Healthcare resource utilization in patients with Alagille syndrome

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Introduction

- Alagille syndrome (ALGS) is a rare, genetic, life-threatening, multisystem disorder, typically diagnosed in the first 3 months of life.[1,2]
- Children with ALGS present with a spectrum of illness, which includes pruritus, xanthomas, end-stage liver disease, renal disease, and complex cardiac conditions.[2]
- Care requirements for patients with ALGS are complex and require a multidisciplinary approach:
  - Management focuses on controlling pruritus, correcting fat-soluble vitamin deficiencies, and additional nutritional support either with oral supplementation, or by nasogastric and gastrostomy feeding if needed.[3,4]
  - Further therapy to treat the consequences of liver disease, as well as surgical and medical treatment of congenital heart defects, may also be required.[5]
- The pruritus caused by cholestasis negatively impacts a patient's quality of life,[6–8] and is often refractory to treatment and may require liver transplantation.[6]
  - Pruritus is one of the most common complications that leads to liver transplant in patients with ALGS.[9,10]
  - Transplant-free survival in patients with ALGS at 18–18.5 years is 24–41%.[4,11]
- The variable presentation and severity of ALGS[3] make it difficult to characterize healthcare resource utilization (HRU) in these patients.

Aim

- To assess the economic burden of ALGS in pediatric patients, by evaluating HRU and costs of treatment using insurance claims data.

Methods

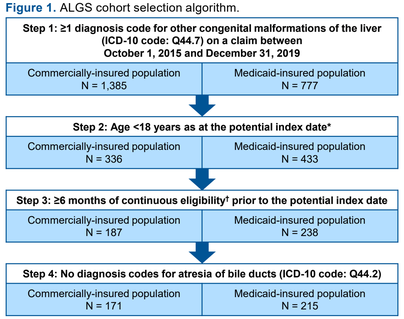
Data sources and cohort selection

- Health insurance claims data from October 1, 2015 through to December 31, 2019 from the IBM® Watson Health MarketScan® Commercial Claims and Encounters (CCAE) and Multi-State Medicaid databases were analyzed retrospectively.
- ALGS is not distinguishable in these databases with unique diagnosis codes. Data from a previous electronic medical record (EMR)-claims-linked analysis of patients with ALGS were used in conjunction with clinical expert opinion to develop a specific algorithm to identify the distinct ALGS cohort (**Figure 1**).
  - Pediatric patients aged <18 years with ≥1 claim with a diagnosis code for other congenital malformations of the liver (International Classification of Diseases, Tenth Revision [ICD-10] code Q44.7) between October 1, 2015 and December 31, 2019 and ≥6 months of continuous eligibility prior to the index date were included.
  - Patients with a history of biliary atresia (ICD-10 code Q44.2) were excluded.
  - Experts were consulted about the ICD-10 codes used to select patients with relevant clinical characteristics, including cholestasis-related conditions, congenital heart diseases, and nutritional deficiencies.
- The study period started on the index date, and the baseline period was defined as 6 months prior to the index date.
- Patients were followed until the end of follow-up or death, whichever occurred earlier, for up to 5 years post-index date.

Study outcomes

- All-cause HRU and costs were assessed throughout the study period. HRU was assessed as the number of healthcare visits experienced by patients.
- Healthcare visits included outpatient visits (primary care, cardiology, gastrointestinal, lab/imaging, and nephrology); inpatient visits; home care visits; emergency department visits; and other visits.
  - Home care visits were defined as any visit with a home healthcare provider.
  - Other visits were defined as visits associated with durable medical equipment or dental and vision care.
- All-cause costs were defined as the costs incurred from the payer perspective and were reported in 2019 US dollars ($).
- HRU and costs were reported as annualized rates, which were calculated by dividing each patient's total HRU or costs by their study period duration.

Figure 1. ALGS cohort selection algorithm.



ALGS, Alagille syndrome; ICD-10, International Classification of Diseases, Tenth Revision.
*The potential index date was defined as the date of a claim that includes a diagnosis code for other congenital malformations of the liver (Q44.7).
†Continuous eligibility was defined as continuous enrollment in commercial or Medicaid insurance plans and continuous prescription drug coverage.

Results

Patient characteristics

- This analysis included 171 commercially-insured and 215 Medicaid-insured patients with ALGS.
- Baseline characteristics for the commercially- and Medicaid-insured populations are shown in **Table 1**.
- The mean ± standard deviation age at baseline among the commercially- and Medicaid-insured populations was 9.0 ± 6.1 years and 7.5 ± 5.4 years, respectively.
- Over half of both commercially- and Medicaid-insured patients had conditions associated with cholestatic liver disease (108 [63.2%] and 158 [73.5%], respectively).
- Sixty-three (36.8%) commercially-insured and 73 (34.0%) Medicaid-insured patients had congenital heart diseases.
- The number of patients with nutritional deficiency was 42 (24.6%) in the commercially-insured population and 64 (29.8%) in the Medicaid-insured population.

Table 1. Baseline characteristics for commercially-insured and Medicaid-insured populations.

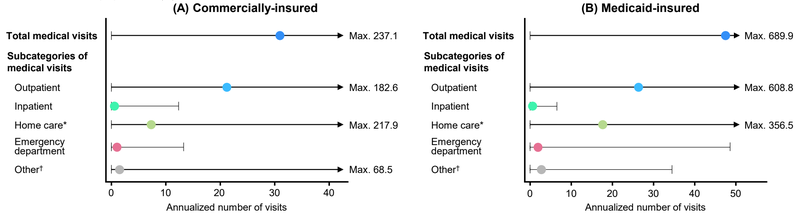
Patient characteristics	Commercially-insured population (N = 171)	Medicaid-insured population (N = 215)
Demographic characteristics at index date		
Age, mean (± SD)	9.0 ± 6.1	7.5 ± 5.4
Age categories (%)		
≥0 to <2 years	33 (19.3)	50 (23.3)
≥2 to <6 years	33 (19.3)	51 (23.7)
≥6 to <10 years	32 (18.7)	40 (18.6)
≥10 to <18 years	73 (42.7)	74 (34.4)
Male (%)	80 (46.8)	110 (51.2)
Clinical characteristics during the 6-month baseline period*		
Conditions associated with cholestatic liver disease† (%)	108 (63.2)	158 (73.5)
Failure to thrive-related condition	46 (26.9)	76 (35.3)
Liver-related condition	96 (56.1)	132 (61.4)
Pruritus-related condition	13 (7.6)	19 (8.8)
Clinical characteristics relevant to ALGS‡ (%)		
Cholestasis	14 (8.2)	20 (9.3)
Cirrhosis	11 (6.4)	12 (5.6)
Hypertension	10 (5.8)	20 (9.3)
Pruritus	12 (7.0)	17 (7.9)
Renal diseases	14 (8.2)	15 (7.0)
Nutritional deficiencies or malnutrition	42 (24.6)	64 (29.8)
Heart defects‡ (%)		
Congenital heart diseases	63 (36.8)	73 (34.0)
Skeletal abnormalities‡ (%)		
Congenital malformation and deformations of the musculoskeletal system and spine	22 (12.9)	17 (7.9)
Rickets	20 (11.7)	27 (12.6)

*Selected characteristics that were reported in ≥5% of the population.
†Conditions associated with cholestatic liver disease were derived from an EMR analysis of patients in the US with ALGS. ICD-10 CM codes pertaining to the most prevalent conditions related to failure to thrive, liver, and pruritus were included for analysis.
‡ICD-10 CM codes were used to identify relevant diagnoses.
ALGS, Alagille syndrome; EMR, electronic medical record; ICD-10 CM, International Classification of Diseases, Tenth Revision Clinical Modification; SD, standard deviation.

All-cause HRU

- The mean study period duration was 1.2 years (range 0.0–3.7) for the commercially-insured population and 1.5 years (range 0.0–3.7) for the Medicaid-insured population.
- Throughout the study period, commercially-insured patients experienced an annualized mean number of 31.0 medical visits (range 1.5–237.1) and Medicaid-insured patients experienced 47.9 visits (range 0.7–689.9) (**Figure 2**).
  - Of these, outpatient visits accounted for the majority of medical visits. Lab/imaging and primary care visits were the most common types of outpatient visits experienced by both populations.
- Commercially-insured patients experienced a mean of 0.4 inpatient visits per year (range 0.0–12.4), with a mean number of 2.8 inpatient days (range 0–71.3) (**Figure 2A**).
- Medicaid-insured patients experienced a mean of 0.4 inpatient visits per year (range 0.0–6.4), with a mean number of 6.3 inpatient days (range 0–365.3) (**Figure 2B**).

Figure 2. Annualized all-cause HRU among patients with ALGS in the commercially-insured population (A) and the Medicaid-insured population (B).



Mean (denoted by colored dots) and range of the overall annualized HRU data are shown. Arrows indicate that the maximum values exceed the maximum value denoted on the x-axis.
*Defined as any visit with a home healthcare provider.
†Defined as visits associated with durable medical equipment or dental and vision care.
ALGS, Alagille syndrome; HRU, healthcare resource utilization.

All-cause costs

- In both the commercially- and Medicaid-insured populations, there was a wide range of inpatient and outpatient costs, with several high outliers.
- Annualized mean total medical costs among commercially-insured patients were $57,029 (range $0–$1,336,236) (**Figure 3**).
  - The biggest driver of total medical costs was inpatient visits (mean $30,725 [range $0–$978,856]).
  - Outpatient costs for this population were also considerable (mean $22,884 [range $0–$885,630]).
    - Lab/imaging costs constituted a substantial proportion of outpatient costs.
- For the Medicaid-insured patients, annualized mean total medical costs were $24,820 (range $0–$1,006,499) (**Figure 4**).
  - As with the commercially-insured population, inpatient costs were the largest contributor to total medical costs (mean $12,673 [range $0–$1,006,499]).
  - Outpatient and pharmacy costs were the second largest contributors (mean $5,784 [range $0–$160,686] and $5,031 [range $0–$159,027], respectively).
    - As with the commercially-insured population, lab/imaging costs contributed to a large proportion of outpatient costs in the Medicaid-insured population.

Figure 3. Annualized all-cause costs in patients with ALGS in the commercially-insured population.

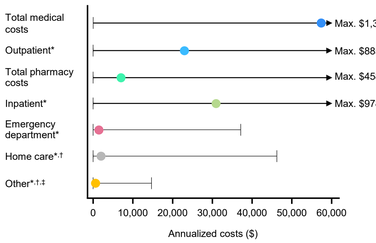
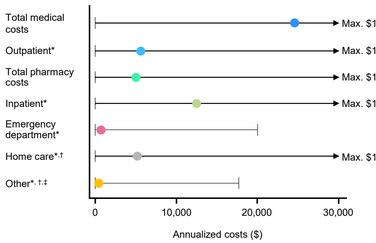


Figure 4. Annualized all-cause costs in patients with ALGS in the Medicaid-insured population.



Mean (denoted by colored dots) and range of the overall annualized cost data are shown. Arrows indicate that the maximum values exceed the maximum value denoted on the x-axis.
*Categories of total medical costs.
†Defined as any visit with a home healthcare provider.
‡Defined as visits associated with durable medical equipment or dental and vision care.
ALGS, Alagille syndrome.

Limitations

- This analysis was limited by patient coding, particularly the absence of a specific ICD-10 code to identify patients with ALGS.
  - The lack of an ALGS-specific ICD-10 code means this analysis likely underestimated the number of patients with ALGS, and the burden of cholestasis-related conditions such as pruritus
  - As the amount of costs reimbursed is limited and the database does not record out-of-pocket expenses (e.g. nutritional supplements and vitamins) or societal costs of treatment (e.g. lost wages, transportation/travel), these findings likely underestimate the economic burden of ALGS.

Conclusions

- **This analysis demonstrates that patients with ALGS have substantial HRU and cost burden in both commercially- and Medicaid-insured populations.**
- **Commercially-insured patients averaged approximately one medical visit every 2 weeks, with higher estimates for Medicaid-insured patients (nearly one medical visit per week), which has a significant impact on patients, caregivers, and care coordination.**
- **Despite the frequent need for outpatient visits, a large percentage of costs were driven by inpatient admissions.**
- **The wide ranges of HRU and medical costs among both commercially- and Medicaid-insured patients suggest that there is no standard course for patients with ALGS.**
  - **A few patients with ALGS incurred very high medical costs compared with the other patients, increasing the overall mean annual costs associated with ALGS care.**
- **This analysis demonstrates the significant HRU and cost burden of ALGS.**
- **The introduction of specific ICD-10 codes to identify patients with ALGS is needed to help further understand the burden of disease in this rare patient population.**

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N H Ebel is a consultant for Mirum Pharmaceuticals, Inc.
A Goldstein and R Howard are full-time employees of and shareholders in Mirum Pharmaceuticals, Inc.
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