Alisha Mavis, MD
Pediatric Hepatologist; Levine Children's Hospital, Atrium Health, Charlotte, NC

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Alagille Syndrome

Alagille syndrome (ALGS) is a multiorgan, systemic syndrome characterized by impaired bile duct function leading to chronic cholestasis, as well as cardiac and vascular abnormalities, vertebral abnormalities, and ocular changes.[1,2] Patients may have all or some combination of these characteristic defects. ALGS is an inherited, autosomal dominant syndrome caused by mutations in genes that regulate the NOTCH signaling pathway; approximately 90% of ALGS is related to pathogenic variants in *JAG1*, with most of the remainder having variants in *NOTCH2*.[2,3] Additional variants and mutations are being identified with genome and next-generation sequencing, and as yet unidentified variants may be present in patients who are clinically diagnosed but genetically negative.[4,5] The variants result in aberrant and inadequate hepatic bile duct development (bile duct paucity); however, NOTCH signaling is also integral to healthy structural development of the heart, kidneys, spine, facial bone structure, and blood vessels.[1]

ALGS is a rare syndrome with an estimated incidence of 1/30,000-50,000 live births; genetic testing will likely refine this estimate.[1] The long-term risks associated with ALGS include progressive liver injury and need for liver transplant, cardiovascular disease, impaired growth, ocular disturbances, vascular complications, and decreased renal function. ALGS is highly variable, ranging from no apparent clinical involvement to severe disease that requires liver transplant.[1] Several natural history studies have shown that elevated bilirubin (≥5.0 mg/dL) in infancy (age 6-12 months) is associated with higher risk for hepatic complications.[1,2,6]

Diagnosis and Challenges

Diagnosis is challenged by the variety of symptoms and heterogeneous phenotypes of ALGS, with some patients having silent disease and others exhibiting severe symptoms at diagnosis.[7] In one review of available data, age at ALGS presentation varied from less than 4 months to 10 years, with most children being diagnosed before 12 months of age.[1] In ALGS, infants typically present with evidence of cholestasis within 3 months of birth. Over time, symptoms of persistent jaundice, poor early childhood growth, xanthomas, and—especially—intense pruritus develop. Cholestasis in infants or children often triggers a workup for ALGS. I find that children without liver symptoms typically are not diagnosed until they are older.

The diagnostic criteria for ALGS includes structural or physical changes in multiple organ systems and laboratory testing suggestive of the disease; genetic testing is not required to make a diagnosis. Hepatic, cardiac, ocular, craniofacial, and skeletal abnormalities are highly prevalent with ALGS, with at least one found in ≥87% of patients; up to 100% of patients have bile duct paucity.[7-9] Recently revised criteria for clinical diagnosis of ALGS require ≥4 of these abnormalities in the absence of genetic confirmation **(Table 1)**.[7] Genetic testing with a multigene panel that includes *JAG1* and *NOTCH2* can be used.[3] In my experience, clinical diagnosis often can be made and medical treatment initiated while waiting for results of laboratory or genetic testing—which may take weeks. With genetic testing, biopsy is no longer a necessity.[3] Liver and kidney function tests, lipid levels (generally elevated in ALGS), and levels of fat-soluble vitamins (generally lower in ALGS) are part of the workup. Imaging tests include spine radiograph, echocardiogram, and abdominal ultrasound.[9] The differential diagnosis includes infectious as well as other hepatobiliary diseases, such as α1-antitrypsin deficiency and biliary atresia.

Intense pruritus associated with ALGS is related to cholestasis and differs from immune-mediated pruritus seen in childhood, such as eczema and atopic dermatitis. It is almost universally present through childhood and into adulthood **(Figure 1)**.[1,2] To improve diagnosis, pediatricians should know to recognize symptoms—such as jaundice, xanthomas, and poor growth, as well as nonresponse to eczema therapies—that suggest a hepatic source of the itch. Redness and edema, intrinsic to histaminic pruritus, generally are absent in cholestatic pruritus.[10] In

Table 1. Revised Diagnostic Criteria for Diagnosis of ALGS

NOTE:
- ≥4 major criteria are required for the diagnosis of ALGS
- With family history of ALGS, presence of *JAG1* mutation is diagnostic, even if none of these criteria are present
- If either genetic mutation or family history is positive, at least 1 major criterion is needed to make the diagnosis

Major Criteria: Organ System (% of Involvement)	**Most Common Findings**
Hepatic (75-100%)	Bile duct paucity, cholestasis
Cardiac/vascular (85-98%)	Peripheral pulmonary artery stenosis; intracranial or intra-abdominal aneurysm
Skeletal (33-87%)	"Butterfly" vertebrae
Renal (19-73%)	Anomalies in renal tubules
Ocular (56-88%)	Posterior embryotoxon—grayish circle in posterior cornea
Facial structure (70-98%)	Broad forehead, deep-set eyes, pointed chin

Adapted from Menon (2022).[7]

the GALA natural history study, 95% had neonatal cholestasis and 74% developed pruritis (n = 761/1028), with a median age at onset at 12 months. Xanthomas developed in 24% (n=243/980), with median age at onset of 25 months.[6]

Management of ALGS

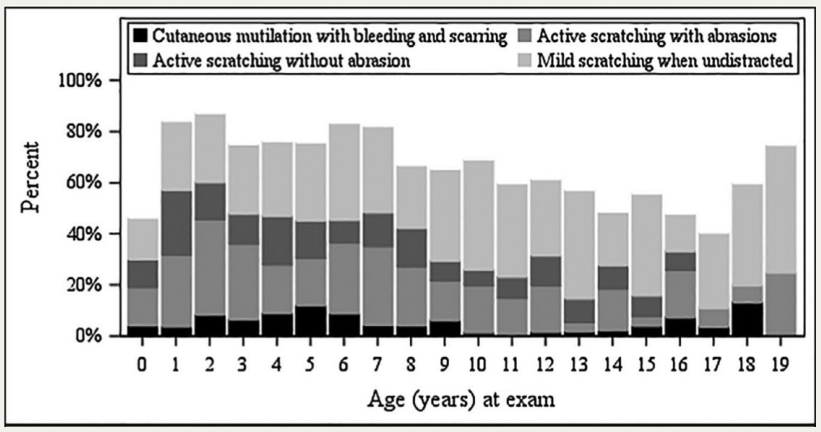
Because of its many manifestations, ideal management of ALGS requires a multidisciplinary approach with coordination between hepatology, cardiology, and renal specialists and open communication with pediatricians and the child's other healthcare providers. Although the pediatrician seems to be centrally located for coordinating, in my experience, hepatology is the medical home for these families. My practice coordinates follow-up for appointments, school performance, additional testing, and symptom management. Some patients stay with us throughout their college years.

Over the long term, the impact of ALGS on liver health is a deep concern, but in the daily life of patients and families, managing cholestatic pruritus has the most immediate impact in terms of improving quality of life. In my practice, pruritus usually has the greatest impact on daily life, appears to be the most debilitating, and is the one symptom that almost all families and patients complain about. My philosophy when speaking with families is to focus first and foremost on current symptoms and to manage those—pruritus, then perhaps growth and nutrition, then long-term liver health as needed. Of available medical therapies for ALGS, choleretic agents are typically the first choice to manage cholestasis and can decrease bile-related hepatotoxicity.[11]

Unresolved pruritus is the most bothersome and often most difficult symptom to manage. It undermines sleep for both the child and the family and, when the child reaches older ages, can affect educational and social development. Pruritus often improves when biochemical markers of cholestasis improve, offering one pathway to treatment.[2] Class of therapies approved to treat ALGS/cholestatic pruritus are summarized in **Table 2**.[7,11]

Fat metabolism and absorption of fat-soluble vitamins are altered in ALGS. These should be addressed and can contribute to malnutrition. Diets should be high in carbohydrates (40%-60%) and fats (30%-50%), with medium-chain triglycerides making up 30% of fats. Vitamins A, D, E, and K should be augmented to achieve healthy levels.[7] Patients should have regular follow-up with pediatric cardiology, neurology, nephrology, and ophthalmology. Children will need to be followed into adulthood and transitioned to adult care, an area of intense research that is still evolving.

Figure 1. Prevalence and Severity of Pruritus Among Patients With ALGS Over Time



Adapted from Kamath (2020).[2]

Table 2. Medical Treatment of Cholestatic Pruritus in ALGS

Class	Mechanism of Action
Choleretic agent	Protects liver and bile ducts; typical first-line medical therapy in ALGS; limited effect on pruritus
Bile acid sequestrant	• Approved for cholestatic pruritus in adults • Minimally effective in ALGS, where lack of bile acids is characteristic; may impede fat-soluble vitamin absorption
Antimicrobial	Induces 6 alpha-hydroxylation of bile cells; mechanism in cholestatic pruritus unclear; side effects include nausea, hepatitis risk
Opioid antagonist	Not approved for pediatric use
Selective serotonin-reuptake inhibitor	Minimal data in ALGS suggest it is effective, but side effects may be limiting
Ileal bile acid transport inhibitors	• Approved for cholestatic pruritus in patients ≥3 months • Approved for cholestatic pruritus in patients ≥12 months
Antihistamine	Limited efficacy due to different pruritus triggers in ALGS than other childhood pruritus

Adapted from Menon (2022),[7] and Rodrigo(2023)[11]

Families and ALGS

A family-centered approach is crucial to successful management, as all family members are affected and may participate in the patient's care. In my experience, families need large-scale education about the syndrome and management, and the pediatric hepatology team provides most of it. The pediatric hepatology team also provides support and direction on where to find information. In general, I find that resources for families are lacking. One excellent resource is the Alagille Syndrome Alliance, where families can share experiences as well as learn about the syndrome and its management.

Parents may wonder about their other current or future children and ALGS risk. Genetic tests may be used to screen family members of patients for existing disease or risk for future children, with genetic counseling to provide context.[3]

Awareness of ALGS can facilitate timely diagnosis, with the caveat that different children present with different symptoms that require individualized, stepwise approaches. Unfortunately, with current knowledge we cannot predict the disease course for any individual child. We only know that over time some percentage will require a transplant, but there is no way to predict when or whether that will occur. I try to keep families in the present and assure them that we will deal with symptoms as they arise. It is important to urge them to live in the here and now with their children. My approach is to emphasize to each family that their job is to love and care for their child as they would any other child, as a healthy child, and to allow their child to participate in life and not have their syndrome define them.

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