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Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome

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Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder characterized by pancreatic exocrine insufficiency and bone marrow failure, often associated with neurodevelopmental and skeletal abnormalities. Mutations in the *SBDS* gene have been shown to cause SDS. The purpose of this document is to provide draft guidelines for diagnosis, evaluation of organ and system abnormalities, and treatment of hematologic, pancreatic, dietary, dental, skeletal, and neurodevelopmental complications. New recommendations regarding diagnosis and management are presented, reflecting advances in understanding the genetic basis and clinical manifestations of the disease based on the consensus of experienced clinicians from Canada, Europe, and the United States. Whenever possible, evidence-based conclusions are made, but as with other rare diseases, the data on SDS are often anecdotal. The authors welcome comments from readers.

Introduction

Management: coordinated care model

Shwachman-Diamond syndrome, first described in 1964 (ref [1–3]), is a multi-system disease involving the bone marrow, pancreas, bony skeleton, and other organs. Decisions about patient management are often difficult to make due to the complexity of the clinical phenotype, rarity of the disease and the paucity of large studies. The last report of consensus guidelines for SDS was published in 2002 (ref [4]). With the identification of the *SBDS* gene in 2003 (ref [5]), diagnostic criteria have changed. DNA analysis may lead to the diagnosis of SDS before the full clinical spectrum is present. Informed clinical surveillance and the early findings from experimental models have further highlighted that mutations in SBDS affect a broad spectrum of functions, which has led to a reexamination of the clinical phenotype and spectrum of the human disease. In particular, neurocognitive manifestations such as learning and behavioral disabilities may be under-recognized. Diversity in how SDS manifests suggests the value of a coordinated multidisciplinary approach to clinical care. Consensus guidelines presented in this document aim to improve health care by highlighting different aspects of SDS and facilitating early diagnosis, prevention and therapy.

General features of SDS

The predominant manifestations of SDS comprise bone marrow failure, pancreatic exocrine dysfunction and skeletal abnormalities.[6–8] In addition, the liver, kidneys, teeth, brain, and immune system may also be affected.[6,9–13] SDS is also associated with a propensity for myelodysplastic syndrome (MDS) and leukemia.[6,9,14–16] SDS is a rare inherited

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marrow failure syndrome with an estimated incidence of 1/76,000 (ref [17]). Although SDS is an autosomal recessive disorder, the ratio of males to females reported in the literature with SDS is 1.7 to 1 (ref [10]).

Hematological manifestations. Neutropenia is the most common hematological abnormality, occurring in nearly all patients. It might be seen in the neonatal period,[6,18] and it can be either persistent or intermittent, fluctuating from severely low to normal levels. In some patients, SDS neutrophils may exhibit defects in migration and chemotaxis.[11,14,19]

Anemia with low reticulocytes occurs in up to 80% of the patients. The red blood cells are usually normochromic and normocytic, but can also be macrocytic.[20] Fetal hemoglobin is elevated in 80% of patients.[21] The anemia is usually asymptomatic. Thrombocytopenia, with platelets less than 150×10^9/l, is variably seen, as are tri-lineage cytopenias. Severe aplasia requiring transfusions has occasionally been reported.[6,22,23]

Bone marrow biopsy usually shows a hypoplastic specimen with increased fat deposition,[6,21] but marrows showing normal or even increased cellularity have also been observed.[10,14] Single-lineage hypoplasia is usually myeloid and occurs in some patients.[9,10] Left-shifted granulopoiesis is a common finding.[6,10] Mild dysplastic changes in the erythroid, myeloid, and megakaryocytic precursors are commonly seen and may fluctuate; however, prominent multilineage dysplasia is less common, and if it occurs, may signify malignant myeloid transformation.

Pancreatic dysfunction, nutrition, and liver disease. Variably severe exocrine pancreatic dysfunction with or without nutrient maldigestion is a hallmark of SDS.[10] Histological specimens of the pancreas have revealed extensive fatty replacement of pancreatic acini with preserved islets of Langerhans and ductal architecture.[3,6] Pancreatic dysfunction is usually diagnosed within the first six months of life and (in 90% of patients) during the first year.[9] Ductular electrolyte and fluid secretion has been shown to remain normal, but the secretion of proteolytic enzymes is severely decreased leading to steatorrhea.[9,24] Spontaneous improvement in pancreatic function can occur in later childhood. By 4 years of age, almost 50% of patients may no longer require pancreatic enzyme supplements as based on evidence of normal fat absorption.[9] Although the causative mechanism is unknown, normalization of fat absorption over the years may remain limited to a subgroup of patients. Despite the relief in subjective symptoms, all patients had a persistent deficit of enzyme secretion in quantitative studies of pancreatic function.[9]

Hepatomegaly is common in young children with SDS. Elevated serum liver enzymes are seen in up to 75% of patients, most often in infants and young children, and tend to resolve with age. Although there are limited longitudinal data, liver disease appears to have little or no long-term clinical consequences.[25] Chronic liver disease has not been observed in a recent series.[26]

Average birth weight is at the 25th percentile. Growth failure with malnutrition is a common feature in the first year of life particularly prior to diagnosis. It is attributable to various factors, including inadequate nutrient intake with or without feeding difficulties, pancreatic insufficiency, and recurrent infections.[6,10] By the first birthday, over half of patients have dropped below the 3rd percentile for both height and weight. After diagnosis, and with appropriate therapy, most children show normal growth velocity, but remain consistently below the 3rd percentile for height and weight.[9]

Other manifestations. SDS-associated bone disease includes skeletal dysplasia[6,10,27–30] and low-turnover osteoporosis.[31] Skeletal dysplasia usually presents with metaphyseal changes in the long bones and costochondral junctions (Fig. 1), but several other less frequent bone anomalies such as supernumerary fingers and syndactyly have also been described.[12,32] In a small cohort, all had some evidence of metaphyseal dysplasia at some point, but the frequency and rate of development are unknown at this time.[27]

Delayed dentition of permanent teeth, dental dysplasia, increased risk of dental caries, and periodontal disease may also occur. On rare occasions, abnormalities of the kidneys, eyes, skin, testes, endocrine pancreas, heart, nervous system, and craniofacial structures have been reported.[6,10,33,34]

How do we diagnose SDS?

Most patients present in infancy with evidence of growth failure, feeding difficulties and/or recurrent

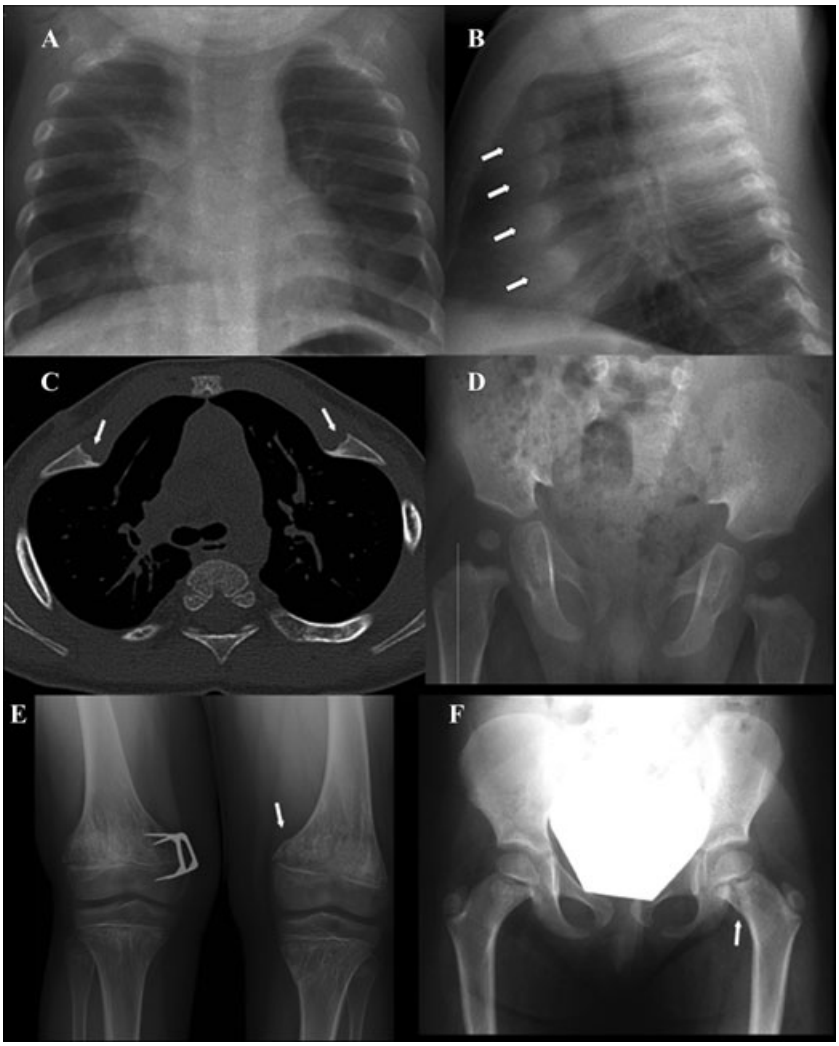

Figure 1. **Skeletal radiographic features in SDS. (A and B) Short ribs with marked cupping and widening of the anterior ends (arrows) in a chest X-ray at 11 months. (C) CT slice shows deformed rib cage with short costae and cupping and irregular widening of the costochondral junctions (arrows). (D) Broad pelvis, short iliac notches, valgus position of femoral necks and wide proximal metaphyses of the femora in pelvic X-ray at 11 months. (E) Marked metaphyseal changes with striated bony structure in both hips and the knees at 14 years. Medial hemiepiphyseodesis was performed on the right distal femur due to genum valgum. A stress fracture in the left distal femur (arrow). (F) Broad femoral necks with abnormal metaphyseal structure and a stress fracture in the left femoral neck metaphysis (arrow).**

infections. Clinical diagnosis is generally made in the first few years of life but occasionally the diagnosis may be established in older children and even adults. The clinical diagnosis (Table 1) is established by (a) documenting evidence of characteristic exocrine pancreatic dysfunction and hematological abnormalities[10,35,36] and (b) excluding known causes of exocrine pancreatic dysfunction and bone marrow failure.

Attention should be given to ruling out cystic fibrosis (the most common cause of pancreatic insufficiency) with a sweat chloride test, Pearson disease (pancreatic insufficiency and cytopenia, marrow ring sideroblasts and vacuolated erythroid and myeloid precursors), cartilage hair hypoplasia (diarrhea and cytopenia, and metaphyseal chondrodysplasia, and more common in certain isolated populations such as the Amish), and other inherited

Table 1. Clinical and molecular diagnostic criteria

Diagnostic criteria
Clinical diagnosis:
Fulfill the combined presence of hematological cytopenia of any given lineage (most often neutropenia) and exocrine pancreas dysfunction
Hematologic abnormalities may include:
a. Neutropenia <1.5 x 109/L on at least 2 occasions over at least 3 months
b. Hypoproductive cytopenia detected on 2 occasions over at least 3 months
Tests that support the diagnosis but require corroboration:
a. Persistent elevation of hemoglobin F (on at least 2 occasions over at least 3 months apart)
b. Persistent red blood cell macrocytosis (on at least 2 occasions over at least 3 months apart), not caused by other etiologies such as hemolysis or a nutritional deficiency
Pancreatic dysfunction may be diagnosed by the following:
a. Reduced levels of pancreatic enzymes adjusted to age [fecal elastase, serum trypsinogen, serum (iso)amylase, serum lipase]
Tests that support the diagnosis but require corroboration:
a. Abnormal 72 hr fecal fat analysis
b. Reduced levels of at least 2 fat-soluble vitamins (A, D, E, K)
c. Evidence of pancreatic lipomatosis (e.g. ultrasound, CT, MRI, or pathological examination of the pancreas by autopsy)
Additional supportive evidence of SDS may arise from:
a. Bone abnormalities
b. Behavioral problems
c. Presence of a first degree-family member diagnosed before with SDS
Other causes pancreatic insufficiency should be excluded, in particular when the *SBDS* gene mutation analysis is negative
Molecular diagnosis: biallelic *SBDS* gene mutation
Positive genetic testing for *SBDS* mutations known or predicted to be deleterious, e.g. from protein modeling or expression systems for mutant SBDS
Caveats:
Many situations arise when molecular diagnosis is NOT confirmatory in the presence of clinical symptoms:
No identified mutations (about 10% of cases)
Mutation on one allele only
Gene sequence variations that have unknown or NO phenotypic consequence:
A novel mutation, such as a predicted missense alteration, for which it is not yet possible to predict whether it is disease-causing.
SBDS polymorphisms on one or both alleles. Large population studies may be needed to exclude a sequence polymorphism as a bona fide irrelevant variant.

bone marrow failure syndromes (such as dyskeratosis congenita).

Exocrine pancreatic phenotype

The clinical diagnosis of the pancreatic phenotype is challenging as most pancreatic function tests lack sufficient sensitivity and/or specificity. This is complicated by the fact that nearly half of subjects with SDS show improvement in exocrine pancreatic function with advancing age. Exocrine pancreatic reserve loss of 98% must occur before signs and symptoms of maldigestion are present. Thus, 72-hour fecal fat balance studies may be normal despite a significant defect in pancreatic acinar function. The terms pancreatic insufficiency (PI) and pancreatic sufficiency (PS) have been coined to discriminate between subjects with PI, who require pancreatic enzymes supplements with meals and those with PS, who invariably have loss of pancreatic reserve but lack clinical evidence of maldigestion.

For these reasons, alternative approaches are recommended to assess patients with a suspected diagnosis of SDS for evidence of pancreatic dysfunction. Serum pancreatic enzyme concentrations are useful markers of the pancreatic phenotype in patients with SDS.[37] Serum immunoreactive trypsinogen concentrations are low (<6 μg/L) in patients with SDS who have PI. However, in patients with PS, serum trypsinogen concentrations are usually above 6 μg/L, and in one fifth of PS patients, measured concentrations are within the reference range. Thus, a low serum trypsinogen is helpful in identifying the pancreatic phenotype, but a normal value does not exclude impaired exocrine pancreatic function. In contrast, serum pancreatic isoamylase activities in SDS patients are uniformly low at all ages, regardless of pancreatic status or trypsinogen concentration. Unfortunately, serum isoamylase activity cannot be used as a sole marker of the SDS pancreatic phenotype because isoamylase production shows age-dependent postnatal development. Healthy infants have low pancreatic isoamylase concentrations (similar to those observed in SDS), which rise and achieve adult values by approximately three years of age.

To overcome these limitations, serum trypsinogen, isoamylase, and age have been incorporated into a diagnostic rule for the SDS pancreatic phenotype, using the Classification and Regression Tree (CART) analysis of Breiman *et al.*[37] With the exception of patients less than 3 years of age, the diagnostic rule effectively distinguished control individuals from patients with a confirmed clinical diagnosis of SDS.

Several alternative non-invasive approaches to establish or exclude pancreatic dysfunction may be considered, including multi-dimensional imaging (ultrasound, CT, or MRI) for evidence of fatty replacement of the pancreas, and fecal enzyme concentrations of pancreatic elastase or chymotrypsin. Concentrations of fecal elastase less than 200 μg/g stool offer evidence of severe pancreatic dysfunction, and a fecal elastase <100 μg/g is suggestive of maldigestion due to exocrine pancreatic insufficiency. Fecal fat balance studies provide direct evidence of the severity of malabsorption, but as mentioned above, they do not indicate a specifically pancreatic cause if fat malabsorption is found.

The "gold standard" method of directly measuring pancreatic secretion using an intestinal marker perfusion technique to quantify timed collections of pancreatic juice during hormonal stimulation with cholecystokinin and secretin provided useful information concerning the pathophysiology of the exocrine pancreas. However, this complex, invasive test has little role in a clinical setting and is largely used only in research studies. Alternative non-quantitative methods of collecting secretions, including aspiration of pancreatic juice with a duodenoscope or single lumen duodenal tube are not recommended because they show considerable test variability and approximately 25% of PS subjects with low pancreatic reserve may be misclassified as having PI.

Hematologic phenotype

The hematologic phenotype is most frequently characterized by intermittent or persistent neutropenia, but cytopenias of other blood cell lineages are frequently present. Red blood cell macrocytosis, high hemoglobin F, and varying degrees of marrow hypoplasia are also typical findings.

Chromosome breakage studies with diepoxybutane or mitomycin C are recommended to exclude Fanconi anemia, unless the history, physical examination and initial work-up are diagnostic for SDS. Bone marrow aspiration and biopsy are essential for initial evaluation and should include assessment of cellularity, differential, iron stain and cytogenetics. Bone marrow cytogenetic finding of i(7q) or del(20q) is highly associated with SDS**.** Virology studies (e.g. Epstein–Barr virus, cytomegalovirus, and B19 parvovirus) may be pursued as clinically indicated to exclude other causes of bone marrow suppression and a failure to thrive.

Skeletal phenotype

When present in association with hematologic or pancreatic abnormalities, characteristic skeletal abnormalities are strongly suggestive of SDS. SDS bone dysplasia is characterized by short stature, delayed appearance but subsequent normal development of secondary ossification centers, and by variable metaphyseal widening and irregularity that is most often seen in the ribs in early childhood and in the proximal and distal femora later in childhood and adolescence.[10,27] Rarely, skeletal involvement may be extremely severe with generalized bone abnormalities.[38] Although metaphyseal changes often become undetectable and clinically insignificant over time, they

may also progress and result in limb deformities, most commonly at the hips and the knees, or stress fractures of the femoral necks (Fig. 1).[27] In addition to metaphyseal chondrodysplasia, SDS associates with early-onset low-turnover osteoporosis characterized by low bone mass and vertebral fragility fractures.[31]

Other clinical findings

Short stature with or without malnutrition is also a common feature of SDS. Hepatomegaly with mild to moderate biochemical abnormalities of the liver are common findings in infants and young children with SDS.

Molecular testing

As the clinical diagnosis of SDS is usually difficult and patients may present at a stage when no clinical pancreatic insufficiency is evident, it is advisable to test most or all suspected cases for mutations in the *SBDS* gene (Table 1). It is noteworthy that about 10% of the SDS patients may be negative for mutations, and that *de novo SBDS* mutations have been identified in some families.

How to monitor a patient after a diagnosis is made?

Recommended baseline testing are listed in Table 2.

Hematology

Hematological evaluation should include complete blood count (CBC), mean corpuscular volume, peripheral blood smear, differential, reticulocyte count, fetal hemoglobin level and coagulation tests in case of clinical bleeding symptoms. If the diagnosis of SDS is suspected or confirmed, bone marrow aspirate smear, biopsy, and cytogenetic evaluation is recommended as a baseline examination (see section IV for further discussion).

Complete blood count is a basic parameter that needs to be monitored: CBCs should be considered every 3–6 months in stable patients. Any clinical complications, including recurrent infections, bruising, asthenia or pallor may require a CBC between scheduled examinations. The purpose of the routine CBC is to determine the baseline profile of the patients, to assess the risk for infections and possibly to detect particular features related to nutritional deficits, such as iron or folate deficiency and to detect evolving marrow abnormalities such as severe marrow failure, myelodysplastic syndrome (MDS), or leukemia.

When infections regularly recur, immunoglobulin levels and post-vaccination antibodies should be screened to exclude an associated immunodeficiency.

Systematic evaluation of neutrophil chemotaxis is not considered a necessity in the usual follow up of patients.

Pancreas

Once the diagnosis of SDS is suspected or established, objective testing for assessment of pancreatic function status is recommended. To determine PS or PI status, serum trypsinogen concentration offers useful screening information:

(a) If values are undetectable or low, a 72-hour fat balance study may be done to confirm PI status. Since most newly diagnosed subjects are infants or children, careful documentation of ingested fat (and other macronutrients) will enable determination of coefficient of fat absorption as well as provide insight into total calorie intake.

(b) If values are 6 μg/L or above, PS status should be confirmed by 72-hour fat balance study as described. Recent studies in patients with cystic fibrosis have, however, shown that duplicate measurements of the coefficient of fat absorption often show wide variation.

(c) Measurement of fecal elastase or chymotrypsin is widely used in Europe as an alternative indicator of pancreatic insufficiency, although it has not been validated in a large series of SDS patients. It has the theoretical advantage of being a specific test of pancreatic function, whereas fat absorption can of course be abnormal in non-pancreatic disorders such as celiac disease.

Baseline fat soluble vitamin levels (A, D, E) and prothrombin time, as a surrogate marker for vitamin K status, should be done. Low values should be correlated with results of pancreatic function testing and in patients with PI, should be repeated approximately one month after instituting enzyme replacement therapy. Persistently low levels in the face of good compliance with enzyme therapy will require fat-soluble vitamin supplements. Fat-soluble vitamins should be monitored on at least a yearly basis, and may include (vitamin K-dependent) coagulation parameters when clinical symptoms are present.

Table 2. Clinical tests at diagnosis and at follow-up

	At Diagnosis	At Follow-up
Genetics		
SBDS gene mutation (test may be offered to family member hematopoietic stem cell transplant donors)	Yes	Yes, if not done at diagnosis
Genetic counselling (molecular test may be offered to family members for screening of carriers)		
Hematology and immunology		
CBC	Yes	2–4 times / year
Bone marrow aspirate and biopsy	Yes	Every 1 to 3 years or as clinically indicated
Fe, folate, B12 levels	Yes	
Hb F levels	Yes	As clinically indicated
IgG, IgA, IgM levels	Yes	–
Post vaccination serology	–	As clinically indicated
Lymphocyte phenotype	–	As clinically indicated
HLA testing	As clinically indicated	As clinically indicated
Gastroenterology		
Pancreatic enzymes (choice based on local availability: serum trypsinogen, isoamylase, 72-hour fat balance test, elastase, etc.)	Yes	
Fat-soluble vitamins A, D, E, and prothrombin time (surrogate for vitamin K)	Yes	1 mo after pancreatic enzyme therapy, then 1-2 times/ year
Other vitamins and micronutrients	–	As clinically indicated
Liver biochemistry panel	Yes	As clinically indicated
Pancreatic imaging	Ultrasound (abdomen)	
Endoscopy	As clinically indicated	
Skeletal system, growth		
Growth evaluation: height, weight and head circumference	Yes	Yearly at follow-up
Skeletal survey	Yes	As clinically indicated
Densitometry		Baseline study: once during prepuberty Follow-up study: once during puberty, then as clinically indicated
Oral and dental care	Yes	Once per year and when clinically indicated

Continued

Table 2. *Continued*

	At Diagnosis	At Follow-up
Development and neuropsychological evaluation	Yes	Standardized developmental screening measure: Infancy/-preschool age Neuropsychological assessment of domains: At ages 6–8, 11–13, 15–17 Intellectual abilities Attention including working memory, sustained attention and divided/dual attention Higher order language Visual-motor integration and speed Executive functioning Academic achievement Behaviour (self report and parent proxy) Adaptive Functioning (parent proxy)

There are no published guidelines on dosing of pancreatic enzyme supplements in SDS patients with PI. Furthermore, there are few published data demonstrating efficacy of enzyme replacement therapy. For this reason, published treatment guidelines for subjects with cystic fibrosis may be considered.[39]

Nutritional status

Newly diagnosed infants with SDS are commonly malnourished. Therefore, careful baseline assessment of height and weight and anthropometric measures are recommended. Once appropriate therapy is introduced, malnutrition should be corrected by one year of age.

Bone

Skeletal survey is recommended at the time of the diagnosis. The follow-up is based on individual clinical and radiological findings. For biochemical assessment and bone mineral density evaluation, see section on bone abnormalities.

Dental

Annual reviews—ideally by a dentist experienced in orthodontic approaches and/or periodontal disease—are generally recommended.

Neurodevelopment

A characteristic pattern of learning and behavioral difficulties is common in SDS.[40] It is therefore important to monitor and support neurodevelopment. Standardized developmental checklists should be used routinely to assess infant, toddler and preschooler development with referrals to specialists (e.g., speech and language therapy, occupational therapy, developmental pediatrician, developmental psychologist) as needed. Serial neuropsychological assessments are indicated, at minimum, when a child is approximately 6, 12, and 15 years of age to correspond with brain development and changes in expectations at school.

Hematological complications

Definition of hematological complications

While neutropenia (even severe) is a typical feature of SDS, anemia ($<$7 g/dl or 4.3 mmol/L or if symptomatic) and thrombocytopenia ($<20 \times 10^9$/L or if symptomatic) are additional complications that require prompt evaluation and medical decision.

Classification of the different forms of marrow failure in SDS is complex and poorly understood. In general, cytogenetic studies should be performed concurrently with morphology studies. Aplastic anemia (hypoproliferative cytopenia without dysplastic morphology and usually without clonal evolution) and myelodysplastic syndrome (cytopenia with dysplastic morphology and clonal evolution) represent the two main categories of complications. However, most of the common scenarios seen in SDS differ from the standard definitions established by World Health Organization (WHO) criteria,[41] because the bone marrow morphology from SDS patients often bears mild dysplastic changes in the erythroid, myeloid and megakaryocytic series, even in the absence of clonal cytogenetic abnormalities.

Aplastic anemia

Aplastic anemia can be divided into moderate and severe subcategories.[42,43] Severe disease is defined by depression in two of three blood counts (reticulocytes <40,000/μL, platelets <20,000/μL, neutrophils <500/μL) in the presence of a hypocellular bone marrow biopsy (<25% cellularity or <50% cellularity and <30% hematopoietic cells) without significant fibrosis. Moderate disease is defined as failure to meet the criteria for severe disease but with at least two diminished blood counts (reticulocytes <40,000/μL, platelets <40,000/μL, neutrophils <l,500/μL) with a hypocellular bone marrow biopsy.

The diagnosis of aplastic anemia is usually, but not always, considered in the absence of clonal marrow cytogenetic abnormalities (CMCA). Aplastic anemia may be transient (lasting less than 3 months) or may persist past 3 months, becoming clinically significant (J. Donadieu, unpublished data).

Clonal marrow cytogenetic abnormality

Clonal marrow cytogenetic abnormality (CMCA) is defined by: two or more bone marrow cells (out of twenty) with gain of the same chromosome or cytogenetic abnormality or three or more cells with loss of the same chromosome, as detected by G-banding; or a cytogenetic abnormality detected by fluorescence *in situ* hybridization (FISH) analysis in higher frequency than the reference values of the lab, as well as higher than in the concurrently tested control sample.

Diagnostic criteria for MDS and AML

The critical component for MDS is dysplastic morphology, as defined by the WHO.[41] Published criteria for MDS in children include two out of the following three items: chronic trilineage cytopenia, prominent bi-lineage cytopenia, clonal marrow cytogenetic abnormality, marrow myeloblast count between 5–29%.[44,45] However, since cytogenetic abnormalities as well as mild dysplastic features occur in some SDS patients without progression to AML, the markers that discriminate MDS from the aplastic phase are still debatable. AML is defined by a marrow myeloblast count of ≥20% (WHO)[41] or ≥30% (French American British classification).[46]

There are two current classification systems for pediatric MDS,[44,45] but the prognostic significance of the systems has not yet been studied. A literature review[47] reveals that subjects with SDS commonly show clonal marrow cytogenetic abnormalities (CMCA), MDS or AML. Among those identified with CMCA/MDS in childhood, approximately 50% progressed to overt leukemia over a range of 1 to 37 years. Remarkably, males constituted 68% and 92% of all subjects with CMCA/MDS and leukemia, respectively.

The bone marrow cytogenetic abnormalities i(7q) and del(20q) are quite common in SDS, occur less frequently in other malignancies or marrow failure syndromes, and can regress spontaneously.[16,48] These specific cytogenetic changes may be relatively specific for SDS and, in isolation, may not be an absolute harbinger of malignancy. In general, cytogenetic abnormalities of unclear clinical significance should be interpreted in the context of the marrow morphology and blast count.[14,15,48–54] Of these patients, some developed severe aplasia, while others progressed to more severe MDS/AML. SDS patients may also present with MDS at the stage of refractory cytopenia with dysplasia[14,15,48–54] or with excess blasts, some of whom progress to AML.

Various types of AML have been described in SDS patients: AML-M0, M2, M4, M5, and M6. Acute lymphoblastic leukemia and juvenile myelomonocytic leukemia were rare. AML-M6 was particularly common in SDS, occurring in about 30% of cases with classifiable leukemia. Malignant myeloid transformation into MDS and AML in SDS patients while on G-CSF therapy has been reported,[49,55,56] but the causal relationship is unproven. SDS-related leukemia carries a poor prognosis if treated with chemotherapy alone. However, due to the improving outcome of stem cell transplantation in patients over the past years, the prognosis of SDS with secondary leukemia has improved accordingly, but data are still limited.

Surveillance

In cases presenting with severe pancytopenia, bone marrow aspirate, biopsy, and cytogenetic examination are mandatory. However, the indications for routine bone marrow smear and bone marrow cytogenetics are controversial. To date, in the absence of severe cytopenia, bone marrow cytogenetic analysis has not generally been predictive of outcome. However, non-i(7q) abnormalities of chromosome 7, particularly monosomy 7, are associated with poor outcomes and may present with advanced

MDS/AML or progress from earlier stages of MDS. In addition, systematic bone marrow cytogenetic examination may have a role in surveillance in patients receiving long-term therapy with granulocyte colony-stimulating factor (G-CSF, see below).

In summary, bone marrow aspirate and biopsy are recommended at the time of diagnosis of SDS, in cases of CBC changes, and annually in patients who are treated with G-CSF therapy. In a patient with stable clinical status and complete blood counts (not on G-CSF), a bone marrow aspirate with cytogenetic examination can be proposed routinely every 1–3 years.

Treatment of hematologic and infectious complications

Cytopenias

Thrombocytopenia and anemia may require respective chronic transfusions, with institution of an iron-chelation program as clinically indicated. If transfusions are indicated, blood products need to be irradiated.

Granulocyte colony stimulating factor

The majority of patients do not need granulocyte colony stimulating factor (G-CSF) due to the low incidence of infections. Chronic use of G-CSF should be considered for recurrent invasive bacterial and/or fungal infections in the presence of severe neutropenia. G-CSF given for profound and persistent neutropenia has been effective in inducing a clinically beneficial neutrophil response. Patients may respond to an intermittent schedule with low doses of G-CSF (e.g. 2–3 μg/kg every 3 days) or may require higher doses continuously. The aim of long-term G-CSF treatment is not to obtain normal hematological parameters but to prevent infections. In cases of G-CSF resistance, associated with severe infections, hematopoietic stem cell transplantation (HSCT) should be considered.

Androgens

Data are scarce regarding response rates to androgens in SDS patients. A few patients have received androgens, and responses have been reported. However, androgens are generally not recommended as first line therapy for severe bone marrow failure in SDS. Underlying liver abnormalities seen in SDS may lead to higher liver toxicity than that seen in Fanconi anemia. The use of androgens should probably be reserved for patients who do not have severe bone marrow failure, and for whom an HSCT donor is unavailable.

Prevention and treatment of infections

Patients with acute infectious episodes, suggested by fever or any acute symptoms need to be evaluated urgently. Some patients can be treated with oral antibiotics, while patients with severe neutropenia or those suspected to have severe infections should be hospitalized and treated with intravenous antibiotics with broad-spectrum coverage until improvement. G-CSF treatment should also be considered during infections in patients with severe neutropenia. In cases of recurrent infections or severe chronic stomatitis with profound neutropenia, long-term G-CSF therapy may be considered (see above).

Bleeding episodes

In the presence of thrombocytopenia or low vitamin K-dependent coagulation factors, bleeding may occur. Mild to moderate bleeding episodes can be treated with local measures (xylometazoline 0.05% nose spray), tranexamic acid, or aminocaproic acid. When coagulation is affected by low vitamin K and/or, rarely, abnormal liver function, vitamin K should be administered. Platelet transfusions are indicated in an SDS patient with severe bleeding and thrombocytopenia. Prophylactic administration of platelets should be considered for patients with platelet counts of $<10 \times 10^9$/L or for those with a known tendency to have significant bleeding episodes.

For surgery or invasive procedures, platelets should be transfused as clinically indicated. When known or suspected coagulation defects are present, infusion of fresh frozen plasma or plasma-derived coagulation products (such as prothrombin complex, containing factors II, VII, IX, and X) may be indicated.

Female patients suffering from blood loss during menstruation may benefit from pharmacologic treatment to induce amenorrhea.

MDS and AML: chemotherapy

In MDS secondary to SDS, standard chemotherapy regimens are not indicated and an attempt should be made to provide HSCT on an urgent basis. High dose chemotherapy is therefore mainly indicated for conditioning prior to HSCT.

Standard chemotherapy for AML can be effective to temporarily control the disease. However,

chemotherapy alone has been unsuccessful in obtaining a prolonged complete remission in SDS. Therefore, due to a high risk of persistent aplasia, an urgent search for a related or unrelated donor for HSCT should be initiated and minimal chemotherapy to provide interim disease control should be considered.

Hematopoietic stem cell transplantation

Indications for HSCT. The criteria for considering patients for HSCT (related or alternative) include:

(a) Severe cytopenia [hemoglobin <7 g/L (4.3mmol/L), absolute neutrophil count $< 0.5 \times 10^9$/L with recurrent infections, platelet count $<20 \times 10^9$/L]
(b) MDS with excess blasts
(c) Overt leukemia

In cases of frank leukemia, the patient may be started on chemotherapy to reduce tumor load before HSCT, but an effort to find a donor should be made at the time of diagnosis because of the high risk of therapy-related aplasia.

In considering the indications for HSCT, one should also allow for the possibility of spontaneous recovery from aplasia. Depending on the level of potential immediate risks of the severe cytopenia, a monitoring period of up to 3 months can be considered while concurrently initiating the process of HLA typing and donor search.

Conditioning regimen and GVHD prophylaxis. At present, HSCT provides the only curative option for the hematological complications in SDS. Reported cases of SDS patients who have undergone HSCT include no more than 80 patients worldwide.[57,58] Many different conditioning/supportive regimens in small groups of patients render general conclusions and recommendations difficult. Globally, it appears that the results depend on the type of donor (genotypically identical donor transplants better than matched unrelated donor or MUD transplants) in almost all reports. However, the indications for HSCT also appear to be a clear determinant of survival. The survival of patients receiving a transplant for aplastic anemia is about 80%, while the survival of patients receiving a transplant for MDS or acute leukemia remains between 30 and 40%. This disparity is likely due in part to differences in the ages of recipients, because aplastic anemia is usually a complication in the first decade of life, whereas MDS/AML is more likely a complication of the second or third decade (younger patients generally have better outcomes following HSCT). Most data have been collected over the past 20 years, and current results may be more promising due to better standards for donor searches and treatment of complications.

Complications from chemotherapy or HSCT are more common in SDS patients than in patients with idiopathic blood dyscrasias. In a review of 36 patients with SDS who had been treated with chemotherapy alone[9,14,20,33,49–51,59–63] or with HSCT with or without irradiation, 83% died from complications related to the therapy, including prolonged severe aplasia, infections, cardiotoxicity, neurological and renal complications, veno-occlusive disease, pulmonary disease, post-transplant graft failure, and GVHD. Toxicity, particularly cardiac toxicity,[64] seems more frequent if the indication is MDS/acute leukemia rather than aplastic anemia. Recently, an attenuated conditioning regimen has been proposed in order to limit toxicity.[65,66]

Treatment of pancreatic dysfunction, nutrition and liver disease

Pancreatic enzymes

The clinical response to enzyme treatment in patients with SDS, in contrast to patients with cystic fibrosis for whom there may be additional intestinal factors, is usually excellent, although growth may continue to be restricted for skeletal reasons. The natural history of SDS suggests that pancreatic function may improve to sufficient levels in many patients to allow them to discontinue enzyme supplementation as they become older. The pancreatic status of all patients should therefore be reassessed from time to time, according to their clinical progress.

Once the diagnosis is made, and steatorrhea confirmed, pancreatic enzyme replacement should be started. The initial dose should be 2,000 lipase units/Kg body weight/day. The dosing guidelines for subjects with cystic fibrosis disease (maximum 10,000 lipase units/kg body weight/day) should be followed.[39] Pancreatin is taken with all meals and snacks that contain protein, fat or complex carbohydrates. In children with persistent fat malabsorption despite optimal dose of replacement, an H_2-receptor antagonist or proton pump inhibitor may be given

in addition. Higher requirements of pancreatic enzymes should alert the clinician to the possibility of a concomitant unrelated enteropathy.

Enteric-coated enzyme preparations prevent gastric acid-peptic degradation and therefore deliver a higher concentration of enzymes to the intestine than uncoated preparations. The capsules should be swallowed whole, without chewing. If the patient cannot swallow capsules, they can be opened and the enteric-coated granules mixed with milk, juice or pureed fruit. The resulting mixture should be swallowed immediately without chewing. Pancreatin is inactivated at high temperatures, and excessive heat should be avoided when the granules are mixed with liquids or food.

Vitamin supplements

Blood levels of fat-soluble vitamins should be measured every 6 to 12 months in young children, and supplementary therapy started if values are low. It is important to ensure compliance with pancreatic enzyme supplementation, as deficiencies of these vitamins are an indirect marker of fat malabsorption.

Dietary advice and surveillance

Height and weight should be documented at every clinic visit. All patients should receive an evaluation by a dietitian. Poor appetite and behavioral feeding difficulties are common. Such children should have a careful psychology assessment and support offered to the family by a clinical psychologist.

If oral intake is suboptimal nutritional supplements should be considered. If there are ongoing concerns about poor weight gain despite adequate pancreatic enzyme replacement therapy, it may be necessary to assess the child for other causes or conditions such as gastro-esophageal reflux, food allergy and enteropathy.[67]

In severe cases of persistent failure to thrive or feeding difficulties, as a last resort a gastrostomy insertion can be considered to allow overnight feeding, but weaning should be attempted once the patient is stable.

Treatment of dental complications

Oral and dental problems are common in children with SDS[68]. Ulceration of the oral mucosa can be associated with neutropenia. The frequency and severity of the ulceration is variable. Enamel defects have been noted, in both the deciduous and permanent dentitions. Areas of faulty mineralization of the dental surface can lead to decay and can be severe in some cases. Gastric acid reflux can lead to tooth surface loss or erosion. Regular dental care and appropriate advice from an early age are crucial to minimize these oral and dental problems.

Treatment of bone abnormalities

Treatment and follow-up

Bone deformities due to metaphyseal chondrodysplasia, usually located at the hips or the knees, may require orthopedic consultation and surgical interventions. Low-turnover osteoporosis may result from a primary defect in bone metabolism that is related to the bone marrow dysfunction and neutropenia. Efforts should be made to optimize general preventive measures such as nutrition and intake of fat-soluble vitamins, as well as to promote weight-bearing exercise. Supplementation with vitamin D (in addition to other fat-soluble vitamins) and calcium should be commenced if dietary intakes are not sufficient. It is presently unknown whether bisphosphonates, anti-resorptive agents used to treat postmenopausal high-turnover osteoporosis, are safe and efficacious in SDS osteoporosis. Optimal treatment for SDS osteoporosis remains to be established.

Radiography and bone densitometry. Assessment of bone dysplasia (Tables 2 and 3): at diagnosis, radiographic skeletal survey; follow-up based on individual clinical and radiographic findings, X-rays for detection of deformities or stress fractures (hips, knees). Assessment of osteoporosis: bone densitometry by DXA, at prepuberty (baseline study), during pubertal years, postpubertal follow-up studies based on individual findings (low BMD, vertebral compressions, multiple peripheral fractures). Caution should be exercised when interpreting DXA results in patients with SDS; small body size and delayed pubertal development affect BMD results.

Biochemistry. Serum 25-OH-vitamin D and plasma parathyroid hormone (PTH) should be monitored as part of routine follow-up and maintained within normal limits after the diagnosis.

Neurodevelopmental consequences and support

Deficits in cognitive abilities across numerous domains of functioning are evident in the majority of individuals with SDS at varying levels of severity

Table 3. Longitudinal changes in skeletal phenotype in SDS

When?	What?	Where?
Infancy and early childhood	Delayed appearance of secondary ossification centers	Wrist, hand, femur
	Wide, irregular metaphyses	Ribs, wrist
	Osteopenia, Wormian bones	Tubular bones, skull
Mid-childhood	Slow development of secondary ossification centers	Wrist, hand, femur
	Irregularity and sclerosis of metaphyses	Femur
	Osteopenia	Tubular bones, spine
Late childhood/ puberty	Irregularity, sclerosis and asymmetrical growth of metaphyses	Femur
	Stress fractures, deformity	Femur
	Compression fractures	Spine
Adulthood	Compression fractures	Spine

indicating heterogeneity. Parental report indicates that over 50% of children experience delayed language development.[6,40] Below average intellectual reasoning abilities are also evident[6,40,69,70] with approximately 1 in 5 meeting the diagnostic criteria for an intellectual disability (i.e., IQ $< 2^{nd}$ percentile).[40] Difficulties in visual reasoning and visual-motor integration,[40,70] higher order language functioning (e.g. understanding figurative expressions, knowledge of synonyms), executive problem solving and attention have also been documented.[40]

Significant behavioral issues are commonly reported. In a study of 32 children / adolescents (ages 6 through 17),[40] 19 percent had prior diagnosis of attention deficit hyperactivity disorder, pervasive developmental disorder or oppositional defiant disorder while an additional 31 percent were reported to have some combination of inattention, restless, impulsivity, and oppositional behavior. In addition, on behavioral rating scales, parents indicated a heightened frequency of attention problems (50%) and social problems (34%). The neurocognitive deficits have been found to be independent of pancreatic involvement, otitis media, having a chronic illness, family environment, and age.[40] Given the structural abnormalities that are evident on neuro-imaging of the brain,[71–73] neurocognitive and neurobehavioral issues are likely the consequences of SBDS gene dysfunction on the brain.

Assessment, monitoring, and treatment

In order to maximize ongoing development, comprehensive assessments using standardized tests and clinical observation to monitor cognitive, behavioral, social, and adaptive functioning are warranted from time of diagnosis through to adulthood. Specifically, during the infancy/pre-school period (diagnosis to 4 years of age), it is advised that comprehensive developmental checklists be used so that referrals to specialists (i.e., speech and language therapist, occupational therapist, developmental pediatrician, developmental psychologist), assessment and intervention can occur at the earliest sign of possible issues. In addition, it is recommended that serial neuropsychological assessments be completed to coincide with key stages of brain maturation, namely 6–8, 11–13, and 15–17 years of age. These age groups also parallel changes in expectations in learning at school. Assessments should include evaluation of intellectual abilities, attention (working memory, sustained attention, and divided/dual attention), higher order language, visual perception, visual-motor functioning, executive skills, academic readiness/achievement, behavior, and functional independence. The identification of an individual's strengths and weaknesses, consequently leads to individualize recommendations for intervention, which are reviewed and adapted at the follow-up assessment at the next critical stage of development. Counselling for parents should parallel the neuropsychological assessments of their child to support them in enhancing interactions with, and in developing realistic expectations for, their child.

Conflicts of interest

The authors declare no conflicts of interest.

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