# Immune-mediated hepatitis: Basic concepts and treatment

**Free article**

## Abstract

Immunotherapy with immune checkpoint inhibitors (ICIs) has revolutionized advanced cancer management. Nevertheless, the generalized use of these medications has led to an increase in the incidence of adverse immune-mediated events and the liver is one of the most frequently affected organs. Liver involvement associated with the administration of immunotherapy is known as immune-mediated hepatitis (IMH), whose incidence and clinical characteristics have been described by different authors. It often presents as mild elevations of amino transferase levels, seen in routine blood tests, that spontaneously return to normal, but it can also manifest as severe transaminitis, possibly leading to the permanent discontinuation of treatment. The aim of the following review was to describe the most up-to-date concepts regarding the epidemiology, diagnosis, risk factors, and progression of IMH, as well as its incidence in different types of common cancers, including hepatocellular carcinoma. Treatment recommendations according to the most current guidelines are also provided.

**Keywords:**DILI; Drug-induced liver injury (DILI); Hepatitis inmunomediada; Immune checkpoint inhibitors; Immune-mediated hepatitis; Immunotherapy; Inhibidores de puntos de control inmunitario; Inmunoterapia; Tratamiento; Treatment.

The Glasgow Coma Scale: 50-year anniversary

## Abstract

In 1974, Sir Graham Teasdale and Bryan Jennett wrote the "Assessment of coma and impaired consciousness, A practical scale," which has become one of the most influential papers in the history of traumatic brain injury, with more than 10,000 citations as of January 2024. Today, it is one of the most widely used tools in emergency departments, providing a reliable general overview of the patient's consciousness status.

**Keywords:**Consciousness; Glasgow Coma Scale; History; Traumatic brain injury.

# TRAPPC11-CDG muscular dystrophy: Review of 54 cases including a novel patient

## Abstract

The trafficking protein particle (TRAPP) complex is a multisubunit protein complex that functions as a tethering factor involved in intracellular trafficking. TRAPPC11, a crucial subunit of this complex, is associated with pathogenic variants that cause a spectrum of disease, which can range from a limb girdle muscular dystrophy (LGMD) to developmental disability with muscle disease, movement disorder and global developmental delay (GDD)/intellectual disability (ID), or even a congenital muscular dystrophy (CMD). We reviewed the phenotype of all reported individuals with TRAPPC11-opathies, including an additional Mexican patient with novel compound heterozygous missense variants in TRAPPC11 (c.751 T > C and c.1058C > G), restricted to the Latino population. In these 54 patients muscular dystrophy signs are common (early onset muscle weakness, increased serum creatine kinase levels, and dystrophic changes in muscle biopsy). They present two main phenotypes, one with a slowly progressive LGMD with or without GDD/ID (n = 12), and another with systemic involvement characterized by short stature, GDD/ID, microcephaly, hypotonia, poor speech, seizures, cerebral atrophy, cerebellar abnormalities, movement disorder, scoliosis, liver disease, and cataracts (n = 42). In 6 of them CMD was identified. Obstructive hydrocephaly, retrocerebellar cyst, and talipes equinovarus found in the individual reported here has not been described in TRAPPC11 deficiency. As in previous patients, membrane trafficking assays in our patient showed defective abnormal endoplasmic reticulum-Golgi transport as well as decreased expression of LAMP2, and ICAM-1 glycoproteins. This supports previous statements that TRAPPC11-opathies are in fact a congenital disorder of glycosylation (CDG) with muscular dystrophy.

**Keywords:**CDG; CMD; Congenital muscular dystrophy; Glycosylation; Hydrocephaly; LGMD; Retrocerebellar cyst; Talipes equinovarus.

Red Meat Hypersensitivity and Probable Alpha-Gal Syndrome: Prevalence Among Adolescents

## Abstract

**Introduction:**It is unknown whether late adolescents represent a particular risk group for the development of red meat hypersensitivity (RMH) and alpha-gal syndrome (AGS). This age group's physiological changes and eating habits could play a determining role. This study aimed to estimate the self-reported prevalence of RMH and probable AGS among late adolescents.

**Methods:**A cross-sectional study analyzed a sample of 1992 Mexican adolescents between 15 and 18 years of age. The data were obtained with a previously validated questionnaire that asked about the clinical manifestations related to red meat intake. Confidence intervals at 95% (95% CI) were estimated for proportions.

**Results:**In total, there were 19 adolescents with RMH, a prevalence of 1.0% (95% CI: 0.6-1.5%). The main red meats related to symptoms were pork (89.5%), beef (21.1%), lamb (10.5%), and mutton (5.1%). The most frequent manifestations of RMH were gastrointestinal (73.7%), respiratory (63.2%), and cutaneous (63.2%). Once the symptoms were grouped, there were two cases of urticaria (2/19, 10.5%) and six cases with probable anaphylaxis (6/19, 31.6%). Finally, three adolescents were considered probable cases of AGS, which represents a prevalence of 0.15% (95% CI: 0.1-0.4%).

**Conclusion:**Although the prevalence of RMH in late adolescents is low, early detection is justified because approximately one-third present with severe symptoms.

**Keywords:**adolescence; alpha-gal allergy; alpha-gal syndrome; prevalence; red meat allergy.

# Knowing the ropes of vasopressor dosing: a focus on norepinephrine

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# Comprehensive study reveals phenotypic heterogeneity in Klebsiella pneumoniae species complex isolates

## Abstract

Here, we conducted a comprehensive analysis of 356 Klebsiella pneumoniae species complex (KpSC) isolates that were classified as classical (cl), presumptive hypervirulent (p-hv) and hypermucoviscous-like (hmv-like). Overall, K. pneumoniae (82.3%), K. variicola (2.5%) and K. quasipneumoniae (2.5%) were identified. These isolates comprised 321 cl-KpSC, 7 p-hv-KpSC and 18 hmv-like-KpSC. A large proportion of cl-KpSC isolates were extended-spectrum-β-lactamases (ESBLs)-producers (64.4%) and 3.4% of isolates were colistin-resistant carrying carbapenemase and ESBL genes. All p-hv-KpSC showed an antibiotic susceptible phenotype and hmv-like isolates were found to be ESBL-producers (8/18). Assays for capsule production and capsule-dependent virulence phenotypes and whole-genome sequencing (WGS) were performed in a subset of isolates. Capsule amount differed in all p-hv strains and hmv-like produced higher capsule amounts than cl strains; these variations had important implications in phagocytosis and virulence. Murine sepsis model showed that most cl strains were nonlethal and the hmv-like caused 100% mortality with 3 × 108 CFUs. Unexpectedly, 3/7 (42.9%) of p-hv strains required 108 CFUs to cause 100% mortality (atypical hypervirulent), and 4/7 (57.1%) strains were considered truly hypervirulent (hv). Genomic analyses confirmed the diverse population, including isolates belonging to hv clonal groups (CG) CG23, CG86, CG380 and CG25 (this corresponded to the ST3999 a novel hv clone) and MDR clones such as CG258 and CG147 (ST392) among others. We noted that the hmv-like and hv-ST3999 isolates showed a close phylogenetic relationship with cl-MDR K. pneumoniae. The information collected here is important to understand the evolution of clinically important phenotypes such as hypervirulent and ESBL-producing-hypermucoviscous-like amongst the KpSC in Mexican healthcare settings. Likewise, this study shows that mgrB inactivation is the main mechanism of colistin resistance in K. pneumoniae isolates from Mexico.

**Keywords:**Capsule; Colistin-resistance; Hypermucoviscosity; Plasmids; Virulence.

# Identification of Providencia spp. clinical isolates co-producing carbapenemases IMP-27, OXA-24, and OXA-58 in Mexico

## Abstract

Providencia rettgeri, belonging to the genus Providencia, had gained significant interest due to its increasing prevalence as a common pathogen responsible for healthcare-associated infections in hospitals. P. rettgeri isolates producing carbapenemases have been reported to reduce the efficiency of carbapenems in clinical antimicrobial therapy. However, coexistence with other resistance determinants is rarely reported. The goal of this study was the molecular characterization of carbapenemase-producing Providencia spp. clinical isolates. Among 23 Providencia spp. resistant to imipenem, 21 were positive to blaNDM-1; one positive to blaNDM-1 and blaOXA-58 like; and one isolate co-producing blaIMP-27, blaOXA-24/40 like, and blaOXA-58 like were identified. We observed a low clonal relationship, and the incompatibility groups Col3M and ColRNAI were identified in the plasmid harboring blaNDM-1. We report for the first time a P. rettgeri strain co-producing blaIMP-27, blaOXA-24-like, and blaOXA-58 like. The analysis of these resistance mechanisms in carbapenemase co-producing clinical isolates reflects the increased resistance.

**Keywords:**Carbapenemase; IMP; Incompatibility; NDM; Providencia

**Acute promyelocytic leukemia with *PML/RARA* (bcr1, bcr2 and bcr3) transcripts in a pediatric patient**

## Abstract

Patients with acute promyelocytic leukemia (APL) exhibit the t(15;17)(q24.1;q21.2) translocation that produces the promyelocytic leukemia (*PML*)/retinoic acid receptor α (*RARA*) fusion gene. Different *PML* breakpoints yield three alternative molecular transcripts, bcr1, bcr2 and bcr3. The present study reports the simultaneous presence of three *PML/RARA* transcripts in a pediatric female patient diagnosed with APL, according to the clinical characteristics, immunophenotype and karyotype of the patient. The simultaneous presence of the *PML/RARA* transcripts were detected using reverse transcription-quantitative PCR (RT-qPCR). This was confirmed with HemaVision-28N Multiplex RT-qPCR, HemaVision-28Q qualitative RT-qPCR and the AmpliSeq RNA Myeloid Panel. To the best of our knowledge, the pediatric patient described in the present study is the first case found to exhibit all three PML/RARA transcripts (bcr1, bcr2 and bcr3). Additionally, a microarray analysis was performed to determine the expression profile, potential predictive biomarkers and the implications of this uncommon finding. According to the information obtained from molecular monitoring, the results reported in the present study were associated with a good patient prognosis. In addition, upregulated genes that are rare in acute myeloid leukemia were identified, and these genes may be promising diagnostic biomarkers for further study. For example, CCL-1 is present in leukemic stem cells, causing treatment failure and relapse, and α- and β-defensins have been reported exclusively in chronic myeloid leukemia. However, the results of the present study confirmed that they may also be present in APL. Thus, these findings suggested a possible signaling pathway that involves the PML/RARA oncoprotein in APL.

**Keywords:**acute promyelocytic leukemia; bcr1; bcr2; bcr3; pediatric.

***PTCH1* Gene Variants, mRNA Expression, and Bioinformatics Insights in Mexican Cutaneous Squamous Cell Carcinoma Patients**

## Abstract

**Background:**Skin cancer is one of the most frequent types of cancer, and cutaneous squamous cell carcinoma (cSCC) constitutes 20% of non-melanoma skin cancer (NMSC) cases. *PTCH1*, a tumor suppressor gene involved in the Sonic hedgehog signaling pathway, plays a crucial role in neoplastic processes.

**Methods:**An analytical cross-sectional study, encompassing 211 cSCC patients and 290 individuals in a control group (CG), was performed. A subgroup of samples was considered for the relative expression analysis, and the results were obtained using quantitative real-time PCR (qPCR) with TaqMan® probes. The functional, splicing, and disease-causing effects of the proposed variants were explored via bioinformatics.

**Results:**cSCC was predominant in men, especially in sun-exposed areas such as the head and neck. No statistically significant differences were found regarding the rs357564, rs2236405, rs2297086, and rs41313327 variants of *PTCH1*, or in the risk of cSCC, nor in the mRNA expression between the cSCC group and CG. A functional effect of rs357564 and a disease-causing relation to rs41313327 was identified.

**Conclusion:**The proposed variants were not associated with cSCC risk in this Mexican population, but we recognize the need for analyzing larger population groups to elucidate the disease-causing role of rare variants.

**Keywords:**PTCH1; bioinformatics; cutaneous squamous cell carcinoma; genetic variants; mRNA; non-melanoma skin cancer; skin cancer.

**International Society of Paediatric Oncology (SIOP) Global Mapping Programme: Latin American Society of Pediatric Oncology (SLAOP) country-level report**

## Abstract

**Background:**Latin American countries are improving childhood cancer care, showing strong commitment to implement the Global Initiative for Childhood Cancer, but there are scant publications of the situation at a continental level.

**Methods:**As part of the International Society of Paediatric Oncology Global Mapping project, delegates of each country participating in the Latin American Society of Pediatric Oncology (SLAOP) and chairs of national pediatric oncology societies and cooperative groups were invited to provide information regarding availability of national pediatric cancer control programs (NPCCP), pediatric oncology laws, pediatric oncology tumor registries, and training programs and support to diagnosis and treatment.

**Results:**Nineteen of the 20 countries participating in SLAOP responded. National delegates reported nine countries with NPCCP and four of them were launched in the past 5 years. National pediatric tumor registries are available in eight countries, and three provided published survival results. Fellowship programs for training pediatric oncologists are available in 12 countries. National delegates reported that eight countries provide support to most essential diagnosis and treatments and 11 provide partial or minimal support that is supplemented by civil society organizations. Seven countries have a pediatric oncology law. There are three international cooperative groups and four national societies for pediatric oncology.

**Conclusion:**Despite many challenges, there were dramatic advances in survivorship, access to treatment, and availability of NPCCP in Latin America. Countries with highest social development scores in general provide more complete support and are more likely to have NPCCP, training programs, and reported survival results.

**Keywords:**International Society of Pediatric Oncology (SIOP); Latin America; health services; mapping.