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Shwachman Diamond Syndrome – a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment

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Shwachman Diamond syndrome (SDS) is a rare autosomal recessive, multi-system disease characterized by exocrine pancreatic insufficiency, impaired hematopoiesis, and leukemia predisposition. Other clinical features include skeletal, immunologic, hepatic, and cardiac disorders. Around 90% of patients with clinical features of SDS have biallellic mutations in the evolutionarily conserved Shwachman-Bodian-Diamond Syndrome (*SBDS)* gene located on chromosome 7 [1]. The *SDBS* protein plays a role in ribosome biogenesis and in mitotic spindle stabilization though its precise molecular function remains unclear. This review focuses on the clinical presentation, diagnostic workup, clinical management and treatment of patients with SDS.

CLINICAL PRESENTATION

Hematologic Features

Several groups have reported on the hematologic features of patients with SDS [2–5]. The most common hematologic abnormality affecting 88–100% of patients with SDS is neutropenia, typically defined as a neutrophil count less than $1{,}500 \times 10^9$/L. Roughly one-third of patients have chronic neutropenia and the remaining two-thirds have intermittent neutropenia. Anemia, either normochromic-normocytic or macrocytic, with reticulocytopenia has also been described in 42%–82% of patients. Thrombocytopenia (platelet count $<150 \times 10^9$/L) has been reported in 24%–88% of patients and can lead to fatal bleeding. Similar to patients with other marrow failure syndromes, around 80% of patients with SDS have elevated levels of hemoglobin F which is likely a sign of 'stress' hematopoiesis. Cytopenias are usually seen at an early age; presentations at later ages have been reported [6]. Roughly 10%–65% of patients have pancytopenia with some patients developing aplastic anemia [7]. Bone marrow findings

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are variable and may reveal a hypocellular, normocellular, or hypercellular marrow. Marrow cellularity must be interpreted in the context of the patient's peripheral blood counts as cellularity may be patchy and is subject to sampling variation.

Myelodysplastic Syndrome/Malignancy

Similar to other marrow failure syndromes, patients with SDS have an increased risk for myelodysplasia and malignant transformation, in particular, development of acute myelogenous leukemia [8,9]. AML subtypes include AML-M0, AML-M1, AML-M4, AML-M5, and AML-M6. Donadieu et al. [10] reported on 55 patients with SDS, median age of 0.5 years (range, birth to 23) from the French Severe Chronic Neutropenia Registry. With a median follow-up of 8 years (range, 0.3–35.6), 7 patients developed MDS or AML, with an estimated risk of 19% at 20 years and 36% at 30 years. Solid tumors have not been described. The mechanisms underlying this tendency towards malignant transformation are unknown. Marrow cytogenetic clonal abnormalities, particularly involving chromosome 7 [monosomy 7, der(7), i(7q)] and del(20q), have commonly been reported [11]. While certain cytogenetic aberrations, such as monosomy 7, are associated with poor prognosis, the clinical significance of many clonal abnormalities is not clear [12]. Similar cytogenetic abnormalities have been found in patients with MDS or leukemia. A given clonal abnormality may wax and wane over time within a patient and may even become undetectable further complicating clinical interpretation [12]. To date, there have been no reports of progression to AML among SDS patients presenting with i(7q) abnormalities. In contrast, 42% of patients with other chromosome 7 abnormalities either presented with or progressed to advanced MDS or AML [11].

Chromosome instability may play a role in MDS or leukemia development [13]. Some have proposed that an increased risk for cancer evolves from accelerated apoptosis, which may lead to replicative stress and increased risk for evolution of malignant clones in the surviving pool of cells [14]. This model is developed in detail in chapter 13 of this volume. Recently, Austin et al. [15] demonstrated that *SBDS* promotes mitotic spindle stability and regulates chromosome segregation. These results suggest that the high frequency of chromosomal abnormalities seen in the bone marrow of patients with SDS may result, at least in part, from a defect in spindle stability.

Infections and Immune Abnormalities

Patients with SDS are susceptible to recurrent bacterial, viral, and fungal infections, in particular, otitis media, sinusitis, mouth sores, bronchopneumonia, septicemia, osteomyelitis, and skin infections [16]. Neutropenia is likely a contributing factor, as well as possible defects in neutrophil chemotaxis [2,17,18]. Stepanovic et al. [19] demonstrated that neutrophils from patients with SDS were unable to orient and migrate towards a chemoattractant gradient, which is essential for normal neutrophil migration to a site of infection or inflammation. Others have suggested that the neutrophil abnormalities may be due to an abnormal distribution of concanavalin-A receptors on patient's neutrophils or cytoskeletal/microtubular defects [20]. Importantly, despite a deficiency in neutrophil number and function, patients with SDS are able to recruit sufficient neutrophils in response to infections to form abscesses [16].

Defects in lymphocyte mediated immunity also have been described [18,21]. Specifically, decreased proportions of circulating B cells, low immunoglobulin (IgG or IgG subclasses) levels, decreased in vitro B-cell proliferation, and lack of specific antibody or isohemaglutinin production have been reported [11]. In addition, decreased percentages of circulating natural killer (NK) cells, total circulating T lymphocytes, as well as decreased proliferative responses and inverse CD4:CD8 ratios also have been described [18].

Gastrointestinal Features

One of the hallmarks of SDS is exocrine pancreatic dysfunction of varying severities caused by absence of acinar cells. Patients classically present in early infancy with malabsorption, steatorrhea, failure to thrive, and low levels of fat soluble vitamins A, D, E, and K. Importantly, patients with SDS have normal sweat chloride tests, differentiating them from patients with cystic fibrosis whose pancreatic defect involves the exocrine pancreatic ducts. Low serum pancreatic trypsinogen and low isoamylase are useful markers for pancreatic insufficiency in patients with SDS; however, the age of the patient is important in interpretation. Trypsinogen is generally low in SDS patients younger than 3 years of age but increases to the normal range in older patients where it becomes less useful as a disease marker. Serum isoamylase levels are low in patients with SDS of all ages; however, the utility of this test in patients younger than 3 years old is limited since isoamylase levels are also low in healthy children of this age [22]. In addition, fecal elastase levels may be low. Pancreatic enzyme secretion in response to stimulation testing is reduced.

Imaging studies with ultrasound, computed tomography, or magnetic resonance imaging (MRI) often demonstrate a small, structurally abnormal pancreas composed mainly of fat [23]. Pathologic evaluation reveals extensive fatty replacement of the pancreatic acinar tissue and relatively normal pancreatic ducts and islets. For reasons that remain unclear, exocrine pancreatic function spontaneously improves over time in roughly 50% of patients [3,5]. Pancreatic endocrine function generally appears to be intact as evidenced by normal glucose tolerance tests; however, cases of insulin-dependent diabetes mellitus have been reported (see endocrine section).

Hepatomegaly is found in roughly 15% of patients, and 50%–75% of patients will have elevated serum liver enzymes 2–3 times normal [3,5,24]. Pathologic evaluation of the liver has shown severe panlobular fatty changes with nonspecific periportal and portal inflammatory infiltration, varying degrees of periportal, portal and bridging fibrosis, and microvesicular and macrovesicular steatosis in several patients [3,4,25–27]. These abnormalities typically occur early in life and normalize over time without apparent long-term sequelae. However, serious hepatic complications have been reported in patients with SDS following hematopoietic cell transplantation (HCT) [28].

Skeletal Abnormalities

Skeletal abnormalities are commonly reported in patients with SDS. The primary skeletal defects are related to abnormal development of the growth plates, in particular, the metaphyses. Metaphyseal dysostosis has been reported in roughly 50% of the patients, is usually asymptomatic, and most commonly involves the femoral head [4,25]. Other sites that may be affected include the knees, humeral heads, wrists, ankles and vertebrae. Rib-cage abnormalities are found in 30%–50% of patients, including narrow rib cage, shortened ribs with flared anterior ends, and costochondral thickening. Case reports have described respiratory failure in the newborn period as a result of these rib cage abnormalities [29]. Other skeletal abnormalities described in patients with SDS include slipped femoral epiphysis, digit abnormalities (clinodactyly, syndactyly, and supernumerary thumbs), and progressive spinal deformities (kyphosis, scoliosis, and vertebral collapse) [25,30]. Low turnover osteopenia and osteoporosis has also been reported independent of vitamin D deficiency [30,31].

Cardiac Features

Several case reports have described neonatal cardiac manifestations associated with SDS [32–36]. Myocardial necrosis or fibrosis has been primarily seen on histopathology. Savilahi et al. reported 8 deaths from cardiac failure among 16 patients with SDS. Autopsies demonstrated myocardial necrosis in the left ventricle [32]. Recently Toiviainen-Salo et al.

[37] evaluated 8 patients with SDS who did not have any cardiac symptoms. All had normal cardiac anatomy and myocardial structure; however, depressed left ventricular contractility during exercise and subtle right ventricular diastolic dysfunctions were seen. Further studies evaluating the clinical importance of these findings are needed.

There also have been several studies describing cardiac complications following HCT in patients with SDS. Specifically, transient congestive heart failure during induction chemotherapy [38], long-term cardiac hypokinesia after HCT [39], and fatal pancarditis following HCT [40] have been seen. As a result of these and earlier studies raising concern regarding cardiac complications in patients with SDS, several groups have proposed reduced-intensity conditioning regimens that avoid known cardio-toxic therapies such as cyclophosphamide; see HCT section for further details.

Other Features

Insulin-dependent diabetes [4], growth hormone deficiency [21], hypogonadotropic hypogonadism [41] and hypothyroidism (personal communication Dr. Akiko Shimamura) have been described in patients with SDS. Failure to thrive is common and is likely multi-factorial including pancreatic insufficiency, feeding difficulties, recurrent infections, and metaphyseal dysostosis. Despite pancreatic enzyme replacement, many patients tend to remain below the 3rd percentile for height and weight. However, normal height and weight for age does not rule out the diagnosis of SDS. Renal abnormalities including urinary tract anomalies and renal tubular acidosis have also been described [4,25].

MOLECULAR PATHOGENESIS

SDS is an autosomal recessive disorder. Approximately 90% of patients meeting the clinical diagnostic criteria for SDS have mutations in the *SBDS* gene. The carrier frequency for this mutation has been estimated at around 1 in 110 [42]. This highly conserved gene has five exons encompassing 7.9 kb and maps to the 7q11 centromeric region of chromosome 7 [1,42]. The *SDBS* gene encodes a novel 250-amino acid protein lacking homology to known protein functional domains. An adjacent pseudogene, *SBDSP*, shares 97% homology with *SBDS* but contains deletions and nucleotide changes that prevent the generation of a functional protein. Roughly 75% of patients with SDS have *SBDS* mutations resulting from a gene conversion event with this pseudogene [1]. The *SBDS* mRNA and protein are widely expressed throughout human tissues at both the mRNA and protein levels [1,43,44]. The complete absence of *Sbds* expression was lethal in murine models [45]. Although the early truncating *SBDS* mutation 183 TA>CT is common among patients with SDS, patients homozygous for this mutation have not been identified, suggesting that complete loss of the *SBDS* expression is likely lethal in human patients.

CD34+ hematopoietic cells are quantitatively reduced in the bone marrows of SDS patients compared with healthy control marrows [46]. SDS CD34+ cells are also qualitatively impaired in progenitor colony formation and long-term colony formation. The ability of marrow stromal cells from SDS patients to support normal CD34+ cells in long-term colony assays was also diminished [46]. Increased apoptosis [14] and elevated levels of p53 protein [47] have been observed in SDS marrows. Reduction of *Sbds* expression in mouse c-kit+ lineage- hematopoietic cells with lentiviral-mediated RNAi impaired both granulocyte differentiation in vitro and short-term hematopoietic engraftment following transplant in vivo [48]. In a zebrafish model, morpholino-mediated knockdown of sbds resulted in abnormal development of the pancreas and granulocytes [49].

The crystal structure of the Archael SBDS orthologue revealed a tripartite structure without apparent homology to known protein functional domains [50,51]. Data from SBDS orthologs

suggested that SBDS may play a role in ribosome biogenesis, a complex and highly regulated cellular process [1]. The human *SBDS* protein is present throughout the cell and is particularly concentrated in the nucleolus, the primary site of ribosome biogenesis [43]. In studies of human cells, Ganapathi et al. [52] demonstrated that (1) cells from patients with SDS are hypersensitive to low doses of actinomycin D, an inhibitor of rRNA transcription; (2) actinomycin D abolishes nucleolar localization of *SBDS*; (3) SBDS co-sediments with the 60S large ribosomal subunit but not with mature ribosomes or polysome in sucrose gradients; (4) *SBDS* co-precipitates with 28S ribosomal RNA (rRNA); and (5) *SBDS* forms a protein complex with nucleophosmin, a multifunctional protein implicated in ribosome biogenesis, leukemogenesis, and centrosomal amplification. An interaction between SBDS and the 60S ribosomal assembly factor Nip7 has also been described [53]. Downregulation of SBDS in HEK293 cells showed alterations in both the mRNA levels and mRNA polysome loading of genes implicated in nervous system development, bone morphogenesis, and hematopoiesis [53].

Proteomic analysis of proteins associating with the yeast SBDS orthologue SDO1/YLR022C identified over 20 proteins involved in ribosome biogenesis [51]. Yeast carrying mutations in *SDO1* grow very slowly. Genetic studies demonstrated suppression of the *SDO1*−/− slow growth phenotype by mutations in *TIF6* [54]. Tif6 is required for pre-60S subunit synthesis and nuclear export [55]. eIF6, the mammalian ortholog of Tif6, associates with the 60S ribosomal subunit and inhibits the joining of the 60S to the 40S ribosomal subunit [56]. The *TIF6* mutations that suppress the *SDO1*−/− slow growth phenotype were located in a region of Tif6 that reduced the binding of Tif6 to the 60S subunit. *TIF6* mutations also suppress the ribosome biogenesis defects resulting from mutations in *EFL1*, which encodes a cytoplasmic GTPase that promotes dissociation of Tif6 from the 60S subunit *in vitro* [57]. Genetic analysis revealed an epistatic relationship between *SDO1* and *EFL1*, consistent with data that these two genes function coordinately with *TIF6* [54]. In the absence of *SDO1* expression, 60S ribosomal RNA subunit levels were reduced, and export of the 60S subunit from the nucleus to the cytoplasm was disrupted. These data suggest a model wherein Sdo1 might recruit Efl1 to the pre-60S ribosome thereby facilitating Tif6 release to allow joining of the 60S and 40S subunits [54]. How disruption in ribosome biogenesis results in specific phenotypic findings in patients with SDS or why the bone marrow seems to be particularly susceptible to ribosome impairment remain to be defined.

SBDS also functions during mitosis to prevent genomic instability [15]. Cultured cells from SDS patients exhibited an increased incidence of mitotic aberrations, characterized by multipolar spindles and centrosomal amplification, compared with controls. Knockdown of SBDS expression with siRNAs in human fibroblasts recapitulated this phenotype, but only after two weeks in culture suggesting that the mitotic defects were a downstream result of SBDS loss. Loss of SBDS was associated with increased apoptosis when checkpoint pathways were intact, but resulted in aneuploid cells when p53 was inactivated. Aneuploidy is associated with an increased rate of chromosomal rearrangements such as breaks and translocations in animal models [58]. SBDS co-localized with the mitotic spindle by immunofluorescence. Recombinant SBDS bound to purified microtubules *in vitro* resulting in microtubule stabilization both *in vitro* and *in vivo*. These data suggest a novel model for a human cancer predisposition syndrome whereby mitotic spindle instability results in chromosomal aberrations. It is intriguing to speculate that the mitotic and ribosomal functions of SBDS might be related since other proteins such as nucleophosmin [59] and Rrp14 [60] have been shown to function in both ribosome biogenesis and mitosis. Alternatively, it is also possible that these functions might additively contribute to the SDS disease phenotype. Additional mechanistic and biological studies will be required to answer these questions.

DIAGNOSIS, CLINICAL MANAGEMENT AND TREATMENT

Diagnosis

The diagnosis of SDS is largely based on clinical phenotype, with pancreatic exocrine and bone marrow dysfunction being the central features. However, there is considerable phenotypic variability between individuals and even within the same individual over time, making the diagnosis challenging particularly in older patients where symptoms such as steatorrhea may have resolved or neutropenia may be mild and intermittent. Several disorders must be excluded including cystic fibrosis, Pearson's syndrome, Johanson-Blizzard syndrome, severe malnutrition combined with diminished exocrine pancreatic function, as well as other marrow failure syndromes such as Fanconi anemia, dyskeratosis congenita, and severe congenital neutropenia.

Exocrine pancreatic insufficiency may be demonstrated by one of the following: (1) Elevated fecal fat excretion following a 72-hour collection in the absence of concomitant intestinal or cholestatic liver disease with imaging studies showing a small or fatty pancreas and (2) low serum trypsinogen in patients under the age of 3 or low serum isoamylase testing in patients over the age of 3 [22,61]. The use of fecal elastase as a marker for exocrine pancreatic dysfunction in SDS is currently under investigation. Pancreatic stimulation testing with intravenous pancreozymin with or without secretin has been used to evaluate levels of pancreatic enzymes; however, with the advent of serum markers, this invasive procedure has been used less commonly. Signs of marrow failure may include any of the following findings: (1) intermittent or persistent neutropenia (absolute neutrophil count < 1,500/μL) documented at least 3 times over a minimum of 3 months without an apparent cause; (2) hypoproductive anemia with a hemoglobin concentration below the age-related adjusted norms; (3) unexplained macrocytosis; (4) platelet count <150,000/μL without alternative etiology; or (5) hypocellular bone marrow. Aplastic anemia, MDS or leukemia may be the presenting hematologic abnormality of a patient with underlying SDS. Additional supportive features include skeletal abnormalities, hepatomegaly with or without elevated serum aminotransferase levels, and immunologic abnormalities. See Table 1 for our suggested evaluation pathway for SDS.

SDBS genetic testing provides corroborative data in a patient who has been clinically diagnosed with SDS and allows genetic testing to identify affected family members. Up to 10% of patients with clinical features of SDS lack *SBDS* mutations; therefore, the absence (negative test) of the *SDBS* gene mutation does not rule out the diagnosis [1]. It is presently not known whether patients lacking *SBDS* mutations have mutations in an additional as yet unidentified gene(s) for SDS or if they represent a separate distinct disorder. The clinical implications of *SBDS* genetic testing in the diagnosis of patients with SDS has yet to be defined, particularly for those patients who are asymptomatic and lack clinical manifestations of SDS and in those who do not have a positive family history.

Clinical Management

Hematology—All patients with SDS should be monitored by a hematologist. The general recommendation from a clinical consensus conference is to monitor peripheral blood counts for cytopenias every 3–4 months [61]. Marrow evaluation with aspirate and biopsy including cytogenetics to assess for marrow cellularity, MDS, acute leukemia, or other clonal disease is recommended on a yearly basis or more often if clinically indicated [61]. Such regular monitoring allows timely institution of therapy prior to the development of clinical complications. Hematopoietic cell transplantation (HCT) prior to the development of overt leukemia is associated with better outcomes.

For those neutropenic patients with recurrent or severe infections, granulocyte colony stimulating factor (G-CSF) may be considered. Data regarding malignant myeloid transformation into MDS or AML in SDS patients on G-CSF therapy are inconclusive; however, there is no strong evidence that links G-CSF directly to leukemic conversion [62]. Therefore, G-CSF should not be withheld if clinically indicated to treat infection or to prevent recurrent bacterial or fungal infections.

Gastroenterology—Patients with SDS should also be followed by a gastroenterologist for management of exocrine pancreatic insufficiency. Most patients require oral pancreatic enzyme supplementation. However, steatorrhea resolves in roughly 50% of patients; therefore, assessment of continued need for pancreatic enzyme supplementation is indicated. Measurement of the fat soluble vitamins A, D, E, and K should occur with appropriate supplementation as indicated. An abnormal prothrombin time (PT) may be a useful marker of vitamin K deficiency.

Skeletal—Data are lacking on the role of bisphosphonates in patients with SDS. Measures to maximize bone density should be implemented including adequate calcium and Vitamin D intake, and weight bearing exercises. In addition, it is important to screen for and correct any underlying endocrine problems that may contribute to osteopenia such as hypothyroidism or hypoparathyroidism.

Treatment/Hematopoietic Cell Transplantation

The primary causes of death in infancy are related to malabsorption, infections, and thoracic dystrophy. In older patients, the main causes of death are hemorrhage and infections due to associated hematological abnormalities such as marrow aplasia, neutropenia, MDS, or acute leukemia. Supportive measures include transfusions, pancreatic enzymes, antibiotics and G-CSF. The only definitive therapy for marrow failure, MDS or leukemia is HCT.

Due to the rarity of this disease, the literature on HCT for patients with SDS consists primarily of case reports including various conditioning regimens, donor types, and stem cell sources [38,40,63–71]. Poor outcomes have been reported following HCT due to graft failure/rejection, transplant related toxicities, and relapsed leukemia. Significant cardiac and other organ toxicities have been described which are believed to be due to exacerbation of the underlying organ dysfunction by the intensive preparative regimens.

Recently, several groups have published on larger cohorts of patients which enable more meaningful analysis. Cesaro et al. reported 26 patients with SDS from the European Group for Blood and Bone Marrow Transplantation (EBMT) registry given HCT for treatment of severe aplastic anemia (n=16), MDS/AML (n=9), or other diagnosis (n=1; Table 2) [72]. Various preparative regimens were used; however, most included either busulfan (54%) or total body irradiation (TBI, 23%) followed by an HLA matched sibling (n=6), mismatched family (n=1), or unrelated graft (n=19). Most patients were given in vitro (n=4) or in vivo (n=17) T-cell depleted marrow grafts. Graft failure occurred in 5 (19%) patients, and the incidence of grade III–IV and chronic GVHD were 24% and 29%, respectively. With a median follow up of 1.1 years, overall survival was 65%. Deaths were due primarily to infections ± GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that presence of MDS/AML or use of TBI-based conditioning regimens were factors associated with poor outcome.

Donadieu et al. [39] published French neutropenia registry data that included 10 patients with SDS who received HCT for marrow failure (n=5) or MDS/leukemia (n=5). Patients were conditioned with busulfan/cyclophosphamide (n=6) ± ATG or TBI plus chemotherapy (n=4) followed by HLA-matched sibling (n=4) or unrelated (n=6) marrow grafts. With a median follow-up for surviving patients of 6.9 years, the 5-year overall survival was 60%. Marrow

engraftment occurred in 8 patients. Two patients died before engraftment due to infections in the setting of grade IV GVHD and multi-organ dysfunction, and two patients died 10 and 19 months after HCT due to relapse and transplant related toxicity, respectively. The authors note that although the number of patients was small, mortality among patients with MDS/leukemia appeared to be higher than among those with marrow failure. The authors speculated that older age and associated increased comorbidities might also contribute to higher mortality following HCT for patients with MDS/leukemia.

Recently, two groups reported results of reduced intensity preparative regimens that spared cyclophosphamide and TBI. Sauer et al. [73] reported three patients who received conditioning with fludarabine, treosulfan (a busulfan analog), and melphalan ± Campath-1H (n=2) or rabbit ATG (n=1) followed by a HLA-identical sibling (n=1) and matched unrelated (n=1) marrow graft or a 9/10 matched cord (n=1). Patients received HCT due to pancytopenia (n=2) or pancytopenia/MDS (n=1). With a follow-up of 9 and 20 months, two patients are alive. One patient who received a cord blood graft died 98 days after HCT of idiopathic pneumonitis syndrome. Bhatla et al. [74] reported 7 patients conditioned with Campath-1H, fludarabine, and melphalan followed by HLA matched related marrow (n=4) or unrelated peripheral blood (n=2) or marrow (n=1) grafts. Patients underwent HCT due to worsening cytopenias with increasing transfusion dependence (n=5) and/or the appearance of clonal hematopoeisis (n=6). With a median follow-up of 548 (range, 93–920) days, all patients are alive with full donor engraftment. Viral infections were observed in four patients following HCT, likely related to the Campath-1H.

The rarity of the disease combined with an apparent lack of correlation between genotype and phenotype have contributed to the controversy on the role and optimal timing of HCT. A major challenge is identifying those patients who are at risk for MDS or leukemia development. SDS patients with leukemia have been treated with conventional chemotherapy alone; however, some patients fail to regenerate normal hematopoiesis or die from toxicities related to the chemotherapy given. As a result, HCT is the only definitive treatment for patients with bone marrow failure, MDS, or leukemia; however, it appears that patients with SDS may be at increased risk for transplant related mortality (TRM). It is unclear whether the increased TRM is related to complications of the underlying organ dysfunction or due to an as yet undetermined genetically-mediated susceptibility to certain conditioning agents. As a result, there is no clear consensus on when to HCT a patient with SDS.

HCT studies for treatment of other genetic diseases such as Wiskott Aldrich Syndrome and sickle cell disease clearly show benefit when HCT is performed at a younger age, presumably because younger patients are healthier. SDS patients with MDS or leukemia at time of HCT appear to have worse outcomes compared to those with bone marrow failure alone. Thus it seems reasonable that transplant be performed before complications of SDS develop.

Indications for HCT include severe persistent or symptomatic cytopenia, MDS with excess blasts (5–20%), and overt leukemia with high-risk features. Particularly in the era of better supportive care and reduced intensity conditioning regimens, one should consider HCT for those patients with AML and high-risk characteristics including evolution from MDS or abnormal cytogenetics such as monosomy 7 (−7), monosomy 5 (−5), deletion of q arm of chromosome 5 (del5q)) or complex cytogenetics with multiple cytogenetic abnormalities. In addition, molecular alterations including internal tandem duplication of the FLT3 gene (FLT3/ITD), a gene involved in regulation of stem cell differentiation, should also be considered. AML-like treatment has not been shown to provide a curative treatment approach for patients with MDS, and HCT remains the treatment of choice for clinically significant MDS. In general, there is a significant survival benefit when HCT is performed at an earlier phase of disease [75]. For those patients with marrow failure alone, the indications for HCT may include severe

persistent or symptomatic cytopenias or a history of frequent life-threatening infections secondary to intractable neutropenia. However, these general guidelines need to take into consideration donor source and histocompatibility.

CONCLUSIONS

SDS is a rare autosomal recessive multi-system disorder with varying phenotypic presentation. The identification of the *SBDS* gene has greatly expanded diagnostic capabilities; however, mechanistic and biological studies defining *SBDS* gene function are needed to advance our understanding of the molecular pathogenesis of marrow failure and leukemia. To date, studies have not shown any correlation between hematologic or skeletal phenotype and the *SBDS* genotype [30,76]. The complete clinical phenotype, natural history, and risk factors associated with the development of future complications such as aplastic anemia, MDS, or leukemia need to be elucidated in order to better determine the optimal timing of therapeutic intervention. Collaborative efforts are currently underway to develop a longitudinal data registry and tissue repository specifically for patients with SDS for clinical and scientific studies. Equally important will be the development of clinical trials addressing pertinent clinical challenges such as optimal HCT regimens. These new efforts will likely advance our ability to diagnose and better treat patients with SDS.

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Table 1

Recommended workup for patients with SDS

Diagnostic Studies:
Marrow Function
Peripheral blood count with smear, MCV
Reticulocyte count
Bone marrow aspirate & biopsy: pathologic review and cytogenetics, iron stain
Exocrine pancreatic function
Trypsinogen (age < 3yr) or serum pancreatic isoamylase (age >3 yr)
72 hour fecal fat measurement, fecal elastase
+/− Endoscopic pancreatic stimulation testing
Vitamin A, D, E, and K levels
Genetic testing
SBDS mutation analysis
Supportive Studies:
Liver function
ALT, AST, GGT, albumin, prealbumin, prothrombin time
Immune Workup
Immunoglobulin levels (IgA, IgG, IgM)
T and B lymphocyte subset analysis
Additional work up as clinically indicated
Radiological workup
Pancreatic imaging
X-ray evaluation for skeletal abnormalities, in particular metaphyseal dysostosis or thorasic dystrophies
Echocardiogram if clinically indicated
Consultations:
Hematology
Gastroenterology
Endocrinology
Genetics
Developmental assessment
Dental evaluation

Table 2

Summary of recent publications HCT for SDS

Conditioning Regimen (n)	Donor Source(n)	Stem Cell Source (n)	Median Age at HCT (yrs)	Engraftment (n)	GVHD Prophylaxis (n) +/−	Acute GVHD Grade (n)	cGVHD	TRM	OS	Median f/u	Ref
Bu based (14) TBI based (6) Flu (4) Others (2)	Sibling (6) URD (19) Other family (1) T-cell depleted (21)	BM (21) PBSC (3) CB (2)	10.3 (1.2–26.8)	21/26 (81%)	CSP/MTX (14) Other (6) Not specified (6)	I–IV: 15 (71%) III–IV: 5/21 (24%)	4/14 (29%)eligible	35.5% (1 yr)	64.5 %	1.1 (0.05–16.2) yrs	[72]
Bu/CY (3) + ATG (3) TBI/CY (3) TBI/Mel (1)	Sibling (4) URD (6) T-cell depleted (2)	BM (10)	11.2 (1.1–27.7)	8/10 *	CSP/MTX (5) CSP/MTX/ Steroids (2) Other (3)	II (3)/IV (3)	2/10	3/10	60% (5 yr) EFS	7.6 (3.9–16.9) yrs	[39]
Flu/Treo/Mel + Campath-1H (2) + ATG (1)	Sibling (1) URD (2)	BM (2) CB (1)	9.6 (1.5–17)	3/3	CSP/MTX (2) CSP/MMF (1)	II (1)	NR	1/3	2/3	2 yrs, 1.3 yrs	[73]
Campath-1H/Flu/Mel (7)	Sibling (4) URD (3)	BM (4) PBSC (2) BM+CB (1)	8.0 (1.0–29)	7/7	CSP/MTX (6) CSP/steroids (1)	II (1)	NR	0/7	100%	1.5 (0.3–2.5) yrs	[74]

ATG, anti-thymocyte globulin; Bu, busulfan; BM, bone marrow; CB, cord blood; cGVHD, chronic graft-versus-host-disease; CSP, cyclosporine; CY, cyclophosphamide; EFS, event free survival; Flu, fludarabine; f/u, follow up; HCT, hematopoietic cell transplantation; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; n, number; OS, overall survival; PBSC, peripheral blood stem cells; Pt, patient; Ref, reference; TBI, total body irradiation; Treo, treosulfan; TRM, transplant related mortality; URD, unrelated donor; yrs, years;

* Two patients died before engraftment