OPEN

Systematic Review: The Epidemiology, Natural History, and Burden of Alagille Syndrome

*Binita M. Kamath, †Alastair Baker, ‡Roderick Houwen, §Lora Todorova, and ¶Nanda Kerkar

ABSTRACT

Background and Aim: Alagille syndrome (ALGS) is an inherited multisystem disorder typically manifesting as cholestasis, and potentially leading to end-stage liver disease and death. The aim of the study was to perform the first systematic review of the epidemiology, natural history, and burden of ALGS with a focus on the liver component.

Methods: Electronic databases and proceedings from key congresses were searched in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines. This analysis included publications reporting epidemiology, natural history, economic burden or health-related quality of life (HRQoL) outcomes in patients with ALGS.

Results: Of 525 screened publications, 20 met the inclusion criteria. Liver-related features included cholestasis (87%–100% of patients), jaundice (66%–85%), and cirrhosis (44%–95%). Between 15% and 47% of patients underwent liver transplantation and 4% to 14% received partial biliary diversion. Pruritus affected the majority of patients (59%–88%, of whom up to 45% had severe pruritus) and manifested during the first 10 years of life. Children with ALGS had significantly impaired HRQoL compared with healthy controls and those with other diseases. Itching was the symptom that most affected children with ALGS. No study assessed the economic burden of ALGS.

Conclusions: Our findings consolidate information on the clinical course of ALGS, and highlight gaps in knowledge, most notably the absence of any research on the economic consequences of the disease. Further research is needed to establish the incidence of genetically confirmed ALGS. Disease-specific tools are also needed to improve the measurement of symptoms, such as itching, and better understand the impact of ALGS on HRQoL.

Key Words: Alagille syndrome, cholestasis, cholestatic liver disease, clinical burden of illness, health-related quality of life, natural history, pediatric hepatology, pruritus, syndromic bile duct paucity

(*JPGN* 2018;67: 148–156)

What Is Known

- Alagille syndrome is a rare, inherited childhood disorder typically manifesting as cholestasis, and potentially leading to end-stage liver disease and death.
- Genetic confirmation is necessary because clinical presentation and disease severity are highly variable, with some individuals expressing none of the characteristic features of Alagille syndrome.

What Is New

- Pruritus is particularly burdensome for patients and is not well managed.
- Children with Alagille syndrome have significantly impaired health-related quality of life compared with healthy controls and those with other diseases.
- However, assessment of health-related quality of life and disease symptoms is hampered by the absence of disease-specific tools.
- The incidence of Alagille syndrome needs to be re-evaluated now that genetic confirmation is readily available.
- The economic consequences of Alagille syndrome need to be understood.

Received March 10, 2017; accepted February 24, 2018.

From the *Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, University of Toronto, Toronto, Canada, †Paediatric Liver Centre, King's College Hospital, London, UK, ‡Wilhelmina Children's Hospital, University Medical Centre, Utrecht, Netherlands, §Shire International GmbH, Zug, Switzerland, and ¶Division of Gastroenterology, Hepatology & Nutrition, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, MN and University of Southern California, Los Angeles, CA.

Address correspondence and reprint requests to Binita M. Kamath, MBBChir, MRCP, MTR, Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, University of Toronto, Toronto, Canada (e-mail: binita.kamath@sickkids.ca).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

Research was funded by Shire International GmbH. Under the direction of the authors, Dr Kim Wager, an employee of Oxford PharmaGenesis, provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by Oxford PharmaGenesis. Shire International GmbH provided funding to Oxford PharmaGenesis for support in writing and editing this manuscript.

L.T. is currently in Jazz Pharmaceuticals, Oxford, UK.

B.M.K. has served as a speaker and consultant for Retrophin and has received travel expenses from Shire Pharmaceuticals. A.B. has received research funding from Shire Pharmaceuticals. R.H. has served as a consultant for Albireo. L.T. is an employee of Shire Pharmaceuticals. N.K. has served as an advisory board member for Retrophin and Alexion.

DOI: 10.1097/MPG.0000000000001958

Alagille syndrome (ALGS) is a rare autosomal dominant, multisystem disorder that usually presents in the first 3 months of life (1). Mutations/deletions in 2 genes associated with the Notch signaling pathways are known to cause ALGS: *JAGGED1* (encoding the Notch signaling pathway ligand JAGGED1) in 89% of ALGS cases; and *NOTCH2* (encoding one of the Notch receptors) in a small minority of ALGS cases (2,3). In patients with ALGS, disrupted Notch signaling is associated with the abnormal development of the intrahepatic bile ducts (4).

Clinical features of ALGS were traditionally described as bile duct paucity (an increased portal tract-to-bile duct ratio) associated with chronic cholestasis, cardiovascular abnormalities, butterfly vertebrae, posterior embryotoxon, renal anomalies, vascular involvement, and characteristic facies (1). Expressivity (phenotypic severity) of ALGS is highly variable, ranging from no apparent clinical involvement to severe disease that requires liver transplantation. Indeed severe disease may result in death from vascular accidents, cardiac disease, or liver disease (5). Cholestasis is a common feature of ALGS and typically manifests as cholestasis with unremitting pruritus (6). Progressive liver damage can lead to cirrhosis and end-stage liver disease and may ultimately require liver transplantation.

Although mutations causing ALGS have now been identified, diagnostic challenges remain because there are no genotype-phenotype correlations. Improved understanding of the biology and natural history of disease is required to design new therapies and evaluate their efficacy.

Information on the clinical course of this rare disease has been gained from small studies and analyses of patient records over many years. Accordingly, it is difficult to gauge the true extent and consequence of ALGS or which aspects require further research. We conducted the first systematic review of the literature on the epidemiology, natural history, clinical course, quality-of-life, and economic burden of ALGS to bring together this knowledge and highlight any gaps that may drive future research. Although all the clinical features were covered in our searches and data are presented here, the focus of this report is on the liver-related features of ALGS.

METHODS

Electronic medical databases were searched on 13 May 2015 using the OvidSP search platform:

1. MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946–present
2. Embase 1974–present
3. Orphanet.

Supplemental searches were conducted using the proceedings from 11 congresses, which were chosen by the authors as being most relevant (2012–2015, see Supplementary material, Supplemental Digital Content 1, *http://links.lww.com/MPG/B321*) and manual searches of bibliographic reference lists of reviews and meta-analyses. Following author discussion and testing, 2 search strings were devised using a combination of free-text and Medical Subject Heading (MeSH) terms to explore: ALGS and epidemiology or natural history; and ALGS and quality of life or economic burden (see supporting information). Dates for publication database searches ranged from the start of the records to the present, but were restricted to the last 3 years of conference proceedings. In addition to the major publication databases, Orphanet, a specialist database of orphan disease-specific publications, was searched to ensure comprehensive coverage (see Supplementary Information, Supplemental Digital Content 1, *http://links.lww.com/MPG/B321*). Analysis methods and inclusion criteria were specified in advance and documented in a protocol.

Identified publications were screened manually based on the title and abstract in accordance with 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Abstracts were screened for inclusion by 2 independent reviewers, and in case of uncertainty, by a third reviewer (see Supplementary Methods Tables S1A–C, Supplemental Digital Content 1, *http://links.lww.com/MPG/B321*, for eligibility criteria) and data were manually extracted and categorized as follows: epidemiological, clinical presentation, natural history, health-related quality of life (HRQoL), or economic burden of disease (7).

RESULTS

The electronic searches identified 525 publications. The numbers of publications that were included or excluded are shown in Supplementary Figures S1 and S2 (Supplemental Digital Content 2 and 3, *http://links.lww.com/MPG/B322*, *http://links.lww.com/MPG/B323*).

Thirteen publications reported the clinical features of ALGS; 5 publications described HRQoL, 2 provided incidence estimates, and none presented economic data. Studies exploring the epidemiology/clinical features and HRQoL outcomes of ALGS are summarized in Supplementary Results Table S1 (Supplemental Digital Content 4, *http://links.lww.com/MPG/B324*).

Of the 2 publications reporting incidence data, the first was a prospective study published in 1977 before the advent of genetic testing for ALGS. Of the 790,385 live births in the state of Victoria in Australia, 11 had clinical characteristics consistent with ''intrahepatic biliary atresia'' (ALGS); the authors estimated an incidence of ALGS of approximately 1 in 70,000 live births (8). In 2014, this estimate was revised to 1 in 30,000 to 50,000 live births owing to more recent evidence showing that a notable proportion of individuals with the *JAG1* mutation would not have been diagnosed with ALGS on the basis of clinical characteristics alone (9). The authors of this revised estimate, however, do not provide details of how the new value was calculated.

The clinical presentation of ALGS was assessed in 13 studies (10–22). The age at presentation ranged from less than 16 weeks to 10 years (18,22) with the majority of patients diagnosed within the first year of life (12,13,17,21,22). The presenting features included jaundice (11,12,18), growth retardation or failure to thrive (10–12,16,18,19,21,22), cholestatic disease (10–14,17–19,21), cardiovascular complications (10–13,16–19,21,22), hepatomegaly (11,18,22), splenomegaly (18,22), pruritus (10–13,16,18,19,21), xanthomas (10–13,18,21), abnormal liver function results (10–12,17,18,21,22), abnormal facies (10–13,16,19,21,22), and renal disease (10,12–14,16,21,22). The most commonly presented features are shown in Table 1.

Six publications reported pruritus to be a symptom of patients with ALGS (10–13,18,21). Pruritus was reported in at least 80% of patients in 4 of these 6 publications (10,13,18,21). Of the remaining 2 publications, 1 reported pruritus as a prominent symptom in 70% (11) of patients and 1 reported that 45% of patients were classified as having severe itching; the overall incidence of pruritus was not stated in these papers and neither used a scale to measure severity (12).

Pruritus was first evident 6 to 14 months after birth (10,18) and it developed earlier in children with neonatal jaundice than in those who were not jaundiced (7 vs 14 months, respectively; *P* value was not reported) (18). The 6 publications reporting pruritus indicated that it affected the majority of patients. Four of these publications stated that pruritus manifested at some stage during the

TABLE 1. Summary of the clinical characteristics and common clinical features reported in patients with Alagille syndrome

		Clinical characteristics				Clinical features							
References	n	Study period	Mortality	LT	PEBD	Cardiac murmur	Other CV complications*	PS or PPS	Vertebral anomalies/ Butterfly vertebra	Renal abnormalities	Growth Retardation / Failure to thrive	Posterior embryotoxon	Characteristic facies
Alagille et al (10)	80	1960–1985	26%	NR	NR	85%	85%	70%	87%	74%	50%†	89%	95%
Deprettere et al (11)	27	1973–1983	15%	NR	NR	96%	52%	26%‡	33%	NR	73%†	56%	70%
Emerick et al (12)	92	1974–1997	17%	21%	4%	97%	24%	67%	51%	40%	68%§–87%†	78%	96%
Hoffenberg et al (13)	26	1983–1994	11%	31%	NR	96%	NR	83%	48%	19%	NR	85%	92%
Kamath et al (15)	268	1992–2002	11%	NR	NR	NR	NR	Yes‖	NR	NR	NR	NR	NR
Kamath et al (16)	91	1995–2009	13%–14%¶	100%#	14%	88%	23%	NR	NR	40%	Yes‖	NR	86%
Kamath et al (14)	466	NR	NR	NR	NR	NR	NR	NR	NR	39%	NR	NR	NR
Lykavieris et al (18)	163	1960–2000	35%	27%	NR	NR	53%	NR	NR	NR	Yes‖	NR	NR
Lykavieris et al** (17)	38	1960–2000	Yes‖	37%	NR	63%	NR	NR	NR	NR	NR	NR	NR
Narula et al (19)	41	1989–2004	12%	15%	NR	NR	93%	73%‡	24%	NR	83%§	70%	98%
Nischal et al (20)	20	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	95%	NR
Quiros-Tejeira et al (21)	43	1976–1997/ 1980–1997	28%	47%	NR	98%	2.3%	86%	38%	50%	86%§	73%	98%
Subramaniam et al (22)	117	1980–2005	NR	NR	NR	91%	91%	72%‡	37%–39%	23%	51%†	61%	77%

*Including congenital heart disease and structural intracardiac disease.
†Growth retardation.
‡PPS only.
§Failure to thrive.
‖Overall proportion not reported.
¶Based on 1-year and 5-year survival rates, respectively.
#Patients with liver transplant only included in study.
**Only patients with severe haemorrhagic complications.

ALGS = Alagille syndrome; CHD = congenital heart disease; LT = liver transplantation; n = number of patients with a feature; PEBD = partial external biliary diversion; PPS = peripheral pulmonary stenosis; PS = pulmonary stenosis.

first 10 years of life (10–13,18,21) and that it resolved only in a minority of patients at a median age of 12.5 years (range 4–23 years) (18). For the majority of patients, pruritus, however, persists (10,12,18,23) with varying degrees of severity depending on the therapy received and their adherence to treatment (12,18). One publication reported pruritus as a prominent symptom in 70% of patients, with an onset of 9 days to 2 years (median 6 months) (11).

The presence of bile duct paucity was assessed in 7 publications (10–13,17,21,22) and reported in 75% to 100% (10,17,22) of patients with ALGS. It was reported that the prognosis of liver disease in patients with ALGS is worse in children who present with neonatal jaundice (18) and, in 2 other publications, a positive association between bile duct paucity and increased age was stated (12,21). For a summary of the hepatic abnormalities and secondary comorbidities reported in ALGS see Table 2.

Nine publications reported information on cholestasis (10–13,17–19,21,22). In 3 publications (13,18,21), cholestasis was an inclusion criterion and, in a further 6 publications (10–12,17,19,22), patients could be included whether or not they presented with cholestasis.

In 1 study comparing cholestasis in patients with ALGS to that in patients with biliary atresia, based on laboratory characteristics at baseline, patients with ALGS had higher bilirubin levels and higher pediatric end-stage liver disease scores than age-matched patients with biliary atresia ($P < 0.001$) (16).

Six publications reported the presence of xanthomas (10–13,18,21), which affected 30% to 42% (10,12,18,21) of patients, and appeared at a median of 20 to 48 months of age (10,11). In 3 studies, liver transplant was indicated for xanthomas (13,18,21). Three publications reported moderate improvements in xanthomas after patients had reached the age of 10 years (10,12,18), with 1 publication showing that xanthomas had resolved completely at follow-up (median age: 7 years) in patients who had not experienced neonatal jaundice (18). Xanthomas improved with increasing age or following partial external biliary diversion (PEBD) (12), were associated with severe, prolonged cholestasis and high serum cholesterol and were attenuated by falling serum cholesterol (10). Notably, the presence of xanthomas was found to result in a worse 10–year survival rate than absence of xanthomas in patients with a native liver; numerical results were not, however, reported (18).

Growth impairment, development delay or failure to thrive in patients with ALGS was reported in 8 publications (10–12,16,18,19,21,22), with a prevalence ranging between 50–87% (10,12). Growth parameters such as birth weight, length, and body-mass index (BMI) are often measured against age-appropriate growth charts to check for growth impairment. However, the definition of growth impairment was not defined consistently among the studies, which may account for the wide range in the reported proportions of patients with growth impairment. One publication found the birth weight of 84% of patients with ALGS to be appropriate for gestational age (12), but another publication did not (18). In a study that compared features of patients with and without neonatal jaundice, birth weight was found to be low in 29% of individuals who presented with neonatal jaundice and in 5% of children without neonatal jaundice (18). Another study showed that children with ALGS had greater growth impairment than patients with biliary atresia in terms of height, weight, and BMI z-scores (16).

Ten publications described cardiovascular abnormalities (including congenital heart disease, structural intra-cardiac disease and cardiac murmur) in patients with ALGS (10–13,16–19,21,22), the most common of which was cardiac murmur, reported in 63% to 98% (17,21) of patients. Peripheral pulmonary stenosis was also prevalent, reported in 26% to 73% (11,19,22) of patients. Other common cardiac abnormalities included structural intra-cardiac

TABLE 2. Summary of the hepatic abnormalities and secondary comorbidities reported in patients with Alagille syndrome

		Hepatic abnormalities (n/N [%])			Secondary comorbidities (n/N [%])							
References	n	Cholestasis*	Bile duct paucity†	Cirrhosis	Hypercholesterolaemia	Hepatomegaly	Pruritus	Jaundice	Hypertriglyceridaemia	Splenomegaly	Xanthomas	Oesophageal varices	Hepatocellular carcinoma
All patients with ALGS													
Deprettere et al (11)	27	25/27 (93)	22/27 (81)	NR	25/27 (93)	23/27 (85)	19/27 (70)	21/27 (78)	15/21 (71)	17/27 (63)	8/27 (30)	NR	NR
Emerick et al (12)	92	88/92 (96)	69/81 (85)	7/27 (26)	"Majority of patients"	86/92 (93)	41/92 (45)	80/92 (87)	"Majority of patients"	64/92 (70)	39/92 (42)	NR	0
Narula et al (19)	41	38/41 (93)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Subramaniam et al (22)	117	104/117 (89)	77/103 (75)	NR	52/86 (60)	83/117 (71)	NR	NR	NR	41/117 (35)	NR	NR	NR
Patients with cholestasis only													
Hoffenberg et al (13)	26	26/26 (100)	20/25 (80)	NR	20/24 (83)	NR	23/26 (88)	NR	NR	NR	9/24 (38)	NR	0
Quiros-Tejeira et al (21)	43	43/43 (100)	34/41 (83)	19/20 (95)	35/43 (81)	36/43 (84)	38/43 (88)	NR	23/37 (62)	22/43 (51)	18/43 (42)	NR	NR
Lykavieris et al (18)	163	163/163 (100)	NR	41/94 (44)	NR	126/163 (77)	129/160 (81)	107/163 (66)	NR	68/161 (42)	40/163 (25)	29/82 (35)	1/163 (<1)
Other													
Alagille et al‡ (10)	80	73/80 (91)	80/80 (100)	NR	NR	NR	62/73 (85)	NR	NR	30/73 (41)	22/73 (30)	NR	NR
Lykavieris et al§ (17)	38	33/38 (87)	32/32 (100)	10/32 (31)	NR	NR	NR	NR	NR	NR	NR	7/38 (18)	NR

*Chronic or unspecified.
†Interlobular or unspecified.
‡Only patients with bile duct paucity.
§Only patients with severe haemorrhagic complications.
ALGS = Alagille syndrome; N = number of patients assessed for feature; n = number of patients with a feature; NR = not reported.

defects (10,12,16), the most frequent of which were tetralogy of Fallot, ductus arteriosus, septal defects, coarctation of the aorta (10,12,21). Four publications (10,12,17,21) reported that 9% to 24% (10,17) of patients required cardiac surgery, including interventions such as aortopulmonary shunt (21) and ductus arteriosus ligation (12,21).

Nine publications reported the presence of eye abnormalities (10–13,17,19–22), the most frequent of which was posterior embryotoxon, which affected 56% to 95% (11,20) of patients. Seven publications reported the presence of renal abnormalities (10,12–14,16,21,22), occurring in 19% to 74% (10,13) of patients studied for renal involvement. These included glomerular mesangiolipidosis (10,12), renal tubular acidosis (12–14), renal anatomic defects (13,21) and kidney failure (16,18,21). Nine publications identified the presence of skeletal abnormalities (10–13,16–19,21). Vertebral anomalies were the most common, which occurred in 24% to 87% (10,19) of patients investigated for skeletal abnormalities. A history of bone fractures was reported in 2% to 14% (16,21) of patients.

Three publications reported frequencies of PEBD (12,16,24). In these studies, the proportion of patients who underwent PEBD ranged from 4% to 14% (12,16). This literature analysis was not designed to capture studies reporting the outcomes from interventions such as PEBD, but of the studies included in the analysis, 1 study reported no difference in the itching score between patients who had received PEBD and those who had not (24), whereas another reported that 3 of 4 patients experienced relief from pruritus (12).

Seven publications included studies of patients who underwent liver transplant (12,13,16–19,21). In these studies, 15% to 47% (19,21) of patients had a transplant and the median ages at which patients underwent surgery ranged from 4 to 6.5 years (13,21). Frequently reported indications for liver transplant, either alone or in combination, included refractory pruritus (studies n = 4) (12,16,18,21), disfiguring xanthomas (n = 3) (13,18,21), bone fractures (n = 3) (13,16,18), signs of end-stage liver disease (n = 2) (16,18), failure to thrive (n = 1) (12), osteodystrophy (n = 1) (12), bleeding (12,21), synthetic liver failure or dysfunction (n = 3) (12,13,21), recurrent cholangitis (n = 1) (21), malnutrition as a consequence of severe cholestasis (n = 1) (21), and encephalopathy (n = 1) (13). One study reported that 79% (15 of 19) patients who had received liver transplant survived, with a mean follow-up of 4.2 years (range 0.7–12.3 years) (12). The higher surgical risk in patients with ALGS was highlighted, showing that, of the patients who had died following liver transplant, all deaths were due to post-transplant complications (21) and that most deaths occurred within the first 30 days (16). The most common complications following surgery were vascular (20.9%), and biliary tract complications (15.4%) (16). Renal complications were also common (9.9%) and children with pre-existing renal insufficiency were less likely to show improved renal function, suggesting intrinsic renal disease, which is not reversed by liver transplant (16).

Six publications reported bleeding events in patients with ALGS (12,13,16–18,21,22). Intracranial bleeding was the most common type of bleeding episode, occurring in 11% to 14% (12,17) of patients and included subarachnoid hemorrhage, subdural hematoma, epidural hemorrhage, and cerebrovascular accident. In a study that included only patients who had experienced a bleeding event, of 38 patients examined, 49 bleeding episodes occurred during the study period, the majority of which were spontaneous hemorrhages or resulted from surgery (17).

Ten publications reported information on mortality in patients with ALGS (10–13,15–19,21), and across these publications, over a 10- to 40-year follow-up period, mortality was 11% to 35% (13,15,18). The median age of death ranged from 2.3 to 4 years (range 2 months to 31 years) (18,21). Non-cardiac vascular complications were a leading cause of death (15). Five studies reporting the HRQoL of ALGS were identified (23–27); in 1 of these studies, patients with progressive familial intrahepatic cholestasis (PFIC) were also included as a mixed population (26). A summary of studies exploring the HRQoL of ALGS is provided in Table 3.

The HRQoL in children with ALGS has also been compared with that in children with other disorders. One study compared scores on the Pediatric Quality of Life Inventory (PedsQL 4.0) in children with ALGS, alpha-1-antitrypsin deficiency (A1ATD) or PFIC (26), while another compared scores on the Child Health Questionnaire Parent Form 50 (CHQ-PF50) in children with ALGS, attention-deficit/hyperactivity disorder (ADHD) or juvenile rheumatoid arthritis (JRA) (24). In children with ALGS, the mean psychosocial function domain score on the CHQ-PF50 was worse than in children with JRA ($P < 0.0005$), but better than in children with ADHD ($P < 0.0005$) (24). Conversely, the mean physical score on the CHQ-PF50 was worse in children with ALGS than in those with ADHD ($P < 0.0005$) (24). Children with ALGS had a worse mean self-reported physical domain score on the PedsQL than children with A1ATD ($P = 0.0002$) or PFIC ($P = 0.038$), and a worse mean parent-reported physical domain score than children with A1ATD (P value not reported); psychosocial domain scores were not reported in the children with PFIC (26). In this study, children's growth status was positively associated with Peds QL HRQoL scores ($P = 0.008$) (26).

Across the HRQoL studies, pruritus affected 59% to 82% (23,25) of patients. In 1 study, one-third of parents recognized itching as the aspect of ALGS that most affected their children (25). Itching was associated with additional symptoms such as skin damage (23–25), sleep problems (23–25), and mood disturbances (24,25). In 1 study, patients with ALGS who had undergone PEBD had numerically reduced HRQoL on the PedsQL 4.0 compared with healthy peers, and overall HRQoL was significantly and strongly negatively correlated with pruritus severity ($r = 0.74$; P value not reported) measured with the Infant Dermatitis Scale (27).

DISCUSSION

This systematic review confirms that ALGS is a devastating, life-shortening disease of childhood associated multiple morbidities. It, however, also highlights a scarcity of information on the epidemiology, natural history, and burden of the disease.

The only study to directly estimate the incidence of ALGS was published in 1977 (8). While this was a large study involving data from over three-quarters of a million births over 11.5 years, it was conducted before a molecular genetic diagnosis was possible. Due to variable expressivity, ALGS phenotypes are inconstant, meaning ALGS is likely to be underdiagnosed in the absence of molecular genetic confirmation. ALGS is highly penetrant (94%) (5), but variable expressivity of symptom type and severity results in a diverse clinical picture. This clinical diversity and the fact that bile duct paucity and cholestasis can occur in many other diseases can result in the under- or misdiagnosis of ALGS; molecular genetic testing therefore provides valuable confirmation, especially in milder cases. In many of the older studies reviewed, molecular genetic diagnosis was not performed and so it is possible that some of the data were derived from patients with conditions other than ALGS. Moreover, if *JAG1* is deleted, this may be caused by a chromosomal rearrangement or loss of a larger portion of chromosome 20p, resulting in additional manifestations not typically associated with ALGS (28), and this can be missed by standard mutational analyses. Finally, even contemporary studies lack data about the results of *NOTCH2* mutational analysis because this testing has not been readily available until recently. This is 1 of

TABLE 3. Summary of studies exploring pruritus and quality of life in patients with ALGS*

References, country	n	Study design	Age†	Instruments	Outcomes
Abetz-Webb et al (25) USA	26 children, 20 caregivers	Cross-sectional study	6 (< 1–35)	Qualitative interviews assessing itching (pruritus) severity and impact on quality of life	Pruritus severity Itching was the most bothersome symptom reported by all patients and caregivers, across all ages Itching severity (based on caregiver reports): severe, 4 (15%); moderate, 8 (31%); mild, 7 (27%); very mild, 7 (27%) Impact on quality of life: skin damage (76% patients; 80% caregivers), difficulty staying asleep (23% patients; 80% caregivers); difficulty falling asleep (54% patients; 55% caregivers), and mood disturbances (54% patients; 65% caregivers).
Elisofon et al (24) USA	71‡	Cross-sectional study	9.4 (5–18)	CHQ-PF50 (parent-reported), ALGS-specific questionnaire, itching/pruritus assessment	CHQ-PF50, mean (SD) score§: *Physical Domain* ALGS: 43 ± NR ADHD: 58 ± NR; $P < 0.0005$‖ JRA: 42 ± NR *Psychosocial Domain* ALGS: 48 ± NR ADHD: 37 ± NR; $P < 0.0005$‖ JRA: 53 ± NR; $P < 0.0005$‖
Kamath et al (26) USA, Canada	70 children, 98 parents¶	Cross-sectional study	Mean#: ALGS, 9.4; PFIC, 10.3; A1ATD, 9.5	PedsQL 4.0 (parent-reported and child self-reported)	PedsQL Physical Domain, mean (SD) score: *Parent report* ALGS: 74 ± NR A1ATD: 87 ± NR PFIC: NR *Child self-report* ALGS: 73 ± NR A1ATD: 83 ± NR; $P = 0.0002$‖ PFIC: 79; $P = 0.038$‖
Kronsten et al (23) UK	62	Retrospective observational review	7.7 (0.4–18.8)	Pruritus severity	Pruritus severity (at baseline): Mild: 12.9% Moderate: 32.3% Severe: 37.1% Affected quality of life in 19.6% of patients (n = 10)

TABLE 3. *Continued*

References, country	n	Study design	Age[†]	Instruments	Outcomes
Lind et al (27) Netherlands	8 children and their parents[**,††]	Cross-sectional study	9.2 (6.3–14.5)[#]	PedsQL 4.0 (Dutch version; child self-reported and parent-reported), Infant Dermatitis Scale	PedsQL 4.0 score, mean (SD): *Overall QoL* Patient self-report: 75 ± 16 Parent proxy report: 73 ± 14 Healthy peer self-report: 83 ± 15 Healthy peer parent proxy report: 88 ± 12 *Physical domain* Patient self-report: 79 ± 17 Parent proxy report: 76 ± 19 Healthy peer self-report: 84 ± 17 Healthy peer parent proxy report: 89 ± 16 *Psychosocial domain* Patient self-report: 73 ± 17 Parent proxy report: 72 ± 15 Healthy peer self-report: 82 ± 16 Healthy peer parent proxy report: 87 ± 12 Infant Dermatitis Scale score, median: Patient self-report for severity of pruritus: 2.5

[*]Only objectives relevant to the systematic review study questions have been extracted.
[†]Median (range), years unless specified.
[‡]Study included normative data from children with JRA or ADHD.
[§]Values estimated from the bar heights of graphs because numerical values were not reported in the text of the publication.
[‖]*P* versus ALGS population.
[¶]ALGS population only, additional populations: PFIC (children, n = 49; parents, n = 68), A1ATD (children, n = 95; parents, n = 123)
[#]Age of children.
[**]Children were a mixed population of ALGS/PFIC and had undergone partial external biliary diversion.
[††]Study included healthy controls.

A1ATD = alpha-1-antitrypsin deficiency; ADHD = attention-deficit/hyperactivity disorder; ALGS = Alagille syndrome; CHQ-PF50 = Child Health Questionnaire Parent Form 50; HRQoL = health-related quality of life; JRA = juvenile rheumatoid arthritis; NR = not reported; PedsQL = Pediatric Quality of Life Inventory; PFIC = progressive familial intrahepatic cholestasis; QoL = quality of life; SD = standard deviation.

the key limitations of evidence summarized in this review. Another key limitation is that, in rare conditions such as ALGS, study sizes are often small and outcomes data are rare. Given the paucity of suitable studies, we were unable to conduct meta-analyses on clinical features, HRQoL or economic burden. The manner in which studies were reported also complicated data extraction; publications did not meet recommendations for the reporting studies (eg, STrengthening the Reporting of OBservational studies in Epidemiology [STROBE]). In several instances, key information about a study was not reported (eg, the number of sites or the study period) or data were described qualitatively rather than quantitatively. Furthermore, studies were heterogeneous with respect to the study populations and the reporting of treatment outcomes and other variables. Nevertheless, we believe that this review provides a robust summary of the available evidence and identifies areas for further research.

This review confirms that ALGS is a complex, multisystem, developmental disorder that comprises a broad range of clinical features, most commonly evident in infancy or early childhood. This is due to the wide-ranging influence of Notch signaling, a pathway that operates in many tissue cell types, at various developmental stages and that interacts with other developmentally important cellular signaling pathways (29). Of particular relevance to ALGS, Notch signaling regulates the development of intrahepatic bile ducts, craniofacial structures, the heart, kidney, spine, and vasculature. Children with ALGS often manifest extrahepatic features. These are generally structural, resulting from abnormal development, although there may be additional functional abnormalities of the kidneys (eg, renal tubular acidosis) which, in addition to the observation that children with ALGS can be insensitive to growth hormone (30), may contribute to the failure to thrive. When comparing features of patients with or without neonatal jaundice, birth weight was found to be low only in the former group (18). It was also found that patients with neonatal jaundice developed pruritus earlier, were generally worse affected and so had a correspondingly poorer prognosis than individuals without jaundice (18).

Paucity of the bile ducts is present in the vast majority of reported cases (75%–100% (10,17,22)) and appears to be progressive with age. Intrahepatic bile duct paucity is associated with cholestasis that manifests with jaundice, pruritus and potentially disfiguring or disabling xanthomas. Secondary complications of this unremitting cholestasis include fat malabsorption, failure to thrive, and increased bone fracture risk. Four of the publications reporting information about clinical manifestations of ALGS only, however, included patients with hepatic involvement (10,13,18,21); by definition, hepatic complications are likely to affect more patients in these studies than in those studies including patients without overt liver involvement. Thus there is a clear ascertainment bias in most reported studies of ALGS natural history and outcomes.

The combined search results confirm that pruritus is a common symptom and affects 45% to 88% (12,13,21) of children with ALGS. It is severe in a considerable proportion of patients (15%–45% (12,25)) and is associated with skin lesions (23–25), sleep problems (23–25), and mood disturbances (24,25). Based on the studies included in this analysis, treatment of pruritus appears to be suboptimal and the condition persists in many patients (10,12,18). The data available on the severity of pruritus in patients with ALGS are, however, limited, necessitating further study.

HRQoL was lower in patients with ALGS than in healthy individuals in the 1 study to make this comparison (27). In patients with ALGS, HRQoL was also reported to be lower than in several other pediatric disorders (24,26), including JRA. One study showed that in children with ALGS, HRQoL is closely related to the severity of pruritus (27), but this was not corroborated by 2 other studies where the severity of pruritus was not linked to the degree of decrement in HRQoL (24,26). This inconsistency in reporting the relationship between pruritus and HRQoL with the PedsQL, CHQ-PF50 or Infant Dermatitis Scale implies a lack of questionnaire sensitivity to detect change in ALGS-related pruritus. This, combined with the relative lack of useful HRQoL data and inability to derive utility values from the questionnaires used, is a driver for the development of a disease-specific questionnaire and more research into the HRQoL decrements associated with ALGS. A recent study involving patients with ALGS and their caregivers confirmed itching as the most bothersome ALGS symptom, and the investigators used this information to develop a tool to assess the effect of pruritus in pediatric cholestasis (31). While validation of this tool is ongoing, this approach could be used for the development of other measures for the clinical manifestations of ALGS.

Moreover, there is a clear need for the development of an instrument to robustly measure the impact of treatments on HRQoL in patients with ALGS. There are no guidelines recommending an instrument to monitor HRQoL in response to treatment because there are no approved or effective treatments. There is also a lack of data representing the link between abnormalities in organ systems other than the liver and their impact on HRQoL.

The morbidity and mortality associated with ALGS are significant, but current therapy and disease management often fail to adequately control the disorder. Furthermore, the assessment of clinical outcomes in patients with ALGS is challenging, as common clinical manifestations such as pruritus often affect the young. The management of cholestatic liver disease in patients with ALGS currently focuses on controlling pruritus and supporting nutrition and fat-soluble vitamin deficiencies by nasogastric feeding or gastrostomy (32). But symptoms such as pruritus and xanthomas affect many patients, are particularly burdensome and can be so severe as to warrant biliary diversion or liver transplant in their own right. Surgery can, however, confer risk of complications due to bleeding, which may be increased in patients with ALGS (12). Liver transplant and the associated lifelong immunosuppression, carries with it the risk of nephropathy, immune dysregulation or increased risk of infection-related cancers (33). This highlights the need for alternatives to liver transplant that can slow or halt progression of liver disease and ameliorate associated symptoms, such as pruritus and xanthomas. Patient management may be improved by earlier diagnosis and recognition that neonatal jaundice is a poor prognostic factor, particularly if novel therapeutics can improve the prognosis (18).

Lastly, this review did not identify any publications reporting data on ALGS-related costs, resource utilization or overall economic burden. While ALGS is a rare disease, it is both severe and life-threatening, and treatment may involve extended hospitalizations, surgeries, transplantations and other costly interventions. As most patients are children and infants, it can impose an associated economic burden on parents and other informal caregivers. Further research in this area would therefore be informative.

CONCLUSIONS

This systematic review consolidates the information on the clinical presentation and natural history of ALGS, which has been gained from studies often involving small numbers of patients and with many pre-dating the genetic testing that will allow more accurate assessment of disease. Improved understanding of the biology and HRQoL of patients with ALGS, together with improved assessment instruments may help better inform its management and the design of future clinical trials. Research into the economic consequences of ALGS is also needed.

REFERENCES

1. Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet* 2011;20:251–7.
2. McDaniell R, Warthen DM, Sanchez-Lara PA, et al. NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet* 2006;79:169–73.
3. Li L, Krantz ID, Deng Y, et al. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. *Nat Genet* 1997;16:243–51.
4. Morell CM, Fiorotto R, Fabris L, et al. Notch signalling beyond liver development: emerging concepts in liver repair and oncogenesis. *Clin Res Hepatol Gastroenterol* 2013;37:447–54.
5. Dhorne-Pollet S, Deleuze JF, Hadchouel M, et al. Segregation analysis of Alagille syndrome. *J Med Genet* 1994;31:453–7.
6. Guandalini S, Dhawan A, Branski D, et al. Textbook of Pediatric Gastroenterology, Hepatology and Nutrition: A Comprehensive Guide to Practice Switzerland: Springer International Publishing; 2015.
7. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339: b2700.
8. Danks D, Campbell P, Jack I, et al. Studies of the aetiology of neonatal hepatitis and biliary atresia. *Arch Dis Child* 1977;52:360–7.
9. Leonard LD, Chao G, Baker A, et al. Clinical utility gene card for: Alagille Syndrome (ALGS). *Eur J Hum Genet* 2014;22:Article doi:10.1038/ejhg.2013.140.
10. Alagille D, Estrada A, Hadchouel M, et al. Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. *J Pediatr* 1987;110:195–200.
11. Deprettere A, Portmann B. Mowat AP Syndromic paucity of the intrahepatic bile ducts: diagnostic difficulty; severe morbidity throughout early childhood. *J Pediatr Gastroenterol Nutr* 1987;6:865–71.
12. Emerick KM, Rand EB, Goldmuntz E, et al. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology* 1999;29:822–9.
13. Hoffenberg EJ, Narkewicz MR, Sondheimer JM, et al. Outcome of syndromic paucity of interlobular bile ducts (Alagille syndrome) with onset of cholestasis in infancy. *J Pediatr* 1995;127:220–4.
14. Kamath BM, Podkameni G, Hutchinson AL, et al. Renal anomalies in Alagille syndrome: a disease-defining feature. *Am J Med Genet Part A* 2012;158:85–9.
15. Kamath BM, Spinner NB, Emerick KM, et al. Vascular anomalies in Alagille syndrome: a significant cause of morbidity and mortality. *Circulation* 2004;109:1354–8.
16. Kamath BM, Yin W, Miller H, et al. Outcomes of liver transplantation for patients with Alagille syndrome: the studies of pediatric liver transplantation experience. *Liver Transpl* 2012;18:940–8.
17. Lykavieris P, Crosnier C, Trichet C, et al. Bleeding tendency in children with Alagille syndrome. *Pediatrics* 2003;111:167–70.
18. Lykavieris P, Hadchouel M, Chardot C, et al. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut* 2001;49:431–5.
19. Narula P, Gifford J, Steggall MA, et al. Visual loss and idiopathic intracranial hypertension in children with Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2006;43:348–52.
20. Nischal KK, Hingorani M, Bentley CR, et al. Ocular ultrasound in Alagille syndrome: a new sign. *Ophthalmology* 1997;104:79–85.
21. Quiros-Tejeira RE, Ament ME, Heyman MB, et al. Variable morbidity in Alagille syndrome: a review of 43 cases. *J Pediatr Gastroenterol Nutr* 1999;29:431–7.
22. Subramaniam P, Knisely A, Portmann B, et al. Diagnosis of Alagille syndrome-25 years of experience at King's College Hospital. *J Pediatr Gastroenterol Nutr* 2011;52:84–9.
23. Kronsten V, Fitzpatrick E. Baker A Management of cholestatic pruritus in paediatric patients with Alagille syndrome: The King's College Hospital Experience. *J Pediatr Gastroenterol Nutr* 2013;57:149–54.
24. Elisofon SA, Emerick KM, Sinacore JM, et al. Health status of patients with Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2010;51:759–65.
25. Abetz-Webb L, Kennedy C, Hepburn B, et al. The burden of pruritus on patients with Alagille syndrome: results from a qualitative study with pediatric patients and their caregivers. *Hepatology* 2014;60:526A–7A.
26. Kamath BM, Chen Z, Romero R, et al. Quality of life in alagille syndrome is associated with growth failure and cardiac defects. *Hepatology* 2012;56:732A–3A.
27. Lind R, Hoekstra-Weebers J, Verkade H, et al. Quality of life in children after a partial external biliary diversion for progressive familial intrahepatic cholestasis or Alagille's disease. *J Pediatr Gastroenterol Nutr* 2010;50:E155.
28. Kamath BM, Thiel BD, Gai X, et al. SNP array mapping of chromosome 20p deletions: genotypes, phenotypes, and copy number variation. *Hum Mutat* 2009;30:371–8.
29. Andersson ER, Sandberg R, Lendahl U. Notch signaling: simplicity in design, versatility in function. *Development* 2011;138:3593–612.
30. Bucuvalas JC, Horn JA, Carlsson L, et al. Growth hormone insensitivity associated with elevated circulating growth hormone-binding protein in children with Alagille syndrome and short stature. *J Clin Endocrinol Metab* 1993;76:1477–82.
31. Kamath BM, Abetz-Webb L, Kennedy C, et al. Development of a novel tool to assess the impact of itching in pediatric cholestasis. *Patient* 2018;11:69–82.
32. Duché M, Habès D, Lababidi A, et al. Percutaneous endoscopic gastrostomy for continuous feeding in children with chronic cholestasis. *J Pediatr Gastroenterol Nutr* 1999;29:42–5.
33. Riminton DS, Hartung HP, Reddel SW. Managing the risks of immunosuppression. *Curr Opin Neurol* 2011;24:217–23.