Montefiore.

Dr. Ozuah has already accomplished spectacular things. In little more a year as Interim Chairman, he recruited dozens of new faculty members and expanded and enhanced our clinical offerings, including the new Pediatric Rheumatology Program that is featured in this issue. He will continue to build on our strengths to ensure that The Children’s Hospital at Montefiore provides your patients with the world-class care they deserve and you expect from us.

Sincerely,

Spencer Foreman, MD
President
Montefiore Medical Center

Dear Colleague:

I cannot think of a more exciting time to be the University Chairman and Physician-in-Chief for The Children’s Hospital at Montefiore (CHAM). At CHAM, our goal is to provide your patients with expert clinical services in a warm, child-centered environment. That is why I am delighted to introduce you to our newly created state-of-the-art Pediatric Rheumatology Program.

This is an important programmatic addition that brings us closer to our vision of being a leader in improving child health. The Division of Pediatric Rheumatology is led by Norman Ilowite, MD, an internationally acclaimed pediatric rheumatologic physician-researcher, and his colleague, Patricia Irigoyen, MD.

While over three hundred thousand American children will be diagnosed with juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE) and other rheumatologic diseases and disorders this year, only 229 practicing pediatric rheumatologists are available in the U.S. to provide them with specialized care. At CHAM, we are pleased to offer clinical and research rheumatologic programs led by two of these rare subspecialists.

To meet Dr. Ilowite, Dr. Irigoyen and other CHAM specialists, turn to “Meet Our Experts,” a new Pediatric Perspective feature, on pages 4 and 5. As you browse this issue, you’ll find the latest information on JRA therapy, gain insights into diagnostically elusive SLE, discover how CHAM researchers are speeding new biologic therapies to patients, and much more.

Please don’t hesitate to contact our physicians with questions about our rheumatology program, or to learn more about how to refer a patient to a CHAM specialist.

Sincerely,

Philip O. Ozuah, MD, PhD
Physician-in-Chief
University Chairman
The Children’s Hospital at Montefiore
Professor of Pediatrics
Albert Einstein College of Medicine
Phone: 718-741-2462
Email: pozuah@montefiore.org
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Meet Our Experts

Chief, Pediatric Rheumatology, CHAM
Professor of Pediatrics, Albert Einstein College of Medicine

Medical School: SUNY Health Science Center at Brooklyn – Brooklyn, NY
Residency: Pediatrics, George Washington University, Children’s Hospital National Medical Center – Washington, DC
Fellowship: Pediatric Rheumatology and Immunology, University of Washington/Children’s Orthopedic Hospital – Seattle, WA

Dr. Ilowite is an internationally recognized pediatric rheumatologist and clinical researcher with a special interest in systemic and other forms of juvenile rheumatoid arthritis and atherosclerosis prevention in pediatric lupus erythematosus. A sought-after guest lecturer and prolific author, Dr. Ilowite was voted one of the tristate area’s best doctors by New York Magazine in 2006.

Pediatric Rheumatologist, CHAM
Assistant Professor of Pediatrics, Albert Einstein College of Medicine

Medical School: Columbia University – New York, NY
Residency: Pediatrics, Columbia University/Children’s Hospital of New York Presbyterian – New York, NY
Fellowship: Pediatric Rheumatology, Schneider Children’s Hospital/North Shore LIJ Health System – New Hyde Park, NY

Dr. Irigoyen is a pediatric rheumatologist with a special interest in pediatric systemic lupus in the Latino community. Recently awarded a Physician Scientist Development Award by the American College of Rheumatology, Dr. Irigoyen is investigating the genetics of autoantibody production in rheumatoid arthritis in a 16,000-subject study sponsored by the New York Cancer Project.

Chief, Pediatric Nephrology, CHAM
Professor of Pediatrics, Albert Einstein College of Medicine

Medical School: University of Cincinnati College of Medicine – Cincinnati, OH
Residency: Pediatrics, Montefiore Medical Center – Bronx, NY
Fellowship: Pediatric Nephrology, Montefiore Medical Center – Bronx, NY

Dr. Kaskel is a nationally acclaimed pediatric nephrologic clinician and researcher with special expertise in focal segmental glomerulosclerosis (FSGS), for which he leads National Institutes of Health (NIH)-sponsored investigations. Director of the NIH-supported Fellowship Training Program at Albert Einstein College of Medicine, Dr. Kaskel was selected in 2006 as one of the tristate area’s best doctors by New York Magazine.
Director, Pediatric Hematopoietic Stem Cell Transplantation, CHAM
Assistant Professor of Pediatrics, Albert Einstein College of Medicine

**Medical School:** Jefferson Medical College – Philadelphia, PA
**Residency:** Pediatrics, St. Christopher’s Hospital for Children – Philadelphia, PA
**Fellowship:** Chief Fellow, Pediatric Hematology & Oncology; Research Fellow, Molecular Pharmacology, Memorial Sloan Kettering Cancer Center – New York, NY

Dr. Kolb is a leading pediatric hematologic and oncologic physician-researcher with special clinical interest and expertise in stem cell transplant and leukemia therapeutics. As the director of the Pediatric Preclinical Chemotherapy Testing Laboratory at Albert Einstein College of Medicine, Dr. Kolb is the principal investigator in ongoing genetic studies of pediatric solid tumors.

Director, Pediatric Infectious Disease, CHAM
Professor of Pediatrics, Albert Einstein College of Medicine

**Medical School:** Albert Einstein College of Medicine – Bronx, NY
**Residency:** Pediatrics, Montefiore Medical Center – Bronx, NY
**Fellowship:** Infectious Disease, Montefiore Medical Center – Bronx, NY

Dr. Litman is a leading pediatric infectious disease expert who received the William Obrinsky Outstanding Medical Student Teaching Award in Pediatrics in 2004. Dr. Litman has also authored numerous peer-reviewed publications and in 2006 was voted one of the tristate area’s best doctors by *New York Magazine*.

Chief, Division of Rheumatology, CHAM
Associate Professor, Division of Rheumatology and the Department of Microbiology & Immunology, Albert Einstein College of Medicine

**Medical School:** Technion-Israel Institute of Technology – Haifa, Israel
**Residency:** Hadassah University Hospital – Jerusalem, Israel
**Fellowship:** Rheumatology, Albert Einstein College of Medicine – Bronx, NY

Dr. Putterman is an internationally recognized physician-investigator in the field of rheumatology, with special expertise in anti-DNA antibodies, systemic lupus erythematosus (SLE) and lupus nephritis. In addition to directing full-time clinical and research programs, Dr. Putterman is frequently invited nationally and internationally as a guest lecturer.

Chief, Pediatric Gastroenterology & Nutrition, CHAM
Professor of Pediatrics, Albert Einstein College of Medicine

**Medical School:** Washington University School of Medicine – St. Louis, MO
**Residency:** Pediatric and Chief Resident, St. Louis Children’s Hospital – St. Louis, MO
**Fellowship:** Gastroenterology and Nutrition, The Combined Program in Pediatric Gastroenterology and Nutrition, The Children’s Hospital and Massachusetts General Hospital, Harvard Medical School – Boston, MA

Dr. Wershil is a leading pediatric gastroenterologist known both as a clinician and researcher. He has a long-standing research program studying the role of mast cells in gastrointestinal inflammation and allergy. A frequent guest lecturer and prolific author, Dr. Wershil has written more than 100 peer-reviewed publications, book chapters and reviews.
New Treatments Revolutionize Juvenile Rheumatoid Arthritis Outcomes

Not long ago, pediatric rheumatologists had little in their therapeutic arsenal but aspirin, gold shots and steroids to stave off the ravages of juvenile rheumatoid arthritis (JRA). In exchange for symptom relief, young patients endured growth abnormalities, obesity, high blood pressure, acne and osteoporosis. Today, expert rheumatologic care and advanced therapies at The Children’s Hospital at Montefiore (CHAM) ensure a brighter future for kids with JRA.

**Better Therapies Change Treatment Management**

“Because we have new agents to treat the disease, we have changed our strategies about how to manage the illness,” says Norman Ilowite, MD, newly appointed chief of Pediatric Rheumatology, CHAM. “We're less patient – and less willing to accept toxicity from drugs for their efficacy.”

Dr. Ilowite, an internationally recognized JRA expert, led research for the groundbreaking biologic therapeutic etanercept and is the principal investigator for a study of the biologic anakinra – sponsored by the National Institutes of Health (NIH) – that recently showed a 79 percent response rate in patients with systemic JRA, the most severe and therapy-resistant disease subset.

**Autoimmune Disorder Affects 300,000 U.S. Children**

Juvenile rheumatoid arthritis is an umbrella term used to cover several pediatric inflammatory autoimmune disorders that share arthritis as a symptom. Etiology remains unclear, but JRA’s inflammatory response begins in “a genetically predisposed host,” explains Dr. Ilowite, and “may be triggered by a virus, stress” or other factors. The disease affects about 10 to 20 in 100,000 U.S. children each year.
Distinct Disease Subtypes with a Range of Symptoms

Classification for JRA has recently been reorganized – and renamed – by the International League of Associations of Rheumatology (see “JRA or JIA: What’s in a Name?” on page 8), but most U.S. physicians are familiar with a trifold categorization for the disease. Pauciarticular JRA involves four or fewer joints, often larger joints such as knees. Polyarticular JRA includes five or more joints, usually smaller joints such as those in hands and feet. Systemic JRA is characterized by fever and rash in addition to synovitis – and can also involve organs.

“As medications get better, more and more of our patients benefit. We currently want to put patients in remission with no evidence of active arthritis.”

— Norman Ilowite, MD

Presenting signs and symptoms of JRA include swollen, achy joints, a limp, gait disorders, inflamed eyes and – with systemic disease – spiking fever and a salmon-pink rash. At CHAM, pediatric rheumatologists see a range of JRA complications that include uveitis, flexion contractures, osteoporosis, muscle atrophy, atlanto-axial instability, growth retardation, anemia, organ involvement and, in rare instances, macrophage activation syndrome, a multisystem immune response that can involve liver failure, internal bleeding and a DIC-like coagulopathy.

JRA Patients Often Mistakenly Referred to Orthopedists

Smoldering JRA frequently goes untreated – dismissed by parents as growing pains or misdiagnosed as infection or injury: A study that investigated physicians’ referrals for pauciarticular JRA patients revealed that 63 to 75 percent of examining pediatricians referred pauciarticular JRA patients to orthopedic surgeons – rather than rheumatologists – although patients presented with classic symptoms of synovitis.

Making the JRA Differential

While timely diagnosis and treatment of JRA can prevent or reduce permanent synovial and bone damage, identification of synovitis is not always straightforward. “Physical examinations are probably the most challenging thing we do,” admits Dr. Ilowite.

A careful history and serologic tests can help exclude Lyme disease, parvovirus and strep. Dr. Ilowite always asks patients and parents about “morning preponderance to pain, stiffness associated with inactivity and improvement with exercise,” to rule out growing pains, infection or injury. Lab tests are important to ascertain presence of ANA – associated with uveitis –
but are otherwise inconclusive. (For details on disease subset symptoms and lab tests, see “At-a-Glance Rheumatologic Disease,” back page.)

**“HIGHER GOALS” FOR CHAM PATIENTS WITH JRA**

When JRA is suspected, patients benefit from evaluation by a skilled rheumatologic specialist. CHAM’s pediatric rheumatologists are among the most experienced and accomplished in the world: Dr. Ilowite has treated more than 32,000 children with JRA and other rheumatic disease. He is the principal investigator on an NIH research proposal to study the next-wave JRA biologic IL1-trap – and is committed to exploring the most effective and safe therapeutic options for children with complex rheumatologic disease.

Dr. Ilowite admits he has ambitious goals for his patients. “As medications get better, more and more of our patients benefit,” he explains. “We currently want to put patients in remission with no evidence of active arthritis,” an aim that he believes is “achievable” at CHAM.

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**JRA or JIA: What’s in a Name?**

In the hope of differentiating chronic childhood arthritis from adult arthritic disease, rheumatologic experts recently changed the term juvenile rheumatoid arthritis (JRA) to juvenile idiopathic arthritis (JIA). In addition to the appellative change, disease classification has been expanded to include two conditions – spondyloarthropathy and psoriatic arthritis – formerly excluded from the JRA umbrella.

“Even more importantly,” says Norman Ilowite, MD, chief, Pediatric Rheumatology, The Children’s Hospital at Montefiore (CHAM), unlike the old system, “the new classification recognizes the course of the disease after the first six months.”

The previous disease categorization, created in 1977 by the American College of Rheumatologists (ACR), divided arthritis into three groups: pauciarticular, polyarticular and systemic disease.

The new system, approved by the International League of Associations for Rheumatology (ILAR) in 1997, divides childhood arthritis into five expanded subtypes:

- **Oligoarticular arthritis** that involves fewer than five joints in the first six months and may extend to more joints after six months
- **Polyarticular arthritis** involving five or more joints in the first six months
- **Systemic disease** characterized by fever, rash and systemic involvement that may include organs as well as joints
- **Psoriatic arthritis** that includes rash
- **Enthesitis-related disease**, including spondylitis and disease involving the spine, hips and enthesis

“Both classifications are acceptable,” notes Dr. Ilowite, “but most pediatric rheumatologists now use the term JIA.”
Managing Patients With Late-Stage Lyme Disease

Physicians in the tristate area need no advice on diagnosis and treatment of early-stage Lyme disease. Advanced and therapy-resistant Lyme disease, however – with arthritis, neurological involvement and cardiac complications – are more worrisome challenges that raise questions about intravenous antibiotic treatment, controversial long-term oral therapies and the need for specialty support care.

**LONG-TERM ORAL THERAPY NOT EFFECTIVE**

“The scientific community has looked at long-term therapy for Lyme disease, and there is no evidence that antibiotic therapy for more than four weeks is indicated,” says Nathan Litman, MD, director, Pediatric Infectious Disease, The Children’s Hospital at Montefiore (CHAM).

Patients with symptoms of arthritis that persist after initial oral therapy may benefit from “a second, different oral antibiotic,” says Dr. Litman, “and, if they have another episode, may be treated with an intravenous antibiotic.” Patients with meningitis and some with heart blockage should be treated with intravenous antibiotics.

**MULTIMODALITY CARE FOR PATIENTS WITH LATE-STAGE LYME DISEASE**

If late-stage Lyme disease symptoms persist after adequate therapy, children should be swiftly referred to specialty care, ideally at a facility comprehensively staffed by pediatric multidisciplinary specialists.

Among Lyme disease’s relatively rare complications is severe arthritis that may become “an immunologic, self-perpetuating disease,” says Norman Ilowite, MD, chief, Pediatric Rheumatology, CHAM. The condition “can improve with intra-articular steroids” administered by a pediatric rheumatologist, if appropriate antibiotic therapy fails, says Dr. Ilowite, and failing this, CHAM pediatric orthopedic surgeons can perform a synovectomy to remove inflamed joint tissue.

**AT-HOME IV TREATMENT AND ONE-STOP THERAPEUTIC SERVICES**

At CHAM, services are customized with families in mind. Patients who need IV therapy can receive a percutaneous intravascular catheter (PIC) that allows them to “get their daily therapy at home” and avoid school absences, notes Dr. Litman.

And CHAM provides the convenience of under-one-roof treatment that allows a sick child to – in a single visit, if needed – see our experts in rheumatology, infectious disease, cardiology, hematology, neurosurgery and “the entire array of specialists required to treat any pediatric Lyme disease issue,” says Dr. Litman.
Systemic Lupus Erythematosus: 
Outwitting the Great Mimicker

A 10-year-old girl presents with abdominal cramps, fever, weight loss and chest pain.

A teen is seen by a psychiatrist – then a rheumatologist – for headaches, mood swings and declining grades.

A 12-year-old girl goes to the emergency room with a vasculitic rash and returns two years later with fatigue and another year later with arthritis.

Infection? Depression? Systemic JRA? 
No. All three patients have systemic lupus erythematosus (SLE), the great mimicker.

SLE: The Differential to Consider Every Time

Rarely a straightforward diagnosis, SLE often leads frustrated pediatricians and specialists on a circuitous wild goose chase as the disease “slowly declares itself,” says Patricia Irigoyen, MD, attending physician, Pediatric Rheumatology, Children’s Hospital at Montefiore (CHAM). While patients may experience a dizzying “constellation of symptoms,” explains Dr. Irigoyen (see “Nailing the Systemic Lupus Erythematosus Diagnosis” on page 12), complaints are often vague, frequently manifest slowly, come and go – sometimes disappearing for years, sometimes forever – and maddeningly mimic other diseases.

Teen Girls at Higher Risk

An autoimmune disorder that causes multisystem microvascular inflammation and autoantibody generation, SLE’s genesis is unclear, but genetic, environmental, racial and hormonal factors play a role in the development of the disease.

Teenage girls make up the vast majority of the 0.36 to 0.9 out of 100,000 U.S. children who develop SLE each year: 50 to 60 percent of all pediatric lupus patients are teens and the disease strikes nine times more girls than boys in adolescence. Children who are African-American, Asian or Latino are at higher risk than Caucasians. All SLE patients test positive for ANA.
RENAL INVOLVEMENT CAN BE FATAL

The disease’s protean presentation can “pretty much involve any organ that’s involved in any disease,” says Norman Ilowite, MD, chief, Pediatric Rheumatology, CHAM. “And it can involve that organ in any way,” he says.

Patients with SLE may have cardiac, hematologic, cutaneous and pulmonary complications, and two-thirds of patients with SLE will have kidney involvement that ranges from mild to severe, according to Frederick Kaskel, MD, chief, Pediatric Nephrology, CHAM.

Symptoms of renal involvement include proteinuria, hematuria, edema, headache and hypertension, but “more often than not,” notes Dr. Kaskel, “the diagnosis is mixed: A little bizarre behavior. Decreased school performance. People aren’t thinking that it could be a collagen vascular disease.”

Lupus patients with kidney involvement “should be referred immediately,” says Dr. Kaskel, who warns that “renal prognoses can fall from fair to fatal in hours. You either catch it on time, or patients can die.”

SLE SURVIVAL RATES RISE FROM 50 PERCENT TO 95 PERCENT

Today, 95 percent of all SLE patients will survive – an enormous gain from the 50 percent mortality rate of the 1950s – reflecting the efficaciousness of corticosteroids and targeted cytotoxic agents as well as advances in kidney dialysis and transplant technologies.

At CHAM, the pediatric rheumatologic team customizes therapies to reduce flares, maximize therapeutic benefits and minimize toxicities. Creative alternate-day dosing of corticosteroids “reduces side effects as we taper,” says Dr. Irigoyen, and “pulse dosing with a large up-front IV medication catches disease and lowers cumulative dosing later on,” she explains.

STEM CELL TRANSPLANT REBOOTS IMMUNE SYSTEM

When life-threatening SLE is unresponsive to other therapies, CHAM’s pediatric hematologic experts can use advanced stem cell transplant that – in essence – restarts the patient’s immune system. “It’s like a reset button,” explains E. Anders Kolb, MD, director, Pediatric

CHAM’s pediatric rheumatologists are committed to treating the whole patient. They are skilled in identifying and managing all physical, psychosocial and developmental issues related to childhood and adolescent SLE.

Stem Cell Transplantation, CHAM. Dr. Kolb removes the patient’s bone marrow and extracts “the T cells – the cells most likely responsible for causing the lupus,” he says. “The marrow is then reintroduced to the patient so the immune system can reconstitute itself and hopefully prevent the lupus from returning.”

LAUNDRY LIST OF DISEASE- AND THERAPY-ASSOCIATED DISORDERS

As therapeutic advances lengthen SLE patients’ lives, CHAM specialists manage an increasingly long list of disease- and therapy-associated complications. “Infection,” says Dr. Irigoyen, “is the main cause of death for lupus patients today.” Other associated disorders include osteoporosis, growth failure, infertility, hypertension and artherosclerosis.
Patients suspected of having systemic lupus erythematosus (SLE) must meet at least four of the following 11 criteria established by the American College of Rheumatology (ACR) to be definitively diagnosed with SLE:

1. Malar rash: Fixed erythema, flat or raised, over the malar eminences
2. Discoid rash: Erythematous circular raised patches
3. Photosensitivity
4. Oral and nasopharyngeal ulcers
5. Arthritis of two or more peripheral joints
6. Serositis, pleuritis or pericarditis
7. Renal involvement: Proteinuria or cellular casts
8. Neurologic involvement: Seizures or psychosis without other causes
9. Hematologic involvement: Hemolytic anemia, leucopenia, lymphopenia or thrombocytopenia in the absence of offending drugs
10. Immunologic disorder: Anti-dsDNA, anti-Smith, and/or anti-phospholipid
11. Antinuclear antibodies

While the ACR criteria are “useful as a guideline,” says Norman Ilowite, MD, chief, Pediatric Rheumatology, CHAM, “if it looks like a duck and quacks like a duck, it probably is a duck, so … even if patients don’t fulfill four of 11 criteria, the diagnosis may still be lupus.”

**Nailing the Systemic Lupus Erythematosus Diagnosis**

**PIONEERING INVESTIGATOR OF LUPUS-ASSOCIATED ARTERIOSCLEROSIS**

Dr. Ilowite was one of the first pediatric rheumatologists to note lupus-associated cholesterol and investigate arteriosclerosis prevention and treatment. An early architect of the landmark NIH-funded Artherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial and one of its principal investigators, Dr. Ilowite today chairs APPLE’s Writing Committee to determine post-trial access to data.

As therapeutic advances lengthen SLE patients’ lives, CHAM specialists manage an increasingly long list of disease- and therapy-associated complications. Infection is one of the most serious challenges.

**STRATEGIES THAT BOOST TEEN COMPLIANCE**

CHAM’s pediatric rheumatologists are committed to treating the whole patient. They are skilled in identifying and managing all physical, psychosocial and developmental issues related to childhood and adolescent SLE. Therapeutic compliance, for example, is “a huge problem,” says Dr. Irigoyen, who successfully handles compliance issues by “really engaging the patient,” she says. “I treat the complaints that are most important to her – like acne – even if they’re not important to me.”

With the support of a diverse treatment team that includes pediatric sub-specialists, practice nurses, physical therapists, nutritionists, child-life experts, social workers and psychotherapists – and an SLE support group made up of patients and parents – CHAM’s rheumatologic team is finding new strategies to meet SLE’s multiple challenges.
Raynaud’s Phenomenon

Do Cold Fingers Point to Underlying Autoimmune Disease?

Although Raynaud’s phenomenon affects almost one in every 20 adolescent girls, many pediatricians will never actually see the pathology. This rheumatic-associated disorder is hallmarked by dramatic digit color changes that, unfortunately, don’t appear on command in examining rooms.

NUMBNESS AND TRI-PHASED COLOR CHANGE IN FINGERS

Most frequently triggered by cold conditions, Raynaud’s phenomenon causes blood vessels to constrict. Digits undergo a three-staged color change “that starts with white fingers that next turn blue, then red on rewarming,” says Norman Ilowite, MD, chief, Pediatric Rheumatology, The Children’s Hospital at Montefiore (CHAM). Patients’ feet, ears, nose and lips may also chill and become painful and numb.

IDENTIFYING AT-RISK PATIENTS

The disorder is strongly associated with several rheumatologic diseases – 95 percent of all scleroderma patients experience Raynaud’s phenomenon, as do 85 percent of all patients with mixed connective tissue disease.

“The question,” says Dr. Ilowite, “is how to pick the patients who are going to have secondary Raynaud’s phenomenon,” with underlying disease, “from the patients who have primary Raynaud’s.”

Patients who persistently complain of cold, blanched or blue hands should be carefully evaluated. “Most important,” says Dr. Ilowite, “is examination of the nail bed capillaries.” Red striations in this area suggest nail bed capillary abnormalities – a strong indicator of secondary disease. Morning stiffness in joints, shortness of breath and serological presence of ANA also warrant further investigation.

PEDIATRIC RHEUMATOLOGISTS PROVIDE BEST DIAGNOSTIC REASSURANCE

When secondary Raynaud’s phenomenon is suggested, patients should be seen by a pediatric rheumatologic specialist when possible. CHAM is fortunate to have two pediatric rheumatologists – only 229 of these sub-specialized experts practice in the U.S. today – Dr. Ilowite and his colleague, Patricia Irigoyen, MD, at the helm of its pediatric rheumatologic clinical and research programs.

Supported by pediatric specialists in all related disciplines, Drs. Ilowite and Irigoyen expertly manage the most complex Raynaud’s-related rheumatologic conditions or – to parents’ enormous relief – rule them out. Because happily, at the end of the diagnostic day, “95 percent of kids with primary Raynaud’s disease will not have secondary Raynaud’s,” says Dr. Ilowite.
When Henoch-Schonlein Purpura Moves Beyond Garden-Variety Vasculitis

Henoch-Schonlein purpura (HSP), the most common form of childhood vasculitis, usually runs a benign course, and “most patients are fine even without treatment,” says Norman Ilowite, MD, chief, Pediatric Rheumatology, The Children’s Hospital at Montefiore (CHAM). “But HSP is so common that every pediatrician will see a child who won’t do well either in the short term with GI problems or the long run with the kidneys.”

An estimated 2 to 5 percent of HSP patients have serious GI or renal complications, and reportedly 5 to 15 percent of all end-stage renal disease in children is associated with HSP.

AN AUTO-INFLAMMATORY MULTISYSTEM DISORDER

Henoch-Schonlein purpura is a reactive disease that causes inflammation in the skin, joints and kidneys. It affects 15 in 100,000 children each year and occurs twice as often in boys as in girls. Incidence peaks in children ages 3 to 10 – 75 percent of all HSP patients are age 9 or younger —and older children may be at higher risk for more serious disease complications.

HSP WITH NO “P”

As would be expected with this eponymous disease, “you can’t make the diagnosis until you see the rash,” says Dr. Ilowite. Sometimes, however, the disease presents without purpura. “It can be confusing,” says Dr. Ilowite, “because you can start with GI or joint disease and it can be difficult to know what’s causing those things until the rash develops.” On very rare occasions, HSP has been diagnosed – through IgA tissue deposition or GI endoscopy – with no purpura.

GASTROINTESTINAL INVOLVEMENT IN MOST HSP PATIENTS

The most common complaint with HSP is abdominal pain, a presenting sign in 80 percent of all patients. When pain is acute and severe or the patient presents with bloody stools or vomiting, it is essential that “an obstructive series be done to rule out a catastrophic GI event,” says Barry Wershil, MD, chief, Pediatric Gastroenterology, CHAM.
Gastrointestinal complications associated with HSP can include bowel edema, intestinal bleeding and – in 1 to 13 percent of cases – intussusception, a condition that causes the bowel to “fold in on itself,” says Dr. Wershil. “Ordinarily the bowel would simply unfold,” he explains, “but HSP’s inflammation creates a lead point that prevents spontaneous reduction.” Because HSP-associated intussusception is typically small bowel to small bowel – rather than the more common ileo-colonic type – ultrasound of the abdomen rather than barium enema is the preferred imaging modality. Dr. Wershil believes that “a high index of suspicion must be maintained, and the patients must be carefully followed with serial examinations of the abdomen.”

An estimated 2 to 5 percent of HSP patients have serious GI or renal complications, and reportedly 5 to 15 percent of all end-stage renal disease in children is associated with HSP.

Steroid Therapy May Mask Potential Disaster

Experienced care is critical for HSP with abdominal complaints. Steroids are sometimes used to treat GI symptoms in HSP, but Dr. Wershil strongly urges that this therapeutic decision be made by an experienced gastroenterologist because steroidal immunosuppressants can “mask an evolving intra-abdominal disaster,” he says. An undiagnosed intussusception can lead to perforation and peritonitis.

Severe HSP: Lifelong Renal Problems?

The kidneys are HSP’s second most frequently targeted system: Half of all children with HSP will have renal involvement, and 10 percent will develop serious kidney complications. “All patients who present with purpura should have their urine checked,” says Frederick Kaskel, MD, chief, Pediatric Nephrology, CHAM. While mild proteinuria is common, “persistent proteinuria is a poor prognosticator,” says Dr. Kaskel. Patients with hematuria and persistent proteinuria reportedly have a 15 percent chance of developing renal failure.

Kidney complications don’t always show up right away. “You may not have renal involvement at the time of the rash,” says Dr. Kaskel. “It can occur later,” sometimes months or even years after other symptoms resolve. A recent study showed that 35 percent of pediatric patients with severe HSP and glomerulonephritis developed kidney problems as adults.

Highly Experienced Specialty Care Is Crucial

Though life-threatening HSP complications are rare, when emergencies arise, expert sub-specialty evaluation is vital. At CHAM, customized pediatric facilities and proximate care from the metro area’s most experienced pediatric rheumatologists, nephrologists and gastroenterologists give young HSP patients a distinct advantage. Because “for this particular disease,” says Dr. Wershil, “what to see – and what to expect – is really based on prior experience.”
Investigations Speed Next-Generation Biologics to CHAM Patients

Biologic therapies have been widely embraced by the rheumatologic community for their remarkable efficacy and safety profiles. Unlike older therapies that suppress global immunity, biologics can precisely target individual cytokines, cell types or pathways, leave the rest of the immune system untouched, and may be better at sparing patients the infection and toxicities associated with conventional immunosuppressants.

Today at The Children’s Hospital at Montefiore (CHAM) and Albert Einstein College of Medicine (AECOM), rheumatologists are examining next-wave biologic agents that promise to deliver new therapeutic options to patients with arthritis — including children with severe, refractory disease.

**Targeted Therapies Zero In on Multipathway Disease**

The novel therapies that are available and that are currently in development are particularly efficacious for rheumatologic disorders because many rheumatic inflammatory disorders can involve “not just one abnormality in a single cytokine,” explains Chaim Putterman, MD, chief, Division of Rheumatology, Montefiore Medical Center, “but abnormalities in multiple pathways. In lupus, for example, there are abnormalities in B cells, T cells, cytokines and cell-signaling molecules – multiple potential abnormalities, each of which may need to be addressed therapeutically. Therefore, targeting the treatment to the specific defect present in a given patient may be most effective approach, with the least side effects.”

**“Anti-TNF Revolution” Spurs Innovation in Emerging Biologic Therapies**

The first generation of rheumatologic biologics were TNF-blockers – agents that deactivate tumor necrosis factor (TNF), a chemical messenger in arthritic inflammation. The drugs were “a prototypical bench-to-bedside success story,” notes Dr. Putterman, and this “anti-TNF revolution” continues to drive ongoing biologic investigations, he says.

**CHAM Researcher Forges New Ground with Next-Wave Biologics**

Forward-looking researchers are now examining biologics that inhibit interleukin-1 (IL-1), an “accessory protein needed to trigger inflammatory cells,” says Norman Ilowite, MD, chief, Pediatric Rheumatology, CHAM. As principal investigator (PI) of a National Institutes of Health (NIH)-funded study of the IL-1-inhibitor anakinra, Dr. Ilowite reported a 79 percent response rate from patients with systemic juvenile rheumatoid arthritis (JRA) — the most severe and therapy-resistant JRA subset.

Concurrently the PI in a study of another IL-1 inhibitor, IL-1-trap, Dr. Ilowite also hopes to “identify children who will respond to therapy before we give the medicines,” he says. The IL-1-trap trial is the first ever non-industry-sponsored investigation of a JRA therapeutic.

**Futuristic B Cell Inhibitors Slam the Door on Inflammatory Cell Conversations**

In yet another study, Dr. Ilowite and his pediatric rheumatologic team will collaborate with Dr. Putterman and other members of the adult rheumatology team to explore treatment with an anti-CD22 monoclonal antibody. This B cell inhibiting biologic interferes with cellular “costimulation – the conversation,” explains
Dr. Putterman, that occurs “between antigen-presenting cells and B cells” as part of rheumatic inflammation.

RESEARCHERS CREATE RHEUMATOLOGIC GENETIC BANK

At CHAM and AECOM, rheumatologic colleagues will also join forces on an “observational, longitudinal study of systemic lupus erythematosus,” says Dr. Putterman, “to see whether certain serum and urine markers will help predict disease course – or if we can use them to prognosticate flares and relapses.”

The study will bank collected biomarkers and genetic data to allow CHAM researchers – and scientists around the country – to “do cross-sectional studies as well as retrospective and prospective studies with multiple patients,” says Dr. Putterman.

TRANSLATIONAL MEDICINE THAT REALLY TRANSLATES

“There is a very, very close integration,” says Dr. Putterman, “between the clinical and research efforts” at CHAM and AECOM. Dr. Putterman encourages “collaboration between the people providing patient care and the people asking the questions in the lab,” he says, adding, “To improve the lot of patients … we need everybody to be versed in the language of the other.”
State-of-the-Art Nephrologic Care for Pediatric Rheumatologic Patients

Every year the Ira Greifer Children’s Kidney Center at The Children’s Hospital at Montefiore (CHAM) provides advanced nephrologic care to more than 4,000 children with renal disorders – including a significant number of patients with rheumatologic disease.

Kidney involvement is common with systemic inflammation: 50 percent of older children with Henoch-Schonlein purpura (HSP) and two-thirds of pediatric patients with systemic lupus erythematosus (SLE) experience at least mild hematuria and proteinuria, according to Frederick Kaskel, MD, director, Children’s Kidney Center and chief, Pediatric Nephrology, CHAM.

EMERGENCY NEPHROLOGIC INTERVENTION SAVES LIVES

In SLE patients, “it’s not only the blood and protein that worry us,” says Dr. Kaskel, but “the condition’s narrow window” that can move from non-event to near-death “in hours,” he notes. While HSP generally runs a benign course, “I’ve seen patients lose kidneys in an acute
episode,” says Dr. Kaskel, “or be left with diminished function and high blood pressure” that require dialysis and renal transplant.

NEW YORK’S ONLY CERTIFIED PEDIATRIC DIALYSIS CENTER

The Children’s Kidney Center takes a unique approach to pediatric rheumatologic and renal care that provides superb nephrologic specialty treatment and an array of related adjuvant and psychosocial services in a child-friendly environment.

The only certified pediatric dialysis program in New York State, the Center has cutting-edge facilities that offer every available form of at-home and in-patient peritoneal dialysis and hemodialysis – including continuous venovenous hemofiltration (CVVH) for improved solute clearance.

OUTSTANDING TRANSPLANT TRACK RECORD

The Center’s subspecialized nephrologic surgeons are nationally recognized for their expertise: 98 percent of all transplants survive for 10 years or more – the national average is 88 percent. CHAM surgeons have performed more than 1,000 grafts and transplanted kidneys in patients as young as age 2.

CENTER’S FOUNDERS PIONEERED PEDIATRIC NEPHROLOGY

At CHAM, nephrologic excellence is a four-decade tradition. Drs. Henry Barnett, Chester Edelmann and Ira Greifer of Albert Einstein College of Medicine helped “define the field of pediatric nephrology” in the 1960s, notes Dr. Kaskel. The three physicians were among the primary framers of the International Pediatric Nephrology Association (IPNA) and soon after founded the Children’s Kidney Center, named in honor of Dr. Greifer.

CHAM’S CHILDREN’S KIDNEY CENTER IS FIRST

As one of the first comprehensive pediatric renal programs in the world, the Children’s Kidney Center is responsible for a long line of firsts. The Center’s surgeons performed New York’s first pediatric renal transplant in 1972.

Montefiore physician-scientists led the United States’ first multicenter research studies on pediatric nephrotic syndrome – the most common form of chronic childhood kidney disease – and the Center opened the country’s first summer camp for pediatric dialysis patients in 1974.

RESEARCH THAT MOVES THE FIELD FORWARD

Clinical expertise and scientific innovation continues today at CHAM. In addition to directing the Center’s clinical program, Dr. Kaskel leads nephrologic research and is the principal investigator of a National Institutes of Health (NIH)-sponsored multicenter clinical study of focal segmental glomerulosclerosis.

In collaboration with scientists at Johns Hopkins Children’s Center, Dr. Kaskel serves as co-investigator on the largest investigation of pediatric nephrologic disease ever conducted in the U.S., a 55-center study that assesses patients’ kidney dysfunction over a period of years.

METRO AREA’S FOREMOST NEPHROLOGIC PROGRAM

The Children’s Kidney Center is the largest and most comprehensive pediatric nephrologic program in the metro area, with six subspecialists in pediatric nephrology, three transplant surgeons, two pediatric urologists, two dedicated renal pathologists, and experts in child psychiatry, pediatric transplant nursing, nutrition, renal social work and child life issues.

“We have a very large interactive team,” acknowledges Dr. Kaskel. “For family-centered care, the importance of a team can’t be stressed enough.”
<table>
<thead>
<tr>
<th>Type</th>
<th>Risk Factors</th>
<th>Symptoms</th>
<th>Laboratory Findings</th>
<th>That Support Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauciarticular</td>
<td>Affects four or fewer joints—typically larger joints (knee, ankle, wrist)</td>
<td>Stiffness, swelling and/or pain in one to four joints that lasts more than six weeks with gradual onset unrelated to injury or infection; gait disturbance</td>
<td>Typically normal—or very slightly abnormal—CBC, metabolic panel and ESR. RF factor usually negative, but ANA may be present.</td>
<td>Eye involvement—strongly associated with presence of ANA; knee flexion contractures; leg length discrepancies</td>
</tr>
<tr>
<td>Polyarticular</td>
<td>Affects five or more joints—large or small—often symmetrical, e.g., both knees</td>
<td>Stiffness, swelling and/or pain in more than five joints that lasts more than six weeks with gradual onset unrelated to injury or infection; gait disturbance</td>
<td>Varies greatly: some patients have normal lab tests, others show elevated ESR and low hemoglobin. ANA and—less commonly—RF may be positive.</td>
<td>Bone loss, movement limitations, cervical spine fusion, foot deformities; positive RF may indicate adult-type arthritis, scleroderma or other rheumatic disease.</td>
</tr>
<tr>
<td>Systemic</td>
<td>May affect many bodily systems in addition to joints</td>
<td>Swelling and pain in large or small joints concurrent with or preceded by salmon-pink rash and spiking fever that returns to normal at least once a day</td>
<td>Typically shows rising ESR and WBC and platelet counts—but falling hemoglobin.</td>
<td>May have slight elevation of liver enzymes. Severe damage to large and small joints, pericarditis, enlarged liver or spleen, hemolytic anemia, macrophage activation syndrome.</td>
</tr>
</tbody>
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For more information about the Pediatric Rheumatology Program at The Children's Hospital at Montefiore or to refer a patient, call 718-741-2460.
## At-A-Glance Rheumatologic Disease

### Disease Risk Factors

- **systemic Lupus erythematosus**
  - Most common in adolescent girls;
  - Higher incidence when family member has SLE or other connective tissue disorder

### Symptoms

- Patients often present with fever, fatigue, anemia and weight loss.
- Four or more of the following symptoms must manifest for definitive diagnosis:
  - Red rash over cheeks, discoid rash, photosensitivity, mucosal ulcers, serositis, arthritis, renal involvement, neurological involvement, hematologic disorder, immunologic disorder, positive ANA.

### Laboratory Findings

- Positive diagnosis unlikely without presence of ANA. Anti-dsDNA, anti-Smith antibodies and serum complement tests may help confirm diagnosis.
- Elevated ESR, WBC count, platelet count, low complement and reversed albumin-globulin ratio typical with active disease.

### Complications

- Infection; damage to kidneys, heart, lungs, bone marrow and clotting systems, brain and neurological system, gastrointestinal system.
- Therapeutic complications may also put patients at risk for osteoporosis, diabetes, arteriosclerosis and heart disease.

### Other Disease Associations

- Called "the great imitator," SLE may be misdiagnosed as infection, JRA, multiple sclerosis, fibromyalgia or Lyme disease.

## Lyme Disease

- Residency in, or exposure to, deer-tick-infested regions
- Flu-like symptoms, bull's-eye rash, rapid onset arthritis

### Laboratory Findings

- Positive Lyme titer and positive Western blot; elevated ESR and white blood cell counts

### Complications

- Chronic arthritis, Bell's palsy and neurologic involvement
- Unresponsiveness to antibiotic therapy may indicate other infection, JRA, malignancy, or psychogenic disorder.

## Raynaud's Phenomenon

- More common in girls than boys;
- Often associated with underlying rheumatologic disease

### Symptoms

- Cold hands; three-phase color change in fingers: fingertips turn white, then blue, then red on rewarming

### Laboratory Findings

- Positive ANA, positive RF, anticardiolipin antibodies, elevated ESR, or abnormal nail bed capillaries warrant further investigation for underlying disease.

### Complications

- May involve toes, ear lobes, tip of nose. May indicate underlying connective tissue disease.
- When present with shortness of breath, Raynaud's phenomenon may indicate scleroderma; positive ANA may point to SLE; presence of anticardiolipin antibodies may indicate anticardiolipin antibody syndrome. Abnormal nail bed capillaries may indicate SLE, scleroderma, dermatomyositis or mixed connective tissue disease.

## Henoch-Schoenlein Purpura

- Twice as common in boys as girls
- Rash that usually begins with red hives or bumps, then changes to purplish bruise; arthritis; abdominal pain; fever

### Laboratory Findings

- Normal or elevated ESR or C-reactive protein; urinalysis may reveal hematuria or proteinuria.

### Complications

- Kidney involvement and, in rare instances, renal failure; gastrointestinal involvement and, much less commonly, intussusception.
- Presence of antibody pANA points to inflammatory bowel disease or microscopic polyangiitis; can point to Wegener's granulomatosis or related vasculitides.
CHAM in the Media

The Children’s Hospital at Montefiore is frequently in the media spotlight for its cutting-edge research, outstanding medical programs and world-renowned physicians.

CNN, NY 1, MY 9 TV, Fox, CBS, etc.

**CHAM HEART SURGEON DONATES LIFESAVING BLOOD DURING COMPLEX SURGERY**

Samuel Weinstein, MD, a pediatric cardiothoracic surgeon at CHAM, had to take a break from a mercy-mission operation in El Salvador so he could donate his own rare type blood for his 8-year-old patient.

**NEW STUDY INDICATES THAT WEEKDAY TELEVISION OR VIDEO GAMES HURT SCHOOLING**

CHAM physician Iman Sharif, MD, co-authored a study that proves that middle school students who watch TV or play video games during the week do worse in school, although weekend viewing and gaming don’t affect school performance much.

**CELEBRITY JEOPARDY, NBC**

**BIG WIN FOR CHAM & LAW & ORDER: SVU**

Chris Meloni, the *Law & Order: SVU* star, won Celebrity Jeopardy on Nov. 11 and will split his winnings with CHAM’s Child Advocacy Center and the Big Apple Circus. He chose the Child Advocacy Center because it helps the types of people portrayed on “SVU”.

CNN, NBC-TV 4, CBS-TV 2, ABC-TV 7, CBS Early Show, 1010 WINS, News 12, etc.

**CHAM SURGICAL TEAM PERFORMS A RARE TUMOR OPERATION FOR 9/11 VICTIM’S SON**

A team of five CHAM surgeons stopped a tumor from crushing 6-year-old Aiden Fraser’s spine. This marathon operation was a two-stage procedure that removed deformed bones in the child’s neck that had been crushed by a tumor. The surgeons then replaced them with healthy bones taken from the child’s ribs.

Chicago Tribune, San Francisco Chronicle, Connecticut Post, Daily News, etc.