Oral manifestations of sickle cell disease

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Key points

Sickle cell disease is one of the most common genetic diseases caused by a specific mutation in the gene coding for the ß-globin chain.

While systemic complications are well documented, oral complications are less so. They include aseptic pulp necrosis, mucosal lesions, dental eruption delays, bone pain and osteomyelitis of the maxilla, and oral neuropathies.

The oral care of sickle cell patients requires specific precautions such as good management of local anaesthetics, rigorous anti-infective prophylaxis as well as controlled prescription of analgesics.

Sickle cell disease is one of the most common autosomal recessive genetic diseases. It gives rise to abnormally shaped red blood cells with altered function, the primary clinical features being haemolytic anaemia and vascular occlusion. Acute complications are frequent and variable and include chest syndrome, stroke, infection mainly due to asplenia, bone pain and priapism. Other chronic complications which can occur are bone necrosis, nephropathy and heart, lung and skin disorders. Oral lesions are also very common and include aseptic pulp necrosis, mucosal damage due to anaemia, fungal infections due to numerous antibiotic therapies, dental eruption delays, bone pain and osteomyelitis of the maxilla, and oral neuropathies, including of the mental nerve of the chin. The oral care of sickle cell patients requires specific precautions such as good management of local anaesthetics, rigorous anti-infective prophylaxis as well as controlled prescription of analgesics. Regular oral follow-up of sickle cell patients is necessary.

Introduction

Sickle cell disease is one of the most common genetic diseases and predominates in persons of African descent.[1] It is an autosomal recessive blood disorder associated with production of abnormal haemoglobin, caused by a specific mutation in the gene coding for the β-globin chain. This mutation (which substitutes glutamine to valine at position six of the polypeptide) leads to the production of an altered haemoglobin molecule, termed haemoglobin S (HbS), which causes deformation of the red blood cells and concomitant obstruction of blood vessels.[2] In a poorly oxygenated tissue environment, HbS molecules polymerise. This polymerisation leads to the formation of fibres that deform the red blood cells and reduce their plasticity. This, in turn, results in haemolysis, thus creating an anaemia called haemolytic anaemia.[3] In addition, the vascular occlusions further reduce the oxygen supply of the affected organs (Fig. 1).

Persons with sickle cell disease are genetically described as being homozygous S/S, with two identical Glu6Val mutations transmitted by each parent. Sickle cell trait refers to genetic haemoglobin diseases characterised by the presence of HbS associated with another Hb abnormality, with the biological and clinical signs depending on the nature of the association. Some forms are asymptomatic, others are characterised by clinical and haematologic signs close to those of sickle cell disease.[2] Composite heterozygous forms (or double heterozygotes) combine an HbS variant with an HbC variant (HbSC form) or with other variants (OArab, DPunjab, for example), or an HbS variant with a β-thalassemia-related mutation.[2] Thus, severe sickle cell disease includes: (i) homozygous S/S sickle cell anaemia, the most common and severe form; (ii) composite heterozygous sickle cell disease, S/C, S/β, thalassemia and S/β + thalassemia; and (iii) more rarely, composite heterozygous sickle cell anaemia SDPunjab, SOArab, CatsC, or symptomatic heterozygotes.[2]

For newborns at risk, neonatal screening is applied. The diagnosis is made by electrophoresis of haemoglobin. When an abnormality is suspected, it may be necessary to test the forms of Hb present. In this case, different tests are used. Isoelectrofocalisation and high-performance liquid chromatography (HPLC) allow rapid diagnosis of haemoglobinopathy. These two analytical techniques are currently recommended for neonatal screening of sickle cell disease at the international level. Whatever the first-line technique used, it is recommended to use an alternative method in the second line in order to validate the presumed variant (for example, DNA analysis, immunochemistry).[4] In the UK, neonatal screening is universal in England, Scotland and Northern Ireland but not in Wales. In England, sickle cell disease affects one of every 2000 individuals at birth; 380,000 persons have the sickle cell trait, and more than 12,500 are sickle cell patients, with the highest prevalence in the African and Caribbean populations.[5]

The first step in the care of sickle cell patients is to inform the patient and his/her family of the condition. It is a chronic disease, manifested by important and quite varied complications. There are also non-symptomatic complications

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that must be detected in a preventive setting. The disease exhibits variable expression in symptomatology and frequency, which makes the pathology particularly difficult to treat.[6]

While systemic complications are well documented, oral complications are less so. Due to the absence of evidence from randomised controlled trials (RCTs) or quasi-RCTs,[7] the aim of this review is to highlight recent advances on clinical outcomes of systemic and oral manifestations of sickle cell disease as well as suggest therapeutic options for managing oral care. These proposed options are based on: (i) our clinical experience in the management of patients followed in the specialist centre for rare blood cell diseases at Henri Mondor Hospital; and (ii) review of the medical literature using the term 'dental AND sickle cell disease' on MEDLINE. The term 'dental' refers to all dental complications, including dental caries, periodontal disease, odontogenic infection, maxillae bone complications and oral mucosal pathologies.

Systemic manifestations: systemic manifestations are either acute or chronic

Acute complications

Among acute complications, we describe the five most frequent ones.

Complications from bone vascular occlusion occur when the partial pressure of oxygen in the circulation decreases. The red blood cell becomes deformed and takes on a characteristic sickle shape. These rigid red cells become trapped in small blood vessels and thus prevent good oxygenation of the organs. This causes a very violent pain called a vaso-occlusive attack. Acute pain is the most common reason for consultation. These episodes mainly involve bone pain, and more rarely articular pain, which is very intense. These symptoms must be dealt with very quickly because of their intensities, which are often underestimated by practitioners. However, the pain may be due to other pathologies as well, such as infectious arthritis, pericarditis, pancreatitis or any medical-surgical emergency. It is therefore advisable to be cautious when diagnosing any sickle cell patient experiencing a pain crisis.[8]

Acute chest syndrome is the leading cause of death of adult patients with sickle cell disease. It is a radiologically visible and sudden-onset pulmonary infiltrate associated with one or more of the following symptoms: cough, dyspnoea, chest pain, fever. This syndrome occurs most often in patients already hospitalised for another complication. It is essential to look for signs of seriousness and the appearance of clinical complications. A transfusion exchange must be performed when grave signs exist.[9]

Priapism refers to a painful and irreducible prolonged erection that occurs outside of any sexual stimulation and does not lead to ejaculation. At least 40% of sickle cell patients report episodes of priapism. The priapism of sickle cell disease has the distinction of first appearing in childhood and quickly threatening the erectile prognosis. This should be considered a therapeutic emergency.[10]

Infectious complications of sickle cell patients are common and well documented. They are due to anatomic or functional asplenia, which is a consequence of repeated splenic infarction. The spleen plays an essential role in the body's defence mechanisms against infection. Thus, the sickle cell patient is immunocompromised in terms of antibody synthesis and certain effector substances involved in antimicrobial defence. Treatment of any serious sepsis must include urgent antibiotic therapy, especially against pneumococcus and gram-negative pathogens.[11]

Sickle cell disease is the most common cause of strokes in childhood, and stroke is the most serious complication of sickle cell disease. Sickle cell adults with an acute central neurological score urgently need transfusion exchange and brain imaging by CT or magnetic resonance imaging (MRI) with angio-MRI. The complications may include ischaemic stroke or haemorrhagic rupture of an aneurysm.[12]

Chronic complications

Nephropathies are a frequent complication of sickle cell disease. Renal pathologies manifest themselves in various forms, including as glomerulopathies, haematuria and proteinuria,

Fig. 1 Main physiopathological mechanisms of sickle cell disease that lead to septic or aseptic necrosis accompanied by vascular disorders and chronic haemolysis

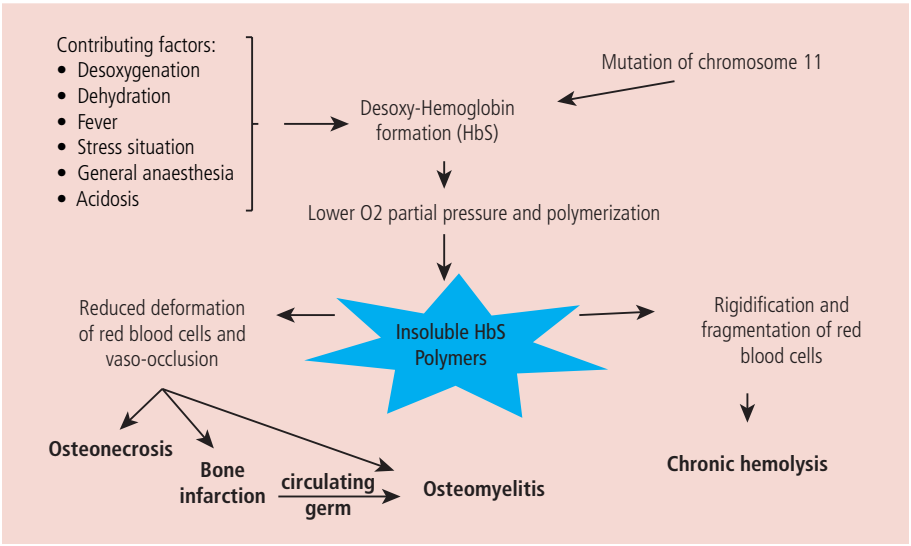

Table 1 Prevalence of oral pathologies in sickle cell patients. The frequency of pulpal necrosis is unknown to date. Periodontal pathologies are the subject of much controversy and are not referenced in this table

Main oral pathologies in sickle cell patients	Frequency (reference)
Pallor of oral mucosa	70% (10)
History of mandibular pain	20% (10)
Delayed dental eruption	23% (10)
History of neuropathy of the lower alveolar nerve	27,5% (10)
Mandibular osteomyelitis	5% (18)
Pulp necrosis	unknown
Radiological image	70-100% (30)

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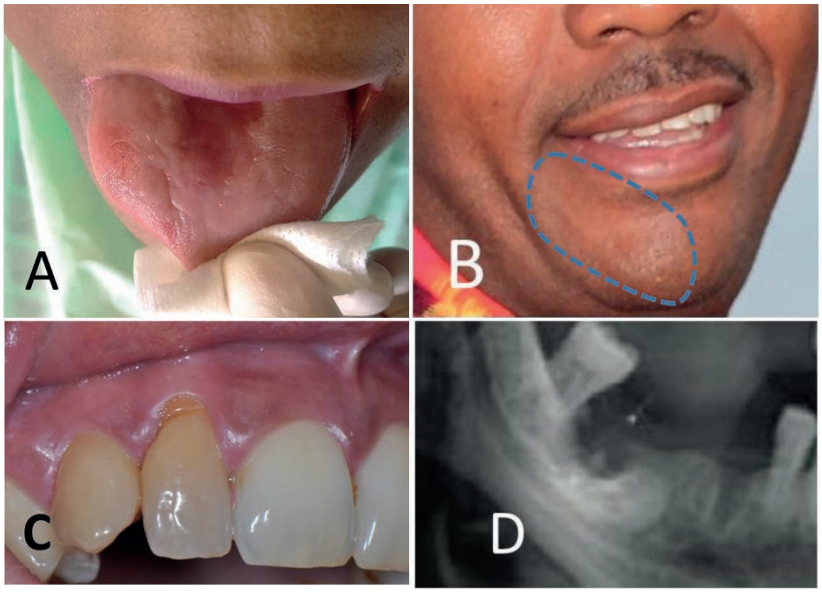


Fig. 2 Illustration of the oral manifestations of sickle cell disease. A) Homolateral localised atrophy of the lingual papillae. B) Labial hypoaesthesia (surrounded area) disturbs the symmetry of the smile. C) Dyschromia of the lateral incisors secondary to aseptic necrosis without any dental or periodontal lesion. D) Delayed bone healing after avulsion of the second lower right molar with onset of necrosis of the alveolar wall

which can lead to major renal insufficiency. The physiopathological mechanisms are renal vascular occlusions. Dialysis and kidney transplantation should be considered as a last alternative to conventional treatments. The use of nephrotoxic drugs (such as penicillin) is therefore not recommended in these patients. Moreover, these patients must be given hydration treatment in order to limit this chronic complication.[13]

Chronic pain of bone origin can occur as part of this pathology. Aseptic osteonecrosis of the femoral or humeral heads is detected early in cases of persistent mechanical inguinal or shoulder pain. MRI confirms the diagnosis. In acute situations it is sometimes difficult to differentiate osteomyelitis from bone infarction.[14] Acute bone infection should be considered in cases of intense, focused and fixed bone pain that persists for more than ten to 15 days and is resistant to transfusion and analgesics.

In fact, all organs can present chronic pathologies, mainly due to vascular defects. However, cardiac, pulmonary or cutaneous lesions are the most frequent apart from neuropathies and bone disorders.[12]

Oral manifestations

There are different oral manifestations of sickle cell disease, however, most are not specific to the disease. The most common are the paleness of the oral mucosa (like in every anaemia), delayed tooth eruption, papillary atrophy of the tongue, mandibular osteomyelitis, nerve damage to the inferior alveolar nerve, orofacial pain and pulpal necrosis of healthy teeth (aseptic necrosis).[15–18]

In this article, we aim to detail these manifestations as well as several more specific oral complications related to sickle cell disease without being pathognomonic.

Dental pathologies

Pulp necrosis refers to the death of the pulp accompanied by its destruction. Clinically, this is observed as a change in the colour of the crown due to the impregnation of hard tissues, including dentin, by decomposing blood pigments (Fig. 2C). Thermal tests do not provoke any reaction, demonstrating the insensitivity of the tooth. Mechanical opening of the pulp chamber is accompanied by a putrid odour. An association between sickle cell disease and pulp necrosis on otherwise clinically healthy teeth has been reported.[19] The presence of healthy necrotic teeth is 8.33 times higher in a patient with sickle cell disease compared to a non-sickle cell patient, because of vascular occlusions of the pulpal microcirculation. Clinical interrogation frequently reveals painful dental episodes in the past. However, this feature is not essential and there are many cases of pulpal necrosis without any painful history.

A priority in sickle cell disease management is the prevention of infection by antibiotic prophylaxis. Due to the previously described asplenia, individuals with sickle cell disease are more likely to have infections. Long-term antibiotic prophylaxis with penicillin is therefore often prescribed to children. However, there was no significant difference in the frequency of carious lesions between sickle cell children and healthy controls.[16] Antibiotic prescription in adults is less systematic.[16] On the other hand, a higher rate of oral fungus infection has been found in sickle cell patients.[16] Indeed, the multiplication of antibiotic therapies is responsible for modification of the oral bacterial microflora and the emergence of normally saprophytic fungi.

Finally, in children aged 0 to 13 years, it was noticed that a delay in dental eruption was 1.7 times more common in sickle cell disease compared to the unaffected population.[15] A change in tooth shape and size, however, has not been demonstrated.[19]

Pathologies of the oral mucosa and periodontium

Altered pallor of the oral mucosa is the most frequent oral manifestation observed. It is secondary to the decrease in haematocrit. The mucosa may sometimes be yellowish in colour because of the haemolytic nature of the anaemia.[18] These manifestations are not specific and may be visible in any haemolytic anaemia (autoimmune for example).

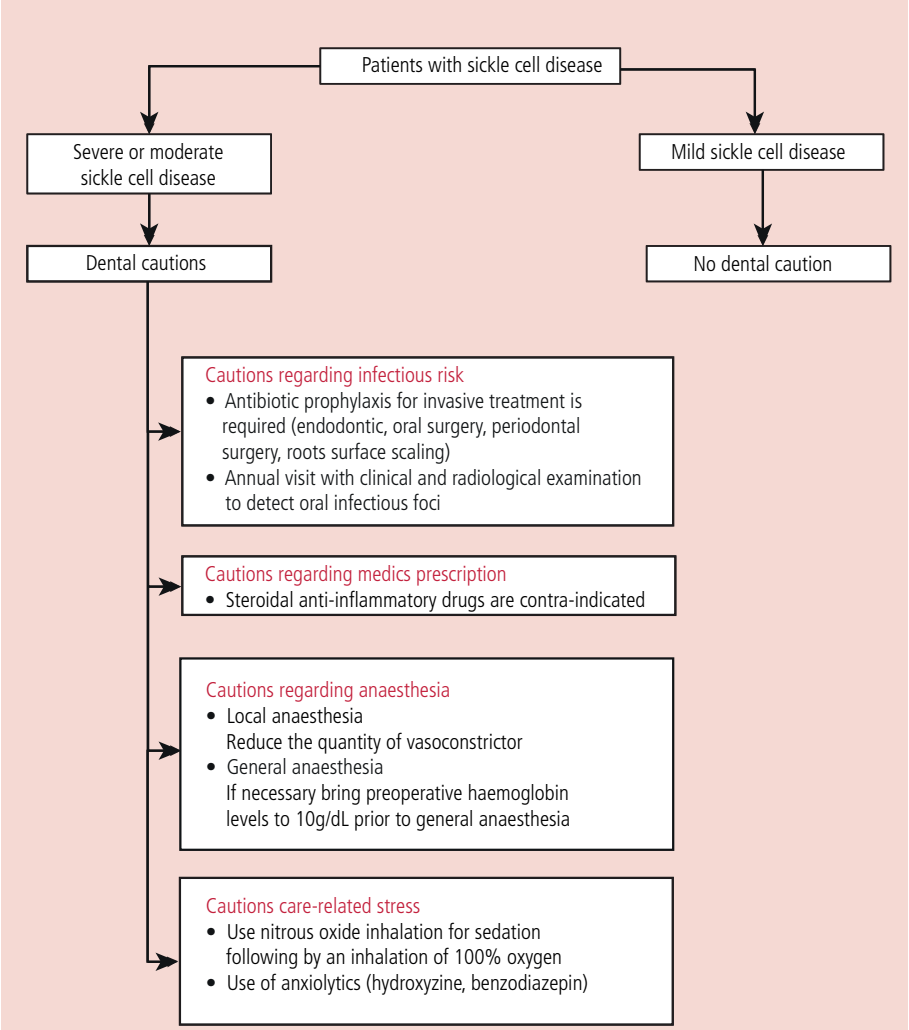
Atrophy of the papillae of the tongue is often observed (Fig. 2A), although less common than that in pernicious anaemia (vitamin B12 deficiency, also called Biermer's anaemia). The condition affects usually the entire tongue, which appears smooth and reddish.[20]

Currently, most studies do not show a link between specific periodontal disease and sickle cell disease.[21] However, a study on cohorts of both homozygous and heterozygous (that is, sickle cell trait) patients reported that only the heterozygous form is correlated with periodontal disease.[21] The authors explained this discrepancy by the fact that the density of trabecular bone is decreased by the pathology in heterozygotes, making it more susceptible to the consequences of periodontitis.[21] Moreover, the gingiva can be the location of blood extravasation leading to gingival enlargement.[22]

Bone manifestations

Bone pain is secondary to vascular occlusive attacks that lead to bone ischaemia and the appearance of small areas of necrosis. These

Fig. 3 Flow chart of cautions for dental care



painful events are more frequent in the mandibular bone and more specifically in its posterior area because of a less developed vascular network there and less arterial replacement in the case of arterial thrombus.

Such bone pain can be caused by hypoxia (resulting from infection, respiratory failure, change in blood pressure, for example due to altitude, prolonged effort) or dehydration (high summer heat, high fever, intense physical effort). Other triggers have been found such as general anaesthesia, stress or surgery. This bone necrosis can be observed by radiological examination. There are indeed radiolucent lesions of small size consistent with the painful episodes. These radiological lesions are still visible long after the episode.[23,24]

Bone lesions may also be visible radiologically throughout the skeleton and at the level of the maxilla (osteoporotic appearance due to medullary hyperplasia, radiopaque lesions corresponding to areas of ischaemia, osteomyelitis lesions, bone growth retardation) (Fig. 2D).[23]

Osteomyelitis appears secondary to bone infarction. It is a bone infection whose pathogens are most often of haematogenous origin. The frequency of bone infections in sickle cell disease can be explained by the hyposplenism of these patients and bone hypovascularisation, particularly during vascular-occlusive attacks that make the tissue particularly susceptible to infection. The germs are transmitted by blood and are often of digestive origin (cholecystitis or gastroenteritis), which explains the frequency of *Salmonella* among the germs responsible for infections of sickle cell patients. However, one study reported 16 cases of osteomyelitis of the mandible in sickle cell patients without a *Salmonella* strain;[25] in this study there was a predominance of *Staphylococcus aureus* present in the oral cavity. The hypothesis is that germs propagate locally.[25]

It is often very difficult to differentiate early bone infarction from osteomyelitis. In both cases, bone pain is associated with fever, and interpretation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be difficult. Standard X-ray examinations do not permit a differential diagnosis.[26] One diagnostic technique is to perform blood cultures to identify a pathogen. MRI can also be a diagnostic aid.[23] The complications of osteomyelitis consist of the occurrence of pathological fractures or the appearance of a chronic osteitis that can cause fistula. The treatment consists of an adapted antibiotic therapy associated with surgical drainage.

Neuropathy of the mental nerve

Loss of chin sensitivity can be caused by infarction of the vascularisation of the lower mental nerve or its branches.[27,28] The prevalence of neuropathy in the mental nerve is 2.2 times more common in patients with sickle cell anaemia than in the general population (Fig. 2B).[15] It is also noted that neuropathy occurs concomitantly with a pain crisis. The neuropathy also results in reduced sensitivity of the lower lip on the affected-nerve side. The sensitivity returns gradually but usually only after several months. Every practitioner should be cautious about the fact that nerve damage can lead to a decrease in tooth sensitivity and thus negativity of dentinal tests when the teeth are not necrotic.[17]

Therapeutic precautions in odontology

Infection risks are at the forefront of oral management. The French recommendations for adult sickle cell patients call for an annual consultation to ensure that a dental examination and the necessary care are performed each year.[29] Neither the UK National Institute for Health and Care Excellence (NICE) nor the National Institutes of Health in the USA provides guidelines for dental care in sickle cell patients. Routine care can be provided, but prevention of dental infections implies that screening and treatment should be a priority to avoid occlusive vascular pain. Some sickle cell patients have functional asplenia or have undergone splenectomy. In this case, they must receive antibiotic prophylaxis. Antibiotic prophylaxis identical to that used to prevent infective

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endocarditis is recommended in cases of special dental care, including endodontic care (for example, treatment of vital pulp; treatment of non-vital pulp, including treatment of the canal), where there is a risk of bleeding, and all other surgical procedures.[30] Antibiotic prophylaxis is prescribed for periodontal, periapical, and oral mucosal surgery.[30] In cases of osteomyelitis in the mandibular region, various treatments can be considered: sequestrectomy, curettage, debridement, corticotomy or partial bone resection. Appropriate antibiotic coverage and follow-up are indicated.[7,31]

Oral anaesthesia is the subject of recommendations. Locoregional anaesthesia is possible.[29] There is no consensus on the use of vasoconstrictors.[7] On the other hand, it is preferable to obtain deep local anaesthesia to avoid situations of stress which may be responsible for subsequent occlusive vascular pain. Use of a sedative such as an anxiolytic or an equimolar mixture of oxygen and nitrous oxide (MEOPA) can be considered to reduce stress linked to dental treatment.

Conscious sedation is preferable to general anaesthesia, which can cause complications. Precautions are to be taken with MEOPA. To avoid hypoxia upon discontinuation of MEOPA inhalation, administration of 100% O2 for four to five minutes at the end of treatment is advised.[32] If general anaesthesia is unavoidable, some precautions should be considered. Anaemia must be corrected preoperatively (Hg >10g/dl). General anaesthesia should allow all oral care in one session to avoid reoperation.[33,34]

Analgesic drugs are often prescribed. Steroidal anti-inflammatory drugs are contraindicated because of the risk of triggering serious pathologies[29] (for example, hyperalgic or acute chest syndrome). The combination of paracetamol and codeine is the best analgesic solution for these patients.[33,35] The use of morphine and derivative analgesics is also possible (buprenorphine, fentanyl, hydromorphone, nalbuphine, oxycodone and pethidine). These central analgesics are reserved for intense pain that often requires hospitalisation. The cautions for oral care are summarised in Figure 3.

Conclusion

Sickle cell disease is a genetic disorder which requires particularly complex treatment because of its phenotypic pleiotropy. While the general lesions are well known and described, details of the oral repercussions of the disease are rather limited. Understandably, disease management focuses on the vital needs of the patients, such that oral care is often neglected. However, infections in these patients are frequent and feared, which gives an important place to the dentist via his or her role in the prophylaxis of this co-morbidity. Focal infections associated with oral pathologies are widely described among the general population, and they affect patients with sickle cell disease in similar ways but with potentially graver consequences. Epidemiological studies of large cohorts of patients will be needed to more clearly establish the oral manifestations of sickle cell disease.

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