

Selections from international journals

Nahla M. Heshmat

Professor of Pediatrics, Ain Shams University

World Allergy Organ J. 2019;12(3):100018

X-linked agammaglobulinemia (XLA):Phenotype, diagnosis, and therapeutic challenges around the world.

El-Sayed ZA, Abramova I, Aldave JC, Al-Herz W, Bezrodnik L, Boukari R, Bousfiha AA, Cancrini C, Condino-Neto A, Dbaibo G, Derfalvi B, Dogu F, Edgar JDM, Eley B, El-Owaidy RH, Espinosa-Padilla SE, Galal N, Haerynck F, Hanna-Wakim R, Hossny E, Ikinociogullari A, Kamal E, Kanegane H, Kechout N, Lau YL, Morio T, Moschese V, Neves JF, Ouederni M, Paganelli R, Paris K, Pignata C, Plebani A, Qamar FN, Qureshi S, Radhakrishnan N, Rezaei N, Rosario N, Routes J, Sanchez B, Sediva A, Seppanen MR, Serrano EG, Shcherbina A, Singh S, Siniah S, Spadaro G, Tang M, Vinet AM, Volokha A, Sullivan KE.

BACKGROUND: X-linked agammaglobulinemia is an inherited immunodeficiency recognized since 1952. In spite of seven decades of experience, there is still a limited understanding of regional differences in presentation and complications. This study was designed by the Primary Immunodeficiencies Committee of the World Allergy Organization to better understand regional needs, challenges and unique patient features. **METHODS:** A survey instrument was designed by the Primary Immunodeficiencies Committee of the World Allergy Organization to collect both structured and semi-structured data on X-linked agammaglobulinemia. The survey was sent to 54 centers around the world chosen on the basis of World Allergy Organization participation and/or registration in the European Society for Immunodeficiencies. There were 40 centers that responded, comprising 32 countries. **RESULTS:** This study reports on 783 patients from 40 centers around the world. Problems with diagnosis are highlighted by the reported delays in diagnosis >24 months in 34% of patients and the lack of genetic studies in 39% of centers. Two infections exhibited regional variation. Vaccine-associated paralytic poliomyelitis was seen only in countries with live polio vaccination and two centers reported mycobacteria. High rates of morbidity were reported. Acute and chronic lung diseases accounted for 41% of the deaths. Unusual complications such as inflammatory bowel disease and large granular lymphocyte disease, among others were specifically enumerated, and while individually uncommon, they were collectively seen in 20.3% of patients. These data suggest that a broad range of both inflammatory, infectious, and autoimmune conditions can occur in patients. The breadth of complications and lack of data on management subsequently appeared as a significant challenge reported by centers. Survival above 20 years of age was lowest in Africa (22%) and reached above 70% in Australia, Europe and the Americas. Centers were asked to report their challenges and responses (n=116) emphasized the difficulties in access to immunoglobulin products (16%) and reflected the ongoing need for education of both patients and referring physicians. **CONCLUSIONS:** This is the largest study of patients with X-linked agammaglobulinemia and emphasizes the continued morbidity and mortality of XLA despite progress in diagnosis and treatment. It presents a world view of the successes and challenges for patients and physicians alike. A pivotal finding is the need for education of physicians regarding typical symptoms suggesting a possible diagnosis of X-linked agammaglobulinemia and sharing of best practices for the less common complications.

Allergy. 2019;74(6):1125-1134.

Safety and reproducibility of nasal allergen challenge.

Eguiluz-Gracia I, Testera-Montes A, González M, Pérez-Sánchez N, Ariza A, Salas M, Moreno-Aguilar C, Campo P, Torres MJ, Rondon C.

BACKGROUND: The nasal allergen challenge (NAC) is a useful tool for the diagnosis of allergic rhinitis (AR) and local allergic rhinitis (LAR) and might serve to design and monitor allergen immunotherapy. Nevertheless, data about its safety and reproducibility are scarce. **OBJECTIVE:** To investigate the safety and reproducibility of NAC in pediatric and adult rhinitis patients with/without asthmatic symptoms, and in healthy controls. **METHODS:** A retrospective evaluation of the NACs conducted in our Unit for 2005-2017 and monitored by acoustic rhinometry and nasal-ocular symptoms was performed to analyze the safety of two methods for allergen application (metered spray & micropipette) and NAC protocols (NAC with single or multiple allergens/session [NAC-S & NAC-M]). The adverse events (AEs), spirometry values, and rescue medication required for AE were recorded. The reproducibility was examined by a prospective analysis of three repeated NAC-S performed at 1-2-

month interval in AR, LAR and nonallergic rhinitis patients, and in healthy controls. RESULTS: A total of 11 499 NACs were performed in 518 children and 5830 adults. Only four local AE occurred, and 99.97% of NACs were well tolerated. The reproducibility and positive and negative predictive values of three consecutive NAC-S performed in 710 subjects were 97.32%, 100%, and 92.91%, respectively. There were no false-positive results in the 710 analyzed subjects. Safety and reproducibility were comparable between the methods of allergen application and the rhinitis phenotypes. CONCLUSION: The NAC is a safe and highly reproducible diagnostic test ready to be used in the clinical practice in both children and adults with or without asthma.

J Allergy Clin Immunol Pract. 2019;7(6):1803-1812.

Lung lavage granulocyte patterns and clinical phenotypes in children with severe, therapy-resistant asthma.

Teague WG, Lawrence MG, Shirley DT, Garrod AS, Early SV, Payne JB, Wisniewski JA, Heymann PW, Daniero JJ, Steinke JW, Froh DK, Braciale TJ, Ellwood M, Harris D, Borish L.

BACKGROUND: Children with severe asthma have frequent exacerbations despite guidelines-based treatment with high-dose corticosteroids. The importance of refractory lung inflammation and infectious species as factors contributing to poorly controlled asthma in children is poorly understood. OBJECTIVE: To identify prevalent granulocyte patterns and potential pathogens as targets for revised treatment, 126 children with severe asthma underwent clinically indicated bronchoscopy. METHODS: Diagnostic tests included bronchoalveolar lavage (BAL) for cell count and differential, bacterial and viral studies, spirometry, and measurements of blood eosinophils, total IgE, and allergen-specific IgE. Outcomes were compared among 4 BAL granulocyte patterns. RESULTS: Pauci-granulocytic BAL was the most prevalent granulocyte category (52%), and children with pauci-granulocytic BAL had less postbronchodilator airflow limitation, less blood eosinophilia, and less detection of BAL enterovirus compared with children with mixed granulocytic BAL. Children with isolated neutrophilia BAL were differentiated by less blood eosinophilia than those with mixed granulocytic BAL, but greater prevalence of potential bacterial pathogens compared with those with pauci-granulocytic BAL. Children with isolated eosinophilia BAL had features similar to those with mixed granulocytic BAL. Children with mixed granulocytic BAL took more maintenance prednisone, and had greater blood eosinophilia and allergen sensitization compared with those with pauci-granulocytic BAL. CONCLUSIONS: In children with severe, therapy-resistant asthma, BAL granulocyte patterns and infectious species are associated with novel phenotypic features that can inform pathway-specific revisions in treatment. In 32% of children evaluated, BAL revealed corticosteroid-refractory eosinophilic infiltration amenable to anti-TH2 biological therapies, and in 12%, a treatable bacterial pathogen.

Ann Allergy Asthma Immunol. 2019;123(3):284-287.

Systemic reactions to subcutaneous immunotherapy. Effects of dosing and aeroallergen content.

Mustafa S, Bingemann T, Blue H, Conn K, Hanley T, Ramsey A.

Background: Systemic reactions are a known risk of subcutaneous immunotherapy (SCIT) for aeroallergens. Objective: To identify the dose of SCIT that results in the most systemic reactions to SCIT (SCITSRs) and other risk factors for SCITSRs. Methods: We performed a retrospective review of all SCIT encounters from 2013 to 2017 at a multisite allergy/immunology practice. SCITSRs were identified from the electronic health record through immunotherapy encounters in which epinephrine was administered. Collected data included patient demographics, the dose of immunotherapy at the time of the SCITSR, the presence or absence of asthma, and aeroallergen content. The control group was generated randomly from the same cohort during the same period. Results: There were 86,949 SCIT visits, with 81 SCITSRs (0.9 per 1000 injections). A total of 77.8% of reactions occurred at a dose of 1:1 0.1 mL and above. The presence of cat (81.5% vs 63.0%, $P = .01$), dog (67.9% vs 37.0%, $P < .001$), and grass extracts (85.2% vs 67.5%, $P = .01$) were associated with SCITSRs. Asthma was not significantly associated with SCITSRs. The presence of dust mites, trees, weeds, and molds was not associated with SCITSRs. There were no months or seasons where SCITSRs were more likely to occur. Individuals who experienced SCITSRs had a mean (SD) higher number of included aeroallergenic groups compared with controls (5.86 [1.88] vs 5.00 [1.92], $P < .001$). Conclusion: Risk factors for SCITSRs in a multisite allergy/immunology practice included administration of the highest immunotherapy doses; inclusion of cat, dog, and grass extracts; and the number of aeroallergenic groups included in the extract. This information helps further characterize risk for patients receiving SCIT.