Economic burden of congenital athymia in the United States for patients receiving supportive care during the first 3 years of life

Cathleen Collins\textsuperscript{a,b}, Julie J. Kim-Chang\textsuperscript{c}, Elena Hsieh\textsuperscript{d,e}, Abigail Silber\textsuperscript{f}, Matthew O’Hara\textsuperscript{f}, Sarah Kulke\textsuperscript{g,h} and Megan A. Cooper\textsuperscript{h,i}

\textsuperscript{a}Department of Allergy and Immunology, Rady Children’s Hospital, San Diego, CA, USA; \textsuperscript{b}Department of Pediatrics, Division of Allergy Immunology, University of California San Diego, San Diego, CA, USA; \textsuperscript{c}Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA; \textsuperscript{d}Department of Pediatrics, Section of Allergy and Immunology, University of Colorado, Anschutz School of Medicine, Children’s Hospital Colorado, Aurora, CO, USA; \textsuperscript{e}Department of Immunology and Microbiology, University of Colorado, Anschutz School of Medicine, Aurora, CO, USA; \textsuperscript{f}Trinity Life Sciences, Waltham, MA, USA; \textsuperscript{g}Enzyvant Therapeutics, Inc., Cambridge, MA, USA; \textsuperscript{h}Department of Pediatrics, Division of Rheumatology/Immunology, Washington University in St. Louis, St. Louis, MO, USA

\section*{ABSTRACT}

Aims: Congenital athymia is an ultra-rare pediatric condition characterized by the lack of thymus in utero and the naïve T cells critical for infection defense and immune regulation. Patients with congenital athymia receive supportive care to minimize and treat infections, autoimmune phenomena, and autologous graft-versus-host disease (aGVHD) manifestations, but historically, die within the first 3 years of life with supportive care only. We estimated the healthcare resource utilization and economic burden of supportive care over patients’ first 3 years of life in the United States.

Methods: A medical chart audit by the treating physician was used to collect patient data from birth to age 3 on clinical manifestations associated with congenital athymia (clinical manifestations due to underlying syndromic conditions excluded). Using costs and charges from publicly available sources, the total economic burden of direct medical costs and charges for the first 3 years of life (considered “lifetime” for patients receiving supportive care) and differences in economic burden between patients with higher and lower inpatient hospitalization durations were estimated.

Results: All patients (n = 10) experienced frequent infections and aGVHD manifestations; 40% experienced ≥1 episode of sepsis, and 20% had recurrent sepsis episodes annually. The estimated mean 3-year economic burden per patient was US$5,534,121 (2020 US dollars). The annual mean inpatient hospitalization duration was 150.6 days. Inpatient room charges accounted for 79% of the economic burden, reflecting the high costs of specialized care settings required to prevent infection, including isolation. Patients with high inpatient utilization (n = 5; annual mean inpatient hospitalization duration, 289.6 days) had an estimated 3-year economic burden of US$9,926,229.

Limitations: The total economic burden may not be adequately represented due to underestimation of some direct costs or overestimation of others.

Conclusions: Current treatment of patients with congenital athymia (supportive care) presents a high economic burden to the healthcare system.

\section*{Introduction}

Congenital athymia is an ultra-rare (defined as prevalent in no more than 1:50,000\textsuperscript{1}) pediatric condition characterized by the lack of thymus in utero resulting in profound immunodeficiency\textsuperscript{2}. Congenital athymia is typically associated with several genetic and syndromic conditions, including 22q11.2 deletion syndrome, complete DiGeorge syndrome, CHARGE (coloboma, heart defect, choanal atresia, growth or mental retardation, genital hypoplasia, and ear anomalies or deafness) syndrome, forkhead box protein N1 (FOXN1) deficiency, and diabetic embryopathy\textsuperscript{3,4}. Patients are currently often first identified by low or undetectable T cell receptor excision circles (TRECs) during newborn screening for severe combined immunodeficiency (SCID), testing, which is required in all 50 states in the United States (US) as of 2018\textsuperscript{5,6}. Subsequent evaluations of complete and differential blood cell counts and lymphocyte phenotyping by flow cytometry reveal profoundly low naïve T cell counts. While there is no uniformly agreed on naïve T cell number that
defines congenital athymia, one center in the US has used fewer than 50 naïve T cells per cubic millimeter (mm³) or less than 5% of all T cells naïve in type to confirm a diagnosis of congenital athymia⁴.

As a result of their naïve T cell deficiency, patients frequently develop bacterial, viral, and fungal infections involving a range of organs, as well as sepsis⁷,10. Patients with congenital athymia also have the propensity to develop oligoclonal T cell expansion, frequently described as an “atypical” phenotype that can lead to autologous graft-versus-host disease (GVHD)⁴,11. Autologous GVHD can cause aberrant immune cell infiltration and organ damage¹¹,¹², contributing to increased morbidity and mortality. This phenotype develops at some point after birth and presents with an eczematous rash and associated lymphadenopathy⁴,11.

Congenital athymia is managed through supportive care to minimize infection risk and include immediate isolation (in line with other primary immunodeficiencies¹³–¹⁹). Isolation in the hospital typically involves contact and droplet precautions, protocols for infection prevention for staff, and specialized airflow rooms. Recommended isolation and hygiene procedures should also be maintained at home if the patient is discharged, as any interactions with individuals outside the home expose the patient to the risk of infection. Patients are typically placed on prophylactic antimicrobials and immunoglobulin replacement therapy. A proportion of patients require the addition of immunosuppressive therapies when autologous GVHD develops, which have potential adverse events⁴,8,12,17. Congenital athymia requires close clinical management, frequent monitoring with medical tests, and multiple invasive procedures, such as placement of a feeding tube for nutrition and/or insertion of a central line to administer medications or draw blood⁴,9. Long-term immune reconstitution in patients with congenital athymia has been attempted using hematopoietic stem cell transplantation, with poor results⁵. In the US, allogeneic cultured thymus tissue is currently being investigated as a treatment for the disorder at Duke University in Durham, NC¹⁸. Historically, patients typically die within the first 2 to 3 years of life from infections and sequelae of autologous GVHD with only supportive care⁴,19.

Given the rarity of congenital athymia, there is a lack of published evidence characterizing its economic burden on the healthcare system. To our knowledge, this study is the first evaluation of the direct medical costs and charges for treatment with supportive care for patients with congenital athymia.

**Methods**

The total economic burden of supportive care for patients with congenital athymia was calculated using healthcare resource utilization (HCRU) data cost and charge inputs. HCRU data were used to calculate the total economic burden of congenital athymia when patients received only supportive care during the first 3 years of life. Scenario analyses were performed to explore how the economic burden of supportive care for congenital athymia differs based on disease experience/characteristics.

**Utilization of data inputs**

A retrospective, cross-sectional medical chart audit study was conducted with US board-certified/eligible healthcare practitioners (HCPs), currently or previously treating at least one patient with congenital athymia, to determine the utilization of supportive care derived from patient charts for the management of congenital athymia and its sequelae. HCPs across the US were recruited through referrals from the authors, who have experience with treating patients with congenital athymia. All included HCPs were actively practicing in an immunodeficiency-related specialty and treated one or more patients with congenital athymia. Medical chart data for living or deceased patients with a confirmed diagnosis (defined as naïve T cell [CD45RA+/+] count of <100 cells/mm³ recorded at birth or diagnosis) were collected using a web-enabled questionnaire. Data had to be available for at least 12 continuous months before patients were aged 3 years and during which only supportive care was received. Data were collected in the US between November 2020 and January 2021.

The purpose of this study was to estimate the economic burden of supportive care for congenital athymia. Supportive care was considered any treatment contained within the current clinical management of congenital athymia. Although patients with congenital athymia frequently present with associated syndromic conditions, these conditions and their manifestations can vary considerably, are not present in all patients, and are not a result of congenital athymia. To differentiate between clinical manifestations of congenital athymia and syndromic comorbid conditions, clinical experts evaluated and created a list of clinical manifestations associated with congenital athymia based on published literature. Participating HCPs were asked to report clinical manifestations of congenital athymia distinct from syndromic comorbid conditions. HCPs abstracted clinical manifestations and HCRU in a typical year for different direct healthcare resources across the reviewed time period. Clinical manifestations and HCRU data were collected as categorical variables (yes/no) and frequency (e.g. daily, weekly, monthly). Continuous data were collected as mean days of use where appropriate (e.g. inpatient days) or the number of times events occurred (e.g. outpatient visits). This study was reviewed by ADVARRA, a central institutional review board, and was determined to have an exempt status (as defined by the US Department of Health and Human Services regulations found at 45 CFR 46.104). This study was conducted in line with research ethics in accordance with the Helsinki Declaration of 1964 and its later amendments.

While nearly all healthcare utilization was obtained via patient charts, two inputs were not available. Home health use and purchase of home medical and non-medical supplies could not be captured using medical chart data. These utilization inputs were captured from a separate study of caregivers for children with congenital athymia for the time they were receiving supportive care only²⁰.

**Cost and charge data inputs**

Costs and charges associated with the use of healthcare resources were gathered from public sources. Targeted
searches were conducted to identify peer-reviewed studies estimating costs (e.g. central line placement, diagnostics/imaging), national cost databases such as IBM Micromedex RED BOOK (IBM, Armonk, NY), or publicly available hospital chargemaster data\textsuperscript{21–44}. Costs for routine medical and non-medical supplies, such as masks and hand sanitizers, were derived from a US consumer retail website\textsuperscript{45}.

Inpatient hospital room charges were derived from the 2020 chargemaster data from Children’s Hospital, Colorado\textsuperscript{21}, which was considered representative of a real-world care setting for patients with congenital athymia based on clinical experts’ direct experience with and knowledge of the treatment landscape for congenital athymia. In addition, data availability and geographic alignment of this institution with the overall average US consumer price index were taken into consideration to further validate this selection.

**Modeling of mean total economic burden of congenital athymia**

**Base-case analysis**
The total economic burden of congenital athymia for patients who were receiving supportive care for the first 3 years of life was modeled using Microsoft Excel (Microsoft Corporation, Redmond, WA). All data collected from the medical chart audit were analyzed in Q Research Software, Q Professional version 5.8.2.0 (Displayr, Sydney, Australia).

The base-case analysis for the model utilized the overall annual mean HCRU. The mean annual economic burden per patient was calculated, with subgroupings of costs and charges across care categories. The treating physician provided the mean estimated annual utilization of each medical resource through a review of the patient’s medical chart. Annual costs and charges were then multiplied by 3 to estimate the total economic burden per patient for the first 3 years of life.

**High and low inpatient utilization group scenario analysis**
Scenario analysis was conducted comparing two real-world patient scenarios: high and low inpatient utilization groups. These mutually exclusive cohorts were defined as the top and bottom 50% of patients based on inpatient hospital days. Beyond differences in mean inpatient hospitalization duration, cohort utilization for other cost categories was based on cohort-calculated means.

**Minimum and maximum inpatient hospitalization duration scenario analysis**
Minimum and maximum inpatient hospitalization durations were applied to the base-case model. Utilization metrics for all other cost categories were kept consistent with the base-case model.

**Presence or absence of oligoclonal T cell expansion scenario analysis**
Scenario analysis was conducted comparing the economic burden of care for patients with congenital athymia with and without oligoclonal T cell expansion. Utilization metrics for all other cost and charge categories were based on cohort-calculated means.

**Assumptions and other calculations**
Based on the input and expertise of the authors, who have clinical experience caring for patients with congenital athymia, the following assumptions were made in the model. The model assumed that patients were admitted to reverse isolation or bone marrow transplant (BMT) rooms where enhanced infection control protocols are maintained. In addition, it was assumed that 30% of inpatient days required intensive care settings and 70% of inpatient days required isolation room/BMT room settings. The model also assumed that patients requiring intensive care in their first year of life were admitted to the neonatal intensive care unit (NICU), and in their second and third year of life, they were admitted to the pediatric intensive care unit (PICU).

Blended costs were calculated for certain utilization categories to accommodate varying costs for category subtypes. For example, non-emergency outpatient visits consisted of subtypes of the specialist seen (e.g. immunologist, hematologist, pediatrician), each with varying average hourly rates. In these cases, a blended rate was calculated using the proportion of patients seeing each specialist. A similar approach was taken for types of emergency transport service and medication use.

The cost of home medical/non-medical supplies (e.g. masks, gloves) was derived by estimating material use and applying a standard cost per package size or unit of supplies necessary per year. Costs and charges were inflated to 2020 US dollars using the consumer price index, rounded to the nearest dollar.

**Results**

**Patient population**
A total of 10 charts of patients were reviewed in the medical chart audit study; patient demographics and characteristics are listed in Table 1. An equal proportion of patients were male and female. All patients were aged <36 months during the period from which HCRU data were compiled from their medical charts. Most patients (80%) had a condition known to be associated with congenital athymia (40% diabetic embryopathy, 20% DiGeorge syndrome, and 20% CHARGE syndrome). Most patients (70%) had oligoclonal T cell expansion. Seventy percent of patients received a diagnosis of congenital athymia at or within a month of birth. The 30% of patients who were diagnosed with congenital athymia more than 1 month after birth were diagnosed at a median age of 3 months. Among the three deceased patients, the median age at death was 24 months.
**Healthcare resource utilization**

Patients had a mean of 3.3 inpatient hospitalizations for congenital athymia–related problems annually, with an annual mean of 150.6 days spent in an inpatient care setting. On evaluation of inpatient utilization, there was a bimodal distribution for inpatient hospital days; two categories of high and low inpatient utilization groups emerged. Patients with high inpatient utilization \((n = 5)\) had a mean of 289.6 inpatient days and patients with low inpatient utilization \((n = 5)\) had a mean of 11.6 inpatient days annually.

Patients also required frequent non-urgent, routine outpatient visits at a mean of 9.1 visits annually. Emergency transport services were utilized by 30% of patients at a frequency of 1–5 times a year, and the mean annual utilization of emergency room visits was 1.5 times across the full cohort.

Diagnostic or monitoring tests were performed frequently, with 70% of patients utilizing the following tests multiple times per year: chest radiographs (annual mean, 30.4 times), cultures for bacterial infections (16.4 times), tests for viral infections (15.3 times), and ultrasonography (9.6 times).

The use of antimicrobial therapy for prophylaxis was universal, with 100% of patients using antibiotic medications (annual mean duration, 329.5 days), 30% using antiviral medications (244 days), and 90% using antifungal medications (365 days). Antibiotic medications were used to treat active infections for a mean of 17.4 days annually. All patients received immunoglobulin replacement therapy, either intravenously monthly or subcutaneously weekly. 70% of patients required daily immunosuppressive therapies.

Utilization of different medical procedures was high and on average each medical procedure was performed more than once per year; 90% of patients needed feeding tubes placed, 70% of patients required central lines placed, 70% of patients used ventilators, and 70% of patients required sedation. Most patients (80%) underwent four or more different medical procedures in a typical year.

Families used home medical supplies such as gloves, masks, and syringes to assist in the care of a patient with congenital athymia\(^2\). Most caregivers (94%) also reported using non-medical supplies such as high-efficiency particle air filters and home cleaning supplies. Additionally, 50% of families reported utilizing home healthcare services\(^2\).

**Clinical manifestations**

The mean annual frequency of infections, manifestations of autologous GVHD, and sequelae of immunosuppression are presented in Figures 1–3. Patients experienced frequent infections in multiple organ systems, including pulmonary, skin, gastrointestinal, genitourinary, and HEENT (head, ears, eyes, nose, or throat; Figure 1). Of note, sepsis occurred in 40% of patients annually (Figure 3). Moreover, 70% of patients had manifestations of autologous GVHD (Figure 2).

**Base-case analysis: total economic burden per patient in the first 3 years of life**

The estimated mean total economic burden per patient in the first 3 years of life was US$5,534,121 (Table 2). The primary contribution to the total economic burden was inpatient hospital room charges, amounting to US$4,375,548 (Figure 4); these charges comprised US$3,033,373 for isolation or BMT rooms; US$495,557 for NICU rooms; and US$846,617 for PICU rooms. Other costs, not including hospital room charges, amounted to US$1,158,573 (Figure 4). Non-inpatient costs are described in detail in Table 2.

**Table 1.** Congenital athymia patient demographics and characteristics.

| Sex               | All patients \((n = 10)\), n (%) |
|-------------------|----------------------------------|
| Male              | 5 (50)                           |
| Female            | 5 (50)                           |
| Geographic area   |                                  |
| Rural             | 1 (10)                           |
| Urban             | 2 (20)                           |
| Suburban          | 7 (70)                           |
| Race/ethnicity    |                                  |
| Hispanic/Latino White/Caucasian | 8 (80) |
| Black/African American | 1 (10) |
| Unknown           | 1 (10)                           |
| Insurance type    |                                  |
| Private/commercial| 2 (20)                           |
| Medicare/Medicaid/Children’s Health Insurance Program | 5 (50) |
| Veteran’s Administration/ government/military | 1 (10) |
| Other\(^a\)       | 2 (20)                           |

\(^a\) Other was noted as private and state-sponsored secondary insurance.

**Figure 1.** Mean annual infections in patients with congenital athymia. Occurrence of infections across the cohort \((n = 10)\). Annual frequency is reported in those who experienced an infection type at least once. HEENT, head, ears, eyes, nose, or throat.
Supplemental Table 1 provides the costs and charges for each utilization category.

**Scenario analysis: high and low inpatient utilization group**

Patients with high inpatient utilization had a mean annual inpatient hospitalization duration of 289.6 days, and those with low inpatient utilization had a mean annual inpatient hospitalization duration of 11.6 days (Figure 5). The economic burden for each cohort was analyzed separately. The high inpatient utilization group was estimated to incur a mean total economic burden of US$9,926,229 over the first 3 years of life, while the low inpatient utilization group was estimated to incur a mean total economic burden of US$1,284,105 (Figure 4). Inpatient hospitalization charges were US$8,702,227 for the high inpatient utilization group and US$348,570 for the low inpatient utilization group (Figure 4). Non-inpatient costs were US$1,224,002 and US$935,535 for the high and low inpatient utilization groups, respectively.
Scenario analysis: minimum and maximum inpatient hospitalization duration
The mean total economic burden for a patient with an inpatient hospitalization duration of 365 days was US$11,763,320 over the first 3 years of life, while the mean total economic burden for a patient with an inpatient hospitalization duration of 0 days was US$1,158,573.

Scenario analysis: presence or absence of oligoclonal T cell expansion
The data were also analyzed based on the presence or absence of oligoclonal T cell expansion (Supplemental Figure 1). Patients with oligoclonal T cells \( (n = 7) \) incurred a mean total economic burden of US$6,554,581 over the first 3 years of life, while patients without oligoclonal T cells \( (n = 3) \) incurred a mean total economic burden of US$2,903,678.

Discussion
To our knowledge, this is the first economic model estimating the burden of managing congenital athymia. Using real-world patient data, we found a substantial economic burden associated with supportive care, with the mean burden per patient in the first 3 years of life exceeding US$5.5 million. Although the economic burden is substantial, it is not unexpected given the complex care required for these patients, including infection prevention and treatment, and prevention and treatment of manifestations of autologous GVHD for patients with oligoclonal T cell expansion. Supportive care does not provide definitive treatment of the immunodeficiency and immune dysregulation that underlie congenital athymia; as a result, patients require the same level of care for up to 3 years before they typically succumb to their illness. During these years, they remain vulnerable to infection and possible autologous GVHD-associated complications.

The most substantial contribution to the total economic burden of supportive care was inpatient hospitalization, accounting for 79% of the total economic burden. Two distinct groups of patients emerged from this study, high and low inpatient utilization groups, which can be seen in the bimodal distribution of the hospitalization data. The high inpatient utilization group incurred US$8.7 million for inpatient expenses alone, while the low inpatient utilization...
group incurred less than US$0.4 million. The high charges associated with inpatient hospitalization represent, in part, the highly structured settings needed to care for patients to minimize their risk for infection. The complexity of this care paradigm has also been shown for patients with other primary immunodeficiencies. In a survey of infection prevention for patients with SCID, Dergousoff et al. found that 59% of patients were admitted to hematopoietic stem cell/hematology/oncology wards, with 89% staying in a private room13. Also contributing to the high charges associated with inpatient hospitalization is the mean number of days spent in the hospital annually. In our study, 30% of patients had an annual mean inpatient hospitalization duration longer than 350 days. In the maximum inpatient hospitalization scenario analysis in this study, patients with a hospitalization duration of 365 days exceeded a mean total economic burden of US$11.7 million.

The high variability of economic burden in this model prompted additional, hypothesis-generating analyses of the data to determine what factors may predispose a patient to a protracted inpatient hospitalization (and thereby incur a substantially higher burden). Among those hypotheses evaluated was that the occurrence of oligoclonal T cell expansion, necessitating further immunosuppression in immunodeficient patients, may lead to higher resource utilization.

Seventy percent of patients in this study had oligoclonal T cell expansion. This atypical phenotype, also described as autologous GVHD or Omenn’s syndrome, develops at some point after birth and is associated with oligoclonal T cell expansion11. The T cells infiltrate organs and cause an eczematous-type rash, lymphadenopathy, transaminitis, and enteropathy10–12. Patients who develop this atypical phenotype require additional diagnostic and monitoring procedures (i.e. skin biopsy), as well as treatment (i.e. total parenteral nutrition for enteropathy) to manage manifestations of autologous GVHD11,46. In our study, these manifestations occurred in pulmonary, skin, lymphatic, and gastrointestinal organs.

We hypothesize that the development of manifestations of autologous GVHD contributes to higher HCRU. In this study, two of three patients without oligoclonal T cell expansion were in the low inpatient utilization group. It is likely that the lack of autologous GVHD-associated complications in these patients reduced their overall HCRU. When evaluated by the presence of oligoclonal T cell expansion, the mean total economic burden was more than two times higher for patients with oligoclonal T cell expansion than for those without (US$66.5 vs. US$2.9 million). Treatment of autologous GVHD with immunosuppressive therapies can lead to adverse effects such as hypertension and renal complications8,12,17; in this study, 20% of patients had kidney damage due to medications. Given that oligoclonal T cell expansion develops at some point after birth, the probability of it developing may increase over time and its presence likely increases the frequency and severity of clinical manifestations. This could account for the variability in the number and type of clinical manifestations observed in this study.

We believe the evaluation of factors leading to the development of oligoclonal T cell expansion is a critical area for future research in congenital athymia.

The rare and severe nature of this condition and the lack of prior analysis on the economic burden of congenital athymia care prevent any direct comparison with prior research. However, results from studies in spinal muscular atrophy (SMA) provide context for interpreting our results as a comparable debilitating pediatric condition. Cost estimates for SMA vary by disease phenotype and age at onset47–50. Type 1 may be comparable to congenital athymia because its disease onset occurs within the first 6 months of life and is often fatal within the first 2 years of life51. Droege et al. recently published an economic assessment of SMA using a claims database, which found that the mean healthcare cost for patients with SMA type 1 was US$137,627 per patient per year in 201847. In a different study, the cost of supportive care was estimated for patients with infantile-onset (index date of first SMA-related diagnosis before 6 months of age) SMA using claims data; the per-patient-per-month cost was estimated to be US$25,517 in 201550. Both studies included costs associated with inpatient hospitalization duration in their calculations (14.1 and 40.8 days, respectively)47,50. The higher economic burden of managing congenital athymia compared with SMA is attributable to prolonged hospitalizations and highly specialized care settings often needed in the care of patients with congenital athymia.

Limitations

An important limitation of our study is the use of hospital chargemaster data for BMT/isolation rooms, and PICU and NICU charge assumptions. Chargemaster data represent the hospital-billed charges for treatment, and, as a result, the chargemaster data are typically higher than the true costs. The authors sought to ensure the transparency of the economic model by utilizing publicly available sources to ensure the model is independently reproducible. In addition, the chargemaster data utilized for inpatient stay were derived from a single chargemaster data source, limiting generalizability. Another limitation is that the chargemaster data for BMT/isolation rooms and PICU and NICU care settings do not include nursing or HCP costs, despite specialized care being a key feature of these sites of care.

Other notable limitations include that some direct costs of congenital athymia management may not be adequately represented, leading to an underestimation of direct costs. For example, the model does not include the potential for productivity losses or other indirect costs associated with congenital athymia on the families20. The frequent need for full-time caregiving for patients with congenital athymia may lead to lost employment opportunities and work productivity. Informal caregiving has also been shown to be associated with adverse impact on work performance52 and earnings53. The model does not account for the costs of isolation (required to prevent exposure to infection). The requirement for patients, caregivers, and families to live in strict isolation often from friends and extended family increases social
isolement and loneliness, which have been shown to negatively impact health and potentially increase economic burden54–56.

While some patients in our study had an underlying genetic defect, care was taken to limit the HCRU to only direct manifestations of congenital athymia. This was achieved by gaining consensus from clinical experts on clinical manifestations associated with congenital athymia vs. syndromic comorbid conditions. Responding HCPs were provided with guidance to report clinical manifestations associated with conditions related to congenital athymia only, separate from those associated with syndromic comorbid conditions.

The differences in HCRU between patients in this study could reflect differences in treatment practices across the responding physicians or variability in the clinical course of the disease, due to infections and development of autologous GVHD.

Our economic model included HCRU data from patients with clinical athymia treated in the US and was developed using US-based costs and charges. It is important to note that country-specific differences in the congenital athymia treatment paradigm or differences in the costs or charges for certain HCRU metrics/sites of care may impact the estimated economic burden. For example, the primary contributor to the economic burden in our study was inpatient hospitalization. Therefore, country-specific variability in charges associated with inpatient hospitalizations would likely translate to differences in the estimated economic burden of congenital athymia. Despite these potential differences, it is clear from our data that patients with congenital athymia have a substantial clinical burden and would likely require considerable care and treatment regardless of the country.

Conclusions

There is a high economic burden associated with supportive care of patients with congenital athymia in the first 3 years of life, exceeding $5.5 million. The economic burden of managing congenital athymia is primarily composed of charges associated with prolonged inpatient hospitalization in specialized-care settings. Also contributing to the economic burden of supportive care are frequent outpatient visits, utilization of diagnostic or monitoring tests, medications for prophylaxis and treatment, home healthcare, and diagnostic or surgical procedures. This high HCRU is a result of the frequent and severe episodes of infections and manifestations of autologous GVHD spanning multiple organ systems in these patients. Further research can elucidate differences in patient experience depending on the severity of clinical manifestations and the development of autologous GVHD. It will be important to evaluate the impact of any future changes in the treatment paradigm on the economic burden of managing congenital athymia.

Transparency

Declaration of funding

This study was supported by Enzyvant Therapeutics, Inc. Enzyvant was involved in the study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the paper for publication.

Declaration of financial/other interests

MC, CC, EH, AS, and MO received consulting fees from Enzyvant Therapeutics, Inc. SK is the vice president of Medical Affairs at Enzyvant (since May 2020) and, therefore, receives financial remuneration in the form of salary, annual bonus, and benefits from the company's long-term incentive plan. Julie J. Kim-Chang declares that she has no conflict of interest.

Peer reviewers on this manuscript have received an honorarium from JME for their review work but have no other relevant financial relationships to disclose.

Author contributions

CC, SK, EH, AS, MO, and MC were involved in the conception and design of the study. All authors were involved in the analysis and interpretation of the data. SK and AS drafted the manuscript, and all authors critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Acknowledgements

We thank Shruti Nambiar (Trinity Life Sciences) and Bhagyashree Oak (Trinity Life Sciences) for their contribution to study design and data analysis, as well as Emily Sharpe, (Trinity Life Sciences) for assistance in creating the first draft of the manuscript. Shruti Nambiar, Bhagyashree Oak, and Emily Sharpe received consulting fees from Enzyvant Therapeutics, Inc. Editorial assistance, funded by Enzyvant Therapeutics, Inc., was provided by Lisa M. Pitchford of JB Ashtin.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Previous presentations

A subset of the data included in this manuscript was submitted and accepted as a poster presentation at the Clinical Immunology Society 2021 Virtual Annual Meeting (14–17 April 2021).

ORCID

Julie J. Kim-Chang http://orcid.org/0000-0002-9799-9054
Elena Hsieh http://orcid.org/0000-0003-3969-6597
Matthew O’Hara http://orcid.org/0000-0003-2131-8563
Megan A. Cooper http://orcid.org/0000-0002-5696-172X

References

[1] REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC In: UNION TEPATCOTE, ed. Official Journal of the European Union 2014. L158.27.5.2014, 1–76.
[2] Markert ML, Hummell DS, Rosenblatt HM, et al. Complete DiGeorge syndrome: persistence of profound immunodeficiency. J Pediatr. 1998;132(1):15–21.
[3] Markert ML, Marques JG, Neven B, et al. First use of thymus transplantation therapy for FOXN1 deficiency (nude/SCID): a report of 2 cases. Blood. 2011;117(2):688–696.

[4] Markert ML, Devlin BH, Alexieff MJ, et al. Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. Blood. 2007;109(10):4539–4547.

[5] Kwan A, Abraham RS, Currier R, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA. 2014;312(7):729–738.

[6] Amatuni GS, Currier RJ, Church JA, et al. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California. Pediatrics. 2019;143(2):e20182300.

[7] Janda A, Sedlacek P, Honig M, et al. Multicenter survey on the outcome of transplantation of hematopoietic cells in patients with the complete form of DiGeorge anomaly. Blood. 2010;116(13):2229–2236.

[8] Markert ML, Alexieff MJ, Li J, et al. Postnatal thymus transplantation with immunosuppression as treatment for DiGeorge syndrome. Blood. 2004;104(8):2574–2581.

[9] Rice HE, Skinner MA, Mahaffey SM, et al. Thymic transplantation for complete DiGeorge syndrome: surgical and medical considerations. J Pediatr Surg. 2004;39(11):1607–1615.

[10] Davies EG, Cheung M, Gilmour K, et al. Thymus transplantation for complete DiGeorge syndrome: European experience. J Allergy Clin Immunol. 2017;140(6):1660–1670.

[11] Markert ML, Alexieff MJ, Li J, et al. Complete DiGeorge syndrome: development of rash, lymphadenopathy, and oligoclonal T cells in 5 cases. J Allergy Clin Immunol. 2004;113(4):734–741.

[12] Markert ML, Devlin BH, Chinn IK, et al. Thymus transplantation in complete DiGeorge anomaly. Immunol Res. 2009;44(1–3):61–70.

[13] Dergousoff BA, Vayalumkal JV, Wright NAM. Survey of infection in complete DiGeorge syndrome and T-cell lymphopenia in Washington state. J Pediatr. 2016;172:127–135.

[14] Griffith LM, Cowan MJ, Notarangelo LD, et al. Improving cellular therapy for primary immune deficiency diseases: recognition, diagnosis, and management. J Allergy Clin Immunol. 2009;124(6):1152–1160.

[15] Rivers L, Gaspar HB. Severe combined immunodeficiency: recent developments and guidance on clinical management. Arch Dis Child. 2015;100(7):667–672.

[16] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[17] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[18] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[19] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[20] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[21] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[22] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[23] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[24] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[25] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[26] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[27] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[28] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[29] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[30] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[31] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[32] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[33] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[34] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[35] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[36] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[37] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[38] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[39] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[40] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[41] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[42] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[43] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.

[44] Rota IA, Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis. 2017;12(1):6.
Caring, LLC. Available from: https://www.payingforseniorcare.com/homecare

[45] Walmart [Internet]. 2021 [cited 2021 January 27]. Bentonville (AR): Walmart. Available from: https://www.walmart.com/search/?query=medical%20supplies&cat_id=976760

[46] Selim MA, Markert ML, Burchette JL, et al. The cutaneous manifestations of atypical complete DiGeorge syndrome: a histopathologic and immunohistochemical study. J Cutan Pathol. 2008;35(4):380–385.

[47] Droege M, Sproule D, Arjunji R, et al. Economic burden of spinal muscular atrophy in the United States: a contemporary assessment. J Med Econ. 2020;23(1):70–79.

[48] Armstrong EP, Malone DC, Yeh WS, et al. The economic burden of spinal muscular atrophy. J Med Econ. 2016;19(8):822–826.

[49] Dangouloff T, Botty C, Beaudart C, et al. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet J Rare Dis. 2021;16(1):47.

[50] Tan H, Gu T, Chen E, et al. Healthcare utilization, costs of care, and mortality among patients with spinal muscular atrophy. J Health Econ Outcomes Res. 2019;6(3):185–195.

[51] Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007;22(8):1027–1049.

[52] Martsolf GR, Kandrack R, Rodakowski J, et al. Work performance among informal caregivers: a review of the literature. J Aging Health. 2020;32(9):1017–1028.

[53] Carmichael F, Charles S. The opportunity costs of informal care: does gender matter? J Health Econ. 2003;22(5):781–803.

[54] James BD, Wilson RS, Barnes LL, et al. Late-life social activity and cognitive decline in old age. J Int Neuropsychol Soc. 2011;17(6):998–1005.

[55] Cacioppo JT, Hughes ME, Waite LJ, et al. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. Psychol Aging. 2006;21(1):140–151.

[56] Mihalopoulos C, Le LK, Chatterton ML, et al. The economic costs of loneliness: a review of cost-of-illness and economic evaluation studies. Soc Psychiatry Psychiatr Epidemiol. 2020;55(7):823–836.