Real-world Disease Burden and Health Care Resource Utilization for Patients with Barth Syndrome Throughout Their Lifespan

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BACKGROUND

- Barth syndrome (BTHS) is an ultra-rare X-linked disorder with an estimated prevalence of approximately 1 in 1,000,000 male births,[1] characterized by cardiac issues, progressive skeletal myopathy, growth delay, neutropenia, and feeding difficulties[2-4]
- Cardiomyopathy develops in most patients before 5 years of age (commonly before 6 months of age)[2-8]
- The US FDA has accepted a New Drug Application (NDA) for elamipretide HCl, the first disease-specific treatment for BTHS, supported by positive data from a Phase-3 Natural History Control Study[9] and additional supporting efficacy and safety data from TAZPOWER Open Label Extension (OLE)[10]
- Long-term results of the TAZPOWER OLE trial in BTHS patients demonstrated significant and durable improvements in functional measures of exercise capacity and muscle strength, and echocardiographic measures of cardiac function, including significant and durable improvements in effort-dependent and effort-independent assessment measures of BTHS[10]
- A natural history study comparing patients from TAZPOWER OLE with untreated, age-matched, natural history control patients with BTHS indicated that elamipretide may attenuate the natural decline in heart function and improve functional capacity in patients with BTHS[9]
- Clinical trials for orphan drugs conducted with small patient populations can establish efficacy and safety, but economic evaluations of orphan drugs aimed at treating ultra-rare orphan diseases are more challenging[1]
- Cost-of-illness or burden-of-disease studies are scarce in rare diseases, presenting significant challenges in the economic evaluation of the costs associated with orphan drugs,[1,11] such as elamipretide, for the treatment of patients with BTHS
- The Barth Syndrome Registry and Repository (BRR) contains data dating back to 2014 and is maintained by the advocacy organization Barth Syndrome Foundation, though it was not designed to capture all inputs that would be required to have a good understanding of claims data due to lack of approved treatments. Additionally, the BRR may introduce bias due to capturing data only from those respondents that are able and willing to participate[12,13]
- In addition, health insurance claims data are associated with key challenges, including data fragmentation, incomplete patient data, and limited utilization insight, as claims data are collected to obtain reimbursement and were not designed for research purposes[14]
- Due to the limited, insufficient data, the metrics payers prefer to assess are not necessarily easily captured;[12] therefore, anecdotal evidence from patient cases published in the medical literature may be used as a possible source to assess the real-world cost and disease burden of diagnosed BTHS

OBJECTIVE

- We assessed real-world data on health care resource utilization (HCRU) extrapolated from patient cases in the medical literature to increase our understanding of the burden of disease and HCRU for infant, adolescent, and adult patients with BTHS

METHODS

- A search of the published medical literature (PubMed) and patient reports and abstracts/presentations (Google) was completed in January 2025 to identify individual cases that assessed the burden of disease and potential cost of BTHS throughout a patient's lifespan
- Cases were also identified from Stealth BioTherapeutics' Expanded Access Program (EAP) for elamipretide in BTHS in the United States
- Real-world disease burden and HCRU for infant, adolescent, and adult patients with BTHS were summarized, with key areas of common HCRU being identified from the cases (i.e., medical procedures, interventions, medications, hospitalizations, and outpatient visits)
- Results from the patient cases were compared with data inputs reported from the BRR from the medical literature[12]

RESULTS

- Eight (8) confirmed patient cases were identified from the medical literature that demonstrated HCRU associated with BTHS
- Five (5) of these cases described patients that did not receive treatment with elamipretide (**Table 1**)
- Most affected individuals with BTHS in the real-world patient cases from the medical literature presented with symptoms in infancy, including heart failure (specifically cardiomyopathy), neutropenia, skeletal muscle and eating disorders, and prepubertal growth delay
- The diagnostic journey for patients with BTHS has been demonstrated through these cases to be difficult, with the majority of patients receiving BTHS diagnosis after the development of cardiomyopathy or a family member is diagnosed, even in symptomatic patients

Table 1. Burden of Disease Associated with BTHS: Patient Cases from Published Medical Literature

Reference	Reported Presenting Clinical Issues	Health Care Resource Utilization Reported
Elamipretide HCl Presentation to the Cardiovascular and Renal Drugs Advisory Committee NDA 215244 Stealth BioTherapeutics October 10, 2024. Available at: https://www.fda.gov/media/182609/download[15]	• Cardiomyopathy, with LVNC, led to 2 bouts of heart failure • Neutropenia • Cardiac arrhythmia • Multiple gastrointestinal and nutritional issues (difficulty eating, gagging, nausea, throwing up, diarrhea) • Skeletal muscle weakness • Debilitating fatigue • Exercise intolerance • Healing problems • Pain (especially headache, abdominal pain, and leg pain) • POTS • Various metabolic and endocrine abnormalities • Growth delays • Patient died at 28 years of age	• 47 hospitalizations (total of 564 days) • 57 procedures under anesthesia (including gastrostomy, defibrillator implantation, and bone marrow aspiration) • 16 central lines • Weekly physician appointments • Multiple daily medications • Tube feedings
Woiewodski L, Ezon D, Cooper J, Feingold B. Barth syndrome with late-onset cardiomyopathy: a missed opportunity for diagnosis. *J Pediatr.* 2017;183:196-8.[16]	• A male infant presented at age 2 years • Neutropenia • Growth delay • History of the death of a maternal uncle • Acute heart failure (i.e., late onset cardiomyopathy)	• Extensive evaluation over 10 years • BTHS diagnosed after patient presented in acute heart failure • Delay in diagnosis may have led to worse health outcomes and higher health care costs
Vanderford R. Genetic discovery uncovers answers to one patient's lifelong health questions. April 29, 2024. Available at: https://umc.edu/news/News_Articles/2024/04/Barth-Syndrome.html[17]	• Lifetime of cardiovascular issues • Skeletal myopathy • Exercise intolerance	• Diagnosed with BTHS after a cousin's son was born with BTHS • Additional diagnoses have since been made in this family
Tovaglieri N, Russo S, Micaglio E, et al. Case report: Variability in clinical features as a potential pitfall for the diagnosis of Barth syndrome. *Front Pediatr.* 2023;11:1250772.[18] *Two male maternal cousins sharing the same mutation in the TAZ gene with a wide phenotypic variability demonstrated that one was early diagnosed with BTHS due to heart failure as an infant and another diagnosed with BTHS at 33 years of age*	**Patient 1** • 6-year-old, white male born full-term with normal growth parameters • Cardiac examinations revealed cardiomyopathy with impaired left ventricular systolic function with an EF of ~38% • BTHS was clinically suspected because the maternal uncle died for complications of dilated cardiomyopathy at age 7 months • Normal neutrophil count with episodic moderate neutropenia • No significant episodes of hypoglycemia occurred, except for at 3 years of age, during a viral gastroenteritis • Neither skeletal muscle weakness nor growth retardation have been observed until 6 years of age	• BTHS diagnosed by the genetic evaluation • Cardiac function was evaluated by transthoracic echocardiography at age 2 months • Pharmacological treatments for heart failure started with beta-blockers, ACE inhibitors, diuretics, and ivabradine • At 6 years old, cardiac evaluation showed increased wall thicknesses on the inferior wall and on all mid-apical segments, accentuation of the trabecular meshwork, and a slight reduction of systolic function overall (LVEF 47%–48%) • At age 2, during an infection episode accompanied by severe neutropenia, therapy with G-CSF was started and stopped a few months later • Under therapy with Glycosade® to keep blood sugar levels consistent and prevent hypoglycemia • Patient monitored for metabolic alterations from age 2 on, and low citrulline and arginine levels were detected, which have been corrected by increasing supplementation therapy (citrulline, arginine, and vitamin B12)
	Patient 2 • Maternal cousin of Patient 1 • 33-year-old white male with recurrent severe neutropenia since early childhood • Patient has two brothers: one died due to congenital cardiomyopathy at age 1 month and the other is in good health • Cardiac function parameters have always been normal throughout his life until adulthood • Neutropenia observed at birth after an acute urinary tract infection • Cardiac arrest at age 11 • During his adolescence, the patient showed delayed growth in stature and weight and a bone mineral density that was lower than expected for gender and age (calculated T-score—2.9 at spinal level at 15 years of age)	• Patient was hospitalized at 1 year of age for septic shock due to a severe *Pseudomonas aeruginosa* infection • Frequent and important infectious episodes with hospitalization during the first years of life • After repeated neutrophil count examinations with value <500/µl, therapy with 4 µg/Kg G-CSF was started on alternate days at 4 years of age, with good recovery of neutrophil count and no other infectious episodes • At age 11, after discontinuation of G-CSF therapy, the patient was hospitalized again for febrile gastroenteritis with severe dehydration • Patient suffered from cardiac arrest and then septic shock after surgical hemi-colectomy for two colic perforations • G-CSF therapy was reinstated with a contextual normalization of the neutrophil count and only sporadic leukocytosis • In adolescence, because of the associated presence of a hypovitaminosis D condition, supplemental therapy with calcifediol was introduced • At age 23, the T-score at spinal level improved slightly to −2.2, but vertebral fractures (at D11, D12, and L1) were observed. For this reason, the patient was also treated with bisphosphonates by infusion • At age 25, the patient was evaluated by a geneticist for hematopoietic system disorders by DNA sequencing and mutation analysis in a panel of candidate genes, the sequences were found to be normal • The patient had electrocardiogram and echocardiogram for physical activity, normal • At age 33, diagnosis of BTHS made, by elevated MLCL/CL and DNA sequencing • Cardiac evaluation showed a mild EF reduction not requiring therapy

ACE, angiotensin-converting enzyme; BTHS, Barth syndrome; DNA, deoxyribonucleic acid; EF, ejection fraction; G-CSF, granulocyte colony-stimulating factor; LVEF, left ventricular ejection fraction; LVNC, left ventricular noncompaction; MLCL/CL, monolysocardiolipin/cardiolipin; POTS, postural orthostatic tachycardia syndrome.

- Three (3) cases were identified from the medical literature for patients with BTHS in the EAP for elamipretide in the United States (**Table 2**)
- All three patients in the EAP program experienced cardiac difficulties as a result of BTHS
- BTHS was associated with high disease burden and excessive inpatient/outpatient HCRU in these EAP patients, with a positive risk-benefit associated with elamipretide
- These real-world data from the EAP illustrate the transformative potential of elamipretide in addressing severe, refractory cardiac dysfunction in BTHS, demonstrating the therapeutic value of the treatment

Table 2. Burden of Disease Associated with BTHS: Patient Cases from the Elamipretide Expanded Access Program

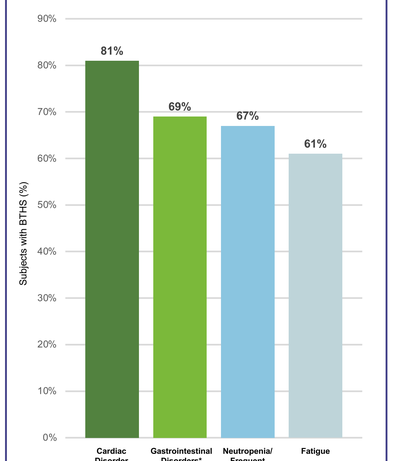
Reference	Reported Presenting Clinical Issues	Health Care Resource Utilization Reported (Including Elamipretide)	Results of Treatment
Koenig MK, Russo SN, McBride KL, Bjornsson HT, Gunnarsdottir BB, Goldstein A, Falk SA. Use of Elamipretide in patients assigned treatment in the compassionate use program: Case series in pediatric patients with rare orphan diseases. *JIMD Rep.* 2022;64(1):65-70.[19]	• Male infant with heart gallop within hours of birth • Diagnosis of BTHS made based on rapid genome sequencing and physical examination • Neutropenia • Severe dilated cardiomyopathy • EF ~ 20%	• Cardiomyopathy unresponsive to maximal medical therapy that included milrinone, sacubitril/valsartan, and carvedilol • At 3 weeks of age, elamipretide was initiated intravenously at 0.25 mg/kg/day • At 4 weeks of age, patient was switched to subcutaneous dosing at 0.5 mg/kg/day and discharged from the hospital on that dose • Additional medications administered since discharge including flignastim, sacubitril/valsartan, carvedilol, and spironolactone • Arginine added to regimen	• EF improved from ~20% to 45-55% during 150 days of elamipretide therapy • Dyskinesia of the LV remained • Neutropenia improved on filgrastim, with normal absolute neutrophil counts • Meeting all developmental milestones at 4 months of age • No adverse events related to elamipretide • Patient tragically passed away at 5.5 months with cause of death undetermined with other significant conditions (BTHS, unsafe sleep environment, and *Klebsiella pneumoniae* bacteremia)
Goldstein AC, Pantano C, Redko M, MacMullen LE, Maeda K, O'Connor MJ. Expanded-access use of elamipretide in a critically ill patient with Barth syndrome. *Genet Med Open.* 2024;2:101859.[20]	• 11-month-old child • Presented in cardiogenic shock • Diagnosed with BTHS	• Clinical status rapidly deteriorated • Placed on ECMO • Elamipretide initiated • Placed on a VAD • Listed for transplant	• By 14.5-months, cardiac function improved • At 16 months, VAD was successfully explanted • By 23 months, the patient was thriving, with the native heart intact
Ortmann L, Velasco D, Cole J. Expanded-access use of elamipretide in a newborn with Barth syndrome: a case report. *Eur Heart J Case Rep.* 2025;9(2):ytaf030.[21]	• Diagnosed *in utero* with BTHS • Moderately dilated LV with an LVEF of 20% at birth	• Remained hospitalized and was intubated for several weeks • Medications for haemodynamic support administered • LVEF improved but still below normal • At 1 month of age, therapy with daily IV elamipretide began • Standard-of-care oral heart failure medications initiated (carvedilol 0.05 mg/kg, spironolactone 1.5 mg/kg, and captopril 0.05 mg/kg three times daily)	• Throughout hospitalization, echocardiograms improved with normalization of right-sided function and improved LV function to the low-normal to mildly depressed range • Steady progress and weight gain on all oral feeds • Improvement of LVEF to near-normal levels • Discharged from the hospital 27 days later (continuing elamipretide and oral heart failure medications) • Outpatient follow-up echocardiogram showed improvement of LVEF to 60%

BTHS, Barth syndrome; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; VAD, ventricular assist device.

Patient Case Comparisons with Reported BRR Data

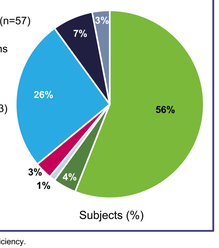
- The published case reports are supported by the documented patient history (**Figure 1**), first manifestations of BTHS (**Figure 2**), delayed diagnosis (**Figure 3**), and health care utilization (**Figure 4**) of individuals with BTHS reported by patients/caregivers in BRR[12]

Figure 1. Commonly Reported Conditions in Patient History in Subjects with BTHS in the BRR[12]



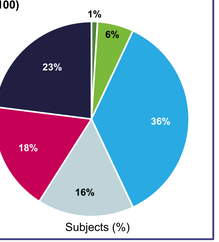
*Commonly reported GI disorders were chronic constipation (n=16), chronic diarrhea (n=20), dysphagia (n=7), feeding difficulties (n=51), and gastroesophageal reflux (GERD) (n=25).

Figure 2. First Manifestations for Patients in the BRR[12]



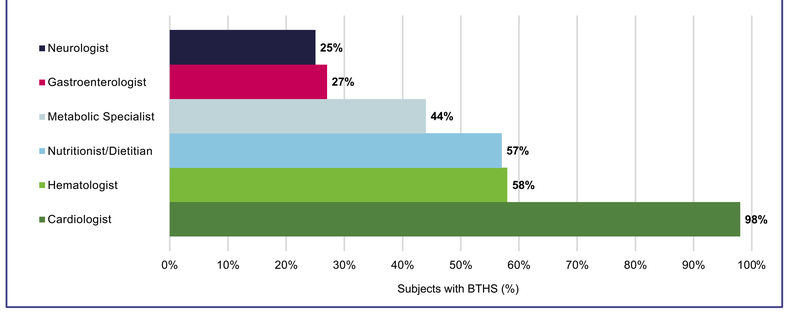
Other: Stroke, hypoglycemia, and carnitine deficiency.

Figure 3. Age at BTHS Diagnosis for Patients in the BRR[12]



- Most subjects (90%, n=90/100) were the first person in the family to be diagnosed (probands), with the others (10%, n=10/100) being diagnosed after a positive BTHS family history[12]

Figure 4. Commonly Visited Specialists Seen Within the Previous Year (Reported by ≥25% of Participants) in the BRR[12]



- Although the cases reviewed in the literature did not specifically list the different specialists seen by the BTHS patients, it was concluded that these specialists would have been a part of the patients' comprehensive care teams due to the BTHS manifestations reported

CONCLUSIONS

- Health economic evaluations for rare diseases are scarce, particularly before there is an FDA-approved treatment available
- The real-world data from patient cases reviewed from the medical literature reflect the cross-sectional and longitudinal participant data from the BRR in regard to diagnostic odyssey, manifestations, and HRCU across a broad range of affected individual age groups
- Patient cases from the EAP reviewed in the literature demonstrate that access to drugs, such as elamipretide, in serious and life-limiting ultra-rare diseases like BTHS, could possibly lessen the disease burden for patients, which will ultimately improve cardiac treatment outcomes
- It should be noted that successful cardiac transplant has no impact on the underlying skeletal myopathy or neutropenia, which indicates that there are still likely additional health care costs associated with BTHS after a successful heart transplant
- Although health economic evaluations for rare diseases are scarce, with a remarkable absence of pharmacoeconomic evidence, a review of the published case report data for patients with BTHS demonstrates that the disease is costly, with associated high disease burden and excessive inpatient and outpatient HRCU, with a positive risk-benefit associated with the therapeutic use of elamipretide

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