Neutropenia in Barth syndrome: characteristics, risks, and management

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Purpose of review
Barth syndrome (BTHS) is an X-linked disease characterized by defective remodeling of phospholipid side chains in mitochondrial membranes. Major features include neutropenia, dilated cardiomyopathy, motor delay and proximal myopathy, feeding problems, and constitutional growth delay. We conducted this review of neutropenia in BTHS to aid in the diagnosis of this disease, and to improve understanding of both the consequences of neutropenia and the benefits of treatment with granulocyte colony-stimulating factor (G-CSF).

Recent findings
In 88 patients with BTHS, neutropenia, that is, at least one count below 1.5×10\textsuperscript{9}/l, was detected in 74 (84%) and 44% had severe chronic neutropenia, with multiple counts below 0.5×10\textsuperscript{9}/l. The pattern of neutropenia varied between intermittent and unpredictable, chronic and severe, or cyclical with mathematically regular oscillations. Monocytosis, that is, monocytes more than 1.0×10\textsuperscript{9}/l, was observed at least once in 64 of 85 (75%) patients. G-CSF was administered to 39 of 88 patients (44%). Weekly average G-CSF doses ranged from 0.12 to 10.92 mg/kg/day (mean 1.16 mg/kg/day, median 1.16 mg/kg/day). Antibiotic prophylaxis was additionally employed in 21 of 26 neutropenic patients. Pretreatment bone marrow evaluations predominantly showed reduced myeloid maturation which normalized on G-CSF therapy in seven of 13 examined. Consistent clinical improvement, with reduced signs and symptoms of infections, was observed in response to prophylactic G-CSF and prophylactic antibiotics. However, despite G-CSF and antibiotics, one adult patient died with multiple infections related to indwelling medical devices and gastrostomy site infection after 15.5 years on G-CSF and a pediatric patient required gastrostomy removal for recurrent abdominal wall cellulitis.

Summary
BTHS should be considered in any men with neutropenia accompanied by any of the characteristic features of this syndrome. Prophylaxis with G-CSF and antibiotics prevents serious bacterial infections in the more severe neutropenic patients although infections remain a threat even in patients who are very compliant with therapy, especially in those with indwelling devices.

Keywords
Barth syndrome, granulocyte colony-stimulating factor, granulocytes, macrophages, monocytes, neutropenia

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\textbf{Curr Opin Hematol} 2019, 26:6–15
DOI:10.1097/MOH.0000000000000472

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BACKGROUND

Peter Barth first reported the syndrome which carries his name in 1983 as an X-linked triad of dilated cardiomyopathy (DCM), skeletal myopathy, and neutropenia with high mortality. He described three affected male infants from a large Dutch family in which 17 boys had died at between 3 days and 31 months of age because of either neutropenic bacterial sepsis or cardiac failure [1]. He subsequently reported cyclic neutropenia and monocytosis [2]. The phenotype of Barth syndrome (BTHS) has expanded steadily and now includes developmental motor and constitutional growth delay, organic aciduria, cardiac endocardial fibroelastosis and left ventricular noncompaction, ventricular arrhythmia, fetal cardiomyopathy/fetal loss, feeding problems, hypoglycemia, lactic acidosis, and characteristic facial features (reviewed in [3]).

Mutations in TAZ (Xq28) as the cause for BTHS were first described in 1996 [4]. TAZ encodes an evolutionarily highly conserved acyltransferase, deficiency of which results in defective remodeling of inner mitochondrial membrane phospholipids, especially that of cardiolipin. The cause of neutropenia in this disease remains the subject of debate; researchers postulated that mitochondrial abnormalities could lead to enhanced apoptosis of myeloid precursors and neutrophils, although the only published clinical study did not demonstrate shortened cell survival despite avid binding of annexin-V to BTHS blood neutrophils [5]. However, TAZ knockdown experiments suggest accelerated apoptosis of myeloid progenitor cells because of increased dissipation of mitochondrial membrane potential, aberrant release of cytochrome C, and activation of caspase-3 [6]. Neutrophil functions, such as directed motility, phagocytosis, and killing, appear to be unimpaired [1,5].

BTHS is still rarely diagnosed, with approximately 200 living men worldwide currently known to the Barth Syndrome Foundation (BSF), although there is evidence for substantial underdiagnosis [3]. To aid in the understanding and diagnosis of this disease, particularly with reference to patterns of neutropenia and associated infection risk, we reviewed clinical data, routine blood counts, and responses to granulocyte colony-stimulating factor (G-CSF) therapy from 88 affected boys.

METHODS

Patients

Patient data were obtained from the Barth Syndrome Registry, National Health Service Specialised Services Barth Syndrome Service, Royal Hospital for Children, Bristol, UK; Department of Pediatrics, University of Florida Health Center, Gainesville, Florida; and the Severe Chronic Neutropenia International Registry (SCNIR), University of Washington, Seattle, Washington. Patients or their parents or guardians gave consent for these studies as approved by the respective review boards. Retrospective clinical data were sourced from a combination of hospital notes and parental questionnaires.

BTHS was diagnosed through a combination of characteristic clinical features (predominantly cardiomyopathy and myopathy) and detection of excessive 3-mean granulocyte count in urine. All were confirmed as having causative mutation of the TAZ gene (Barth Syndrome Registry data). Clinical data on illness and infections were gathered through chart reviews, patient questionnaires, and annual reports of patients in the SCNIR. Complete blood counts (CBC) were examined from three sources: the biennial BSF International Scientific, Medical and Family Conferences; the clinics of the UK national Barth Syndrome Service; or patients’ local hospital clinics. Seventeen neutropenic men underwent a bone marrow examination.

Mathematical analysis

The Lomb periodogram was used to test for statistical significance periodicity in blood cell counts [7–9].

RESULTS

Clinical characteristics

The frequency of common disease characteristics is shown in Table 1. Of those patients showing DCM, 68% manifested symptoms of cardiomyopathy in the first year of life.
Incidence and severity of neutropenia

Absolute neutrophil counts (ANC) were recorded in all 88 patients at first visit to one of the BTHS clinics. The first recorded CBC of 51 (58%) patients revealed an ANC of 1.5 × 10^9/l or less. Follow-up records revealed that 74 of 88 study participants (84%) had at least one ANC less than 1.5 × 10^9/l. 28 of whom (38%) had a mean ANC less than 1.5 × 10^9/l.

Multiple CBCs (two or more counts) were available in 79 of the 88 (90%) patients, 44% of whom met the criteria for severe chronic neutropenia, with multiple ANCs less than 0.5 × 10^9/l over greater than 3 months. Table 2 shows the data on neutropenia frequency in more detail.

Fifty-two patients had more than 10 CBCs; 15 of 52 never received G-CSF. The distribution of ANCs in these 15 patients is shown in Fig. 1a. Despite not receiving G-CSF, some showed wide amplitude of ANC, for example, UPN1 with a range of 0.05–9.24 × 10^9/l in 63 counts (median 1.74).

<table>
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<tr>
<th>Table 1. Disease characteristics of patients</th>
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<td>Frequency within cohort</td>
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The frequency of common diseases characteristics based on patient, family, and clinician observations.

Fourteen of the 88 patients (16%) were not neutropenic on any of their CBCs (1–33 ANCs performed over 0–12.3 years). Mean ANCs in the 14 nonneutropenic patients ranged from 1.95–5.28 × 10^9/l. Twelve of these 14 (86%) nonneutropenic BTHS patients exhibited severe DCM. One other boy (UPN36) who presented with severe DCM was only mildly neutropenic once (ANC 1.35 × 10^9/l) from 72 CBCs taken over 9.58 years.

Monocytosis

Monocytosis (defined as an absolute monocyte count of greater than 1.0 × 10^9/l) was frequent, recorded at some stage in 64/85 patients (75%) with available monocyte counts. Twenty-three of the 64 patients (36%) had absolute monocyte counts of more than 3.0 × 10^9/l on at least one occasion, with the highest monocyte count being 9.69 × 10^9/l. Fifty of 85 patients (59%) had a monocyte count greater than 1.0 × 10^9/l at the time of neutropenia (ANC < 1.5 × 10^9/l); 13 of the 50 patients (26%) had a monocyte count greater than 3.0 × 10^9/l at the time of neutropenia. Seven of the 14 nonneutropenic patients (50%) also had monocyte counts greater than 1.0 × 10^9/l; one patient had two counts more than 3.0 × 10^9/l.

Difference in incidence and severity of neutropenia occurred among affected family members (Fig. 1b, UPN35, 36, and 46). ANCs in members of this family did not correlate with their severity of cardiomyopathy, proximal myopathy, or other symptoms. The severity of neutropenia sometimes changed with time. For example, UPN9 (who has never received G-CSF) had a neutrophil count less than 1.0 × 10^9/l on five of 10 counts (median 0.95 × 10^9/l, range 0.3–1.76 × 10^9/l) performed serially at age 2–5 months, one of eight counts (median 1.25 × 10^9/l, range 0.7–2.5 × 10^9/l) performed serially at 4.75 years, yet none of 17 counts (median 1.3 × 10^9/l, range 1.1–1.9 × 10^9/l) taken over 6 weeks at 9.5 years and four of 21 counts at 12.5 years (median 1.28 × 10^9/l, range 0.45–2.99 × 10^9/l).

Rhythmic fluctuations and cyclic neutropenia

Twenty-seven patients had serial blood counts before G-CSF and eight of the 27 had at least 21 counts, giving an adequate period of blood count profiling for assessment of cyclic neutropenia. Seven boys appeared to have oscillation of blood neutrophils, four of whom are shown in Fig. 2a, c, and d and Fig. 3a.

Only one boy (UPN10, Fig. 3a) satisfied strict mathematical criteria for cyclic neutropenia. His
cycle length ranged from 21 to 29 days with a mean of 23.3 days. It was not clear what effect G-CSF had on cycle duration because of experimentation with dosage and frequency of drug following initiation. In UPN37 (Fig. 2a), aphthous ulceration occurred at nadirs of ANC during the period of study with an average cycle length of 25 days (range 23–28), although this patient did not satisfy mathematical criteria for cyclical neutropenia. Serial counts in two brothers suggested cycling at shorter time intervals, that is, 10 days (range 8–13) and 9 days (6–13), respectively (UPN35, Fig. 2c) and above (UPN36, Fig. 2d), but these patterns were not apparent on repeat profiles on either boy performed 3 years later (data not shown).

**Bone marrow characteristics**

Bone marrow results were available from 19 tests performed in 17 patients. Six patients were tested before commencing G-CSF. The remaining aspirates comprised surveillance tests taken to exclude development of myelodysplasia or leukemia secondary to G-CSF therapy.

The aspirate or biopsy was reported to be hypocellular in three patients; the remainder had normal or had only a modest reduction in cellularity. One patient had mild red cell dysplastic change after 4 years of G-CSF therapy. None of the marrows obtained on G-CSF showed an increase in marrow myeloblasts and no clonal cytogenetic change was detected.

Decreased myeloid maturation was reported for five of six patients prior to G-CSF therapy. The common abnormality was a relative paucity of mature neutrophils in the marrow. One patient was reported to have an arrest at the metamyelocyte stage; the others primarily had reduced numbers of mature neutrophils in the marrow. None of the aspirates were described as showing promyelocyte arrest.

Results were available on 13 patients investigated during G-CSF therapy. Seven marrows showed normalization of myeloid differentiation.
the remaining marrows still showing left-shifted myelopoiesis. Marrow cellularity increased in two of three patients who had marrows performed both before and on treatment with G-CSF. Increased or toxic granulation was observed in two patients.

Increased eosinophils or eosinophil precursors were reported for two of six patients prior to G-CSF therapy and six of 13 patients on therapy, one of whom had increased eosinophils prior to receiving G-CSF.

Responses to granulocyte colony-stimulating factor

G-CSF was administered to 39 of 88 patients (44%). Responses to G-CSF are illustrated in Fig. 3. Some patients were treated just to cover periods of infection or mouth ulceration but in most G-CSF was given on a dosing schedule varying from daily to weekly, the most common regimes being three times weekly or alternate daily. For 17 patients receiving G-CSF on whom detailed data were available, doses averaged over a week ranged from 0.12 μg/kg/day to 10.92 μg/kg/day (mean 1.160 μg/kg/day, median 1.160 μg/kg/day). Each of these treated patients had previously exhibited severe symptomatic neutropenia. For this group of 17 patients, the median ANC pre-G-CSF therapy was $0.47 \times 10^9$/l and mean $0.57 \times 10^9$/l (range 0.00–10.45 $\times 10^9$/l) compared with median ANC of $2.28 \times 10^9$/l, mean ANC of $3.93 \times 10^9$/l (range 0.00–33.89 $\times 10^9$/l) during G-CSF therapy ($P < 0.001$, paired two tailed t-test).

Determining a dose of G-CSF that alleviated symptoms without producing excessively high counts was a problem in some patients because of the wide amplitude of ANC prior to treatment. Figure 4a and b show two examples of patients with marked responses to G-CSF. Careful titration of G-CSF dose (exemplified by UPN10, Fig. 3a) and alternate daily or thrice weekly dosing prevented excessive rises in neutrophil counts in most patients.

Infection risk

A detailed review for significant bacterial infections was conducted in 35 patients under the longitudinal care of the UK NHS Barth Syndrome Service because all retrospective notes could be accessed in this group. Infections prior to introduction of G-CSF therapy included streptococcal bacteremia/
FIGURE 3. G-CSF responses. (a) Neutropenia resolved after treatment with G-CSF in UPN10, the only patient who satisfied strict mathematical criteria for cyclical neutropenia, with an average periodicity of 23.3 days. Doses of G-CSF were steadily titrated down from 5 to 0.5 μg/kg/day to keep ANC above $1.5 \times 10^9/l$ (note logarithmic scale with ANC ranging up to $33.9 \times 10^9/l$). (b) By contrast, UPN69 continues to show irregular periods of neutropenia after commencement of G-CSF at 3 μg/kg/dose three times weekly. (c) Effect of G-CSF on range of ANC in 14 other patients (UPN 5, 8, 13, 19, 20, 23, 34, 38, 39, 40, 41, 44, 58, and 67) with the largest numbers of on and off-therapy CBC. ANC, absolute neutrophil count; CBC, complete blood count; G-CSF, granulocyte colony-stimulating factor.
septicemia (two patients, one resulting in acute tubular necrosis), *Haemophilus* septicemia (one patient, resulting in renal failure requiring renal transplantation), osteomyelitis (two patients), septic arthritis (one), soft tissue abscesses (three), cellulitis (five), balanitis (two) lobar consolidation/pneumonia (four), gingivitis (two), severe recurrent aphthous ulceration (two), urinary tract infections (one), and secondary infection of an underlying keratosis pilaris rash (one). A further UK patient who predeceased this study had neutropenia and skin sepsis; he developed severe neurological handicap secondary to *Haemophilus* septicemia. The overall registry data also identified further instances of *Haemophilus* septicemia (one), pneumococcal bacteremia (one), *Haemophilus* septicemia (one) and *Pseudomonas* cellulitis (one), and four unspecified episodes of bacteremia/sepsis.

Twenty-six of these 35 UK (74%) patients had one or more counts in the severe neutropenic range, 14 (40%) having an ANC of zero on occasions. Of these 26 patients with severe neutropenia, 14 (54%) had experienced severe bacterial infections thought to be secondary to their underlying neutropenia.

Only five patients in the entire group had significant instances of suspected/proven bacterial infection after institution of G-CSF ± antibiotic prophylaxis. One patient died of sepsis after suffering recurrent staphylococcal infections, candidemia (*Candida parapsilosis*) and *Enterobacter cloacae* infection associated with multiple indwelling central venous catheters, an implantable cardioverter defibrillator (ICD) and extensive granulation tissue which formed around long-term gastrostomies. He also required omphalectomy because of long-term umbilical inflammation/infection. All infections occurred despite consistent prevention of neutropenia by G-CSF therapy and death occurred after 15.5 years of G-CSF therapy; there was no evidence of myelodysplastic or malignant change on longitudinal bone marrow monitoring. Four other patients experienced cellulitis either following trauma such as cat scratches or insect bites (three patients) or associated with poor compliance with G-CSF (one). One of these patients also had recurrent localized cellulitis at his gastrostomy site, which necessitated closure of the gastrostomy, despite consistent G-CSF therapy.

From self-reported data on 68 patients in the Barth Syndrome Registry, other more minor infections were seen as follow: ear infections (32%), sinusitis (18%), and urinary tract infections (11%). Thirty-two percentage of parents reported that their children had been admitted to hospital on one or more occasions.

**FIGURE 4.** Exuberant responses to G-CSF. (a) UPN37 showed a range of ANC of 0.1 to 5.9 × 10⁹/l in the year before commencing G-CSF at 3 µg/kg/dose thrice weekly. His ANC ranged from 0.2 to 79.9 in the 6 weeks afterwards, although renal transplantation (required as a consequence of previous *Haemophilus* sepsis) may have contributed to these dramatic changes. By contrast, no events occurred in UPN51 (shown in b), whose ANC rose to 64 × 10⁹/l, from a maximum ANC of 0.6 × 10⁹/l in nine CBCs taken at regular intervals over the previous 2 months, after G-CSF was introduced at 10 mg/kg/day; this necessitated switching to alternate daily dosing. ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor.
more occasions for investigation or treatment of febrile episodes or proven infections.

**DISCUSSION**

Originally BTHS was reported as a composite X-linked syndrome of DCM, skeletal myopathy, neutropenia, and growth delay. More recent data emphasize that motor delay, infections, mouth ulcers, fatigue, and feeding problems (sometimes requiring tube or gastrostomy feeding) are also common features (Table 1). However, tremendous phenotypic diversity and interpatient variability is apparent (reviewed in detail by Clarke et al. [3]).

This phenotypic diversity applies profoundly to neutropenia which this series shows can vary from being persistent and severe, through widely variable and unpredictable (the commonest pattern) to never being neutropenic. No genotype/phenotype correlation has been demonstrated for any aspect of this disease and this is perhaps not surprising when ANC can vary widely even in men within a single family (as shown in Fig. 1b). It should be noted that one member of this family (UPN36, ANC shown in Fig. 1b) was minimally neutropenic just once (at $1.35 \times 10^9/l$, average ANC 4.08) from 72 CBCs taken at between 13 months and 11 years of age despite an otherwise severe disease phenotype.

Rigaud et al. [10] report similar findings in a French cohort in terms of initial ANC, percentage of patients with at least one neutropenic count and those with a median ANC less than $0.5 \times 10^9/l$. However, these authors highlighted a correlation between severity of neutropenia at diagnosis and prognosis; all four patients in that study with an initial ANC $0.5 \times 10^9/l$ or less died by the age of 3 years. By contrast, 22 patients in our cohort had an initial ANC in the same range but only one death occurred (at 23 years, unrelated to infection). It seems likely that wider use of G-CSF in the patients reported in this series compared to the French series (44% versus 27%) contributed to this discrepancy.

BTHS neutropenia has often been described as cyclical. Our analysis of this was hampered by absence of adequately detailed profiles, that is, blood counts taken thrice weekly for 3–6 weeks, in many patients. However, by stringent mathematical analysis, we were able to show definitive cycling behavior – with an average periodicity of 23.3 days – in only one boy (UPN10, Fig. 3a). Several other profiles also showed rhythmic variation (e.g., that of UPN37 in Fig. 2a), which might be easy to confuse with the disease cyclic neutropenia. Several boys with BTHS also showed an intermittent pattern of severe mouth ulceration and gingivitis when neutropenic, which could add to this confusion.

Similarly, none of the patients described by Rigaud et al. [10] exhibited cyclic neutropenia. It is therefore more accurate to describe BTHS patients as having variable neutropenia.

Important differential diagnoses include cyclic, severe congenital, and idiopathic neutropenia. Diagnostic confusion between severe congenital neutropenia and BTHS could occur although only rarely; for example, one patient had nine out of 10 ANC below $0.2 \times 10^9/l$ over a 1-year period. Further features in common between severe congenital neutropenia and BTHS include monocytosis, myelocyte arrest, and eosinophilia or increased numbers of eosinophil precursors on blood/marrow examination [1,11,12].

The cases that we have described stress the serious risks of infection in these children. Further evidence is provided by the family originally described by Barth et al. [1] and an 18% fatality rate because of infection in the French national experience: two deaths from septic shock and two cardiac deaths during unexplained high fever [10]. However, it is intriguing that there were no cases of clostridial infections in this series (even though some children had severe persistent neutropenia) and comparatively few cases of deep tissue cellulitis. Gauging the risk of infection is also not easy because of the highly unpredictable nature of the neutropenia. As one example, UPN37 had mean neutrophil counts of 2.5, 2.17, 2.73, 2.06, 1.59, and $2.21 \times 10^9/l$ in consecutive periods of 2 years yet developed recurrent aphthous ulceration at the nadirs of counts (at 23–28 day intervals, Fig. 2a) in only the last of these periods. This deterioration culminated in *Haemophilus* pneumonia and septicemia, renal failure (requiring paternal allograft), gut ischemia, and *Aspergillus* peritonitis after peritoneal dialysis catheter insertion. His subsequent G-CSF responses are shown in Fig. 4a.

G-CSF usage in BTHS was first reported in 1995 [13]. Thirty-nine of the 88 (44%) patients in the current series have received G-CSF, ranging in frequency from daily to weekly but most typically on a three times per week or daily basis. With averaged doses from 0.12 μg/kg/day to 10.92 μg/kg/day (mean 1.16 μg/kg/day), many boys/men remained intermittently neutropenic (94% of evaluable patients, representative examples can be seen in Fig. 3c). However, these patients were free of significant infections following introduction of G-CSF ± antibiotic prophylaxis in most cases. The notable exception was a man with longstanding severe BTHS manifestations requiring gastrostomy feeding for many years, intravenous feeding requiring central venous catheters, and placement of an ICD to prevent ventricular arrhythmia. He
developed severe granulation reactions at gastrostomy sites, hypertrophic scars at surgical sites, and infections related to central venous catheters, and an ICD despite good control of neutrophil counts by G-CSF over a prolonged period. It is unclear whether some of these were unusual manifestations of BTHS or inanition because of prolonged illness.

Four other boys developed cellulitis: related to nail biting and noncompliance with G-CSF in one patient and suspected cellulitis/reactions of debatable relevance to neutropenia following insect bites and cat scratches in two others. The fourth boy experienced problems with insect bites and recurrent cellulitis around a gastrostomy which eventually necessitated closure. Some patients reported alleviation of aphthous ulceration and reduction in malaise/fatigue although this is hard to evaluate. The French experience included two episodes of severe infection (including one episode of septic shock), whereas patients were receiving G-CSF therapy [10]. These infections underpin the rationale for additional use of antibiotic prophylaxis in a majority of neutropenic UK patients within this series.

Malignancy has been reported in only two boys with BTHS; single cases of juvenile myelomonocytic leukemia (JMML, personal communication, Dr AB de Sousa) and postcardiac transplant Epstein-Barr virus negative T-cell non-Hodgkin lymphoma [14], respectively, neither child having received G-CSF. No other cases of myelodysplasia or leukemia have been reported or are currently known through the Barth Syndrome Registry or SCNIR. Nevertheless, we consider it wise to perform intermittent bone marrow assessments whilst experience of this treatment for BTHS remains limited.

Historically, BTHS has been regarded as extremely rare, with only 450 affected cases ever proven by genetic analysis worldwide. However, with improved case ascertainment and better diagnostic tests now available, a frequency as high as one in 140,000 has been suggested [3]. US Pediatric Cardiomyopathy Registry data showed that 3–5% of all men with cardiomyopathy had BTHS as their underlying diagnosis (Dr Jeffrey Towbin, personal communication). A 2017 Chinese study, using next-generation sequencing to investigate men and sequencing should be www.co-hematology.com or the glucose-6-phosphatase, catalytic subunit 3 (\(G6PC3\)) gene and \(TAZ\) gene and \(TAZ\) sequencing should be included in next-generation sequencing/clinical exome analyses designed to investigate idiopathic neutropenia.

**CONCLUSION**

We recommend that BTHS should be considered within the differential diagnosis of any boy with unexplained neutropenia—whether chronic severe, cyclical, or intermittent in nature. This is most important if neutropenia is accompanied by motor delay, myopathy/ cardiomyopathy, feeding problems, failure to thrive, or suspected mitochondrial disease, although presentation with isolated neutropenia can occur (because DCM is either absent or subclinical or has completely resolved). Particular attention should be paid to boys who lack mutation of \(ELANE\) or the glucose-6-phosphatase, catalytic subunit 3 (\(G6PC3\)) gene (where structural heart abnormalities are also present) [31]. Based on the clinical data summarized in the report, we recommend that neutropenic BTHS men who have recurrent fevers and infections should be treated approximately 3 days per week with G-CSF in doses sufficient to normalize their ANCs. Prophylactic antibiotics, for example, low dose daily penicillin V or trimethoprim–sulfamethoxazole may be helpful.

**Acknowledgements**

D.C.D. is a consultant and receives research support from Amgen, a biopharmaceutical company that produces and markets G-CSF. M.C.M. receives research support from the Natural Sciences and Engineering Research Council of Canada.
C.G.S. and D.C.D. conceived the study, collated and analyzed data, provided clinical care to patients, and wrote the initial draft. All other authors coauthored the study and edited the manuscript. In addition: S.J.G. prepared the figures and analyzed data; C.G.S. and M.K.M. collated data via the Barth Syndrome Registry; B.V. and H.O. collated additional UK and Swiss data, respectively; M.K.D., V.M.B., and K.R.M. organized data collection within the Barth Syndrome community; M.C.M. provided mathematical analysis of cycling behavior; and A.A.B. organized, collated, and analyzed data.

The authors dedicate this study to the memory of Will McCurdy whose large body of neutrophil data stimulated wider use of G-CSF in this condition, better understanding of ANC variability and the development of this study. We also thank the many patients, families, and clinicians who have subsequently collated and contributed blood count data to the Barth Syndrome Registry of the Barth Syndrome Foundation (www.barthsyndrome.org) and the Severe Chronic Neutropenia International Registry, Dr Leo Hamilton for provision of blood count data, and Dr Richard Kelley for comments on our manuscript.

We are indebted to the COGENT Trust for supporting S.J.G. and the early work which made this study possible, and for National Health Service (NHS) Specialised Services for supporting C.G.S. and the development of a coordinated multidisciplinary UK service for BTHS.

Financial support and sponsorship
Ethics approval and consent to participate: Informed consent was obtained from all patients. The Institutional Review Boards at the University of Washington, Seattle, Washington approved the SCNIR to collect data from consented patients (IRB application number 00000996). The Institutional Review Boards at the University of Florida approved the Barth Syndrome Foundation to collect data from consented patients (IRB protocol number 186–2006).

The COGENT Trust (private charity) supported S.J.G. who prepared figures and analyzed data. National Health Service (NHS) Specialised Services supported C.G.S.’s clinical work on Barth syndrome. The SCNIR (D.C.D. and A.A.B.) is supported by an NIH grant, R24AI049393, and by Angen.

Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest


18. This report points to the challenge of diagnosis of Barth syndrome.


20. This recent report points out the world-wide distribution of this rare disease.


Another report pointing out the challenge of recognizing Barth diagnosis.


