



# Sickle Cell Disease Complications Following Air Travel: A Review of the Current Literature



Stanis Okitotsho Wembonyama<sup>1,2</sup>, Olivier Mukuku<sup>3\*</sup>, Patricia Mishika Lukusa<sup>4</sup>, Dieudonné Saghasa Malekani<sup>2</sup>, Léon Mwepu Tshilolo<sup>5</sup>

<sup>1</sup>Département de Pédiatrie, Faculté de Médecine, Université de Lubumbashi, Lubumbashi, République Démocratique du Congo

<sup>2</sup>Conseil Médical de l'Aviation, Kinshasa, République Démocratique du Congo

<sup>3</sup>Institut Supérieur des Techniques Médicales de Lubumbashi, Lubumbashi, République Démocratique du Congo

<sup>4</sup>Ecole de Santé Publique, Université de Lubumbashi, Lubumbashi, République Démocratique du Congo

<sup>5</sup>Centre Hospitalier Monkole, Kinshasa, République Démocratique du Congo

**Corresponding Author:** Olivier Mukuku, MSc, Institut Supérieur des Techniques Médicales de Lubumbashi, Lubumbashi, République Démocratique du Congo. Tel : +243-997925649, Email: [oliviermukuku@yahoo.fr](mailto:oliviermukuku@yahoo.fr)

Received May 5, 2021; Accepted June 21, 2021; Online Published October 17, 2021

## Abstract

Every year, the number of people using commercial aircraft is estimated at two billion, and more than 300 million people take long-haul flights. Sickle cell patients may be at risk during the air journey because significant hypobaric hypoxia may occur at cruising altitude. This literature review reports complications related to air travel such as painful crises, serious spleen complications (spleen infarcts) requiring a splenectomy, or even sudden death. Prevention of these complications includes environmental protection (maintaining pressure inside the aircraft cabin in a hypobaric condition) and individual prophylaxis (general recommendations for all travelers and specific measures for sickle-cell patients). In order to assess complications associated with air travel in sickle-cell patients, an assessment of their ability to fly is necessary. In addition, the flight fitness assessment identifies patients who will need additional oxygen during flight. When prescribed by the passenger's physician, additional oxygen is provided by most airlines. Knowing these elements makes it possible to anticipate problems and provide appropriate responses to patients.

**Keywords:** Air Travel, Sickle Cell Disease, Hypoxia, Altitude

**Citation:** Wembonyama SO, Mukuku O, Lukusa PM, Malekani DS, Tshilolo LM. Sickle cell disease complications following air travel: a review of the current literature. Int J Travel Med Glob Health. 2021;9(4):4-9. doi:10.34172/ijtmgh.2022.02.

## Introduction

Sickle cell disease (SCD) is a hereditary (autosomal recessive) hemoglobin disease that causes abnormal hemoglobin expression. It is the most common genetic disease globally, with about 300 000 births per year,<sup>1</sup> two-thirds of which occur in Africa.<sup>2</sup> It is a real public health problem in sub-Saharan Africa, affecting approximately 12 to 15 million people.<sup>3</sup> Estimates in the Democratic Republic of the Congo show that 2% of newborns are sickle cell patients, and about 40 000 sickle cell children are born every year.<sup>4,5</sup> The disease is characterized by chronic hemolysis, inflammation, immune deficiency, heterogeneous clinical phenotype, and visceral involvement. The pathogenic mechanism in SCD is mainly due to chronic inflammation associated with oxidative stress.<sup>6,7</sup> Clinically, this disease is characterized by potential manifestations including repeated vaso-occlusive crisis (VOC), splenic sequestration, hepatic sequestration, an elevated risk of cerebral vasculopathy (ischemic stroke), an episode of acute chest syndrome, severe chronic anemia, leg ulcers, priapism, or even pulmonary

arterial hypertension.<sup>8-10</sup> Sickle cell patients are also at risk of life-threatening complications such as sepsis.

In a healthy person, red blood cells are generally discoid; in a sickle cell patient, they curl, deform into a chipped sickle when deoxygenated. The resulting deformation (called "erythrocyte sickling") alters blood flow through micro vascularization, causing vascular damage, tissue hypoxemia, stroke, and even organ damage. These local ischemias can be very serious, leading to painful VOC and risks of serious organic complications (spleen, kidney, brain, lungs, bone, digestive tract).<sup>10</sup>

Air travel has emerged as one of the most popular, safe, and convenient forms of travel. In recent decades, the number of people traveling by commercial aircraft has been estimated at two billion.<sup>11-13</sup> Air travel is considered safe because of the accident, as all decisions are taken after carefully considering its safety impact. Nevertheless, air travel can be accompanied by some health complications.<sup>14</sup> Health care workers face more and more questions about this mode of transportation,

which are not always easy to answer. Although most people travel quietly on airplanes and the recommendations for sickle cell patients are sometimes ignored, certain features need to be recalled. Air transport can expose sickle cell patients to an increased risk of disease-related complications. Several factors, such as prolonged hypoxia, dehydration, temperature changes, and stress, can contribute to SCD's complications on air travel. The purpose of this article is to address the cardiorespiratory effects of flight, the risk of SCD's complications during air travel, and procedures to be followed to assess the fitness to fly in sickle cell patients.

### Epidemiology of Air Travel Complications of Sickle Cell Disease

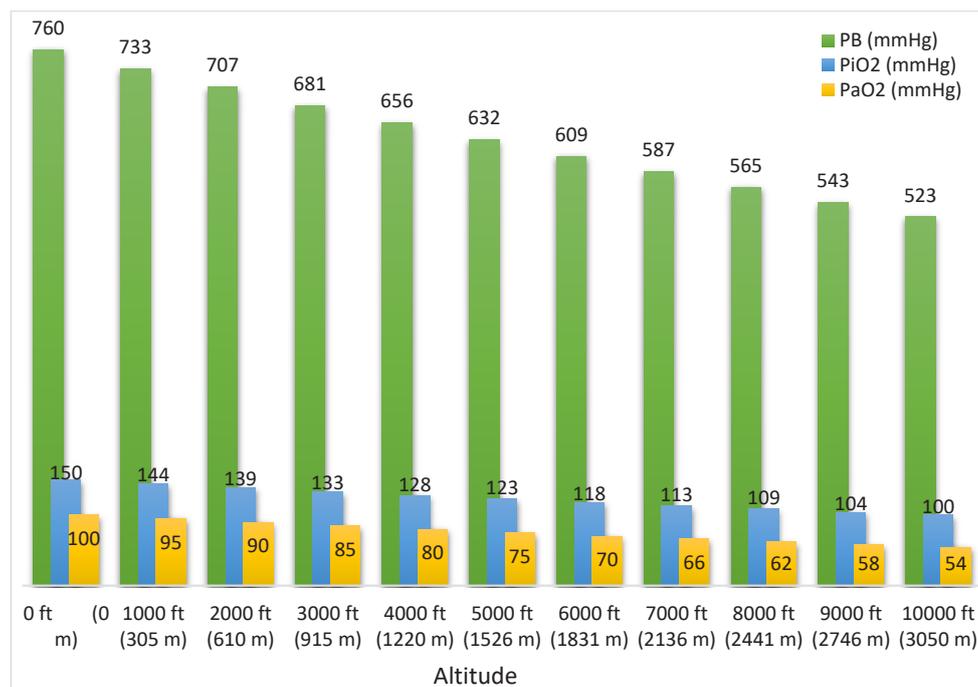
Air travel can exacerbate passengers' underlying diseases, and new conditions may manifest during flight.<sup>15</sup> The actual impact of the problem is difficult to assess because airlines are not obliged to report medical incidents on their airplanes. In addition, there is no standardized national or international register to provide reliable data or to read medical events in flight<sup>14,16</sup> clearly. There are very few case series studies or even systematic studies related to medical problems in the sickle cell population.<sup>17</sup> Most of the publications explicitly focused on the air travel-related complications of SCD before the 2000s, and the majority were splenic complications. However, compared to healthy travelers, the sickle cell population is at significant risk of health complications when traveling by air. An American study conducted by Claster et al<sup>18</sup> reported that the average VOC per patient was 10.8% in sickle cell patients and 13.5% in composite heterozygous subjects (HbSC or HbS beta-thalassemia) on an air trip. This study identified the risk of altitude-induced hypoxemia causing painful VOC in adult sickle cell patients.

### Effects of Altitude on Cardiopulmonary Function

Above sea level, the oxygen percentage is 21% in the air, and the barometric pressure (BP) varies around 760 mm Hg. In the troposphere, this pressure is inversely proportional to altitude, i.e., as altitude increases, BP gradually decreases. However, the percentage of oxygen does not vary up to 18,000 meters. This decrease in BP is similarly associated with the decrease in the partial inspiratory oxygen pressure ( $PiO_2$ ) and the partial arterial oxygen pressure ( $PaO_2$ ) (Figure 1).<sup>19</sup>

Normal flights reach cruising altitude between 25 000 and 45 000 feet (between 7000 and 14 000 m). In the aircraft cabin, the pressure during flight keeps the BP inside the aircraft higher than outside, even if the cruising altitude is high. To keep  $PiO_2$  and  $PaO_2$  safe during commercial aircraft flights in the cabins are pressurized.<sup>20</sup> According to International Civil Aviation Organization (ICAO) regulations, cabin pressure in commercial aircraft must not exceed that measured at 8000 feet, but in practice, it is typically between 5000 and 7500 feet.<sup>11</sup>

At these cabin altitudes, the  $PiO_2$  in commercial aircraft cabins (122 and 108 mm Hg) is significantly lower than the sea level (149 mm Hg). During flights, this decrease in  $PiO_2$ , in turn, leads to a decrease in  $PaO_2$  and a decrease in oxygen saturation of hemoglobin ( $SaO_2$ ).<sup>13,20-22</sup> Decreased  $PaO_2$  during air travel led to stimulation of chemoreceptors and increased minute ventilation as a reflex. Although the individual variability should be considered, the increase in minute ventilation following high altitude hypoxia is a key consequence of the increase in tidal volume and not the increase in respiratory rate. Generally, this increase in minute ventilation is well tolerated by healthy travelers as they are characterized by a large ventilation reserve.<sup>23</sup> The hypoxic ventilatory response occurs as a compensatory response to this hypobaric hypoxia in the airplane's cabin. Also, it causes



**Figure 1.** Oxygen Pressures Relative to Altitude and Barometric Pressure. Note. ft: feet; m: meter; BP: Barometric pressure;  $PiO_2$ : Partial inspiratory oxygen pressure;  $PaO_2$ : oxygen partial blood pressure.

other physiological responses (increase in cardiac output, increase in heart rate, and vasoconstriction of pulmonary arterioles and small arteries).<sup>20,25</sup> It has been shown to lead to a fall of SaO<sub>2</sub> to approximately 90%, which healthy travelers well tolerate. This decrease in SaO<sub>2</sub> not only varies with altitude but is also influenced by age, PaO<sub>2</sub> basal values, and minute ventilation.<sup>19,25</sup> Passengers with medical conditions associated with hypoxia, such as cardiac and respiratory conditions or severe anemia, may not tolerate reduction of BP without additional oxygen support.<sup>11,26-29</sup>

### **Pathogenesis of Complications of Sickle Cell Disease in Air Transport**

As mentioned above, during flights, hypobaric hypoxia in the aircraft cabin can cause a severe decrease in PaO<sub>2</sub> and physiological decompensation in some sickle cell patients. In addition, this situation is aggravated in sickle cell patients with a hemoglobin (Hb) level below 8.5 g/dL, reflecting a decrease in the Hb concentration of the red blood cells and a decrease in the amount of oxygen transported. Sickle cell patients were shown to have a large increase in ventilatory response due to an increase in alveolar dead space, which in turn would be caused by lower Hb concentrations, thus decreasing the amount of oxygen being managed in the pulmonary capillaries.<sup>30</sup> Furthermore, hypoxemia may lead to vascular occlusions by stimulating red blood cell sickling, inflammation, oxidative stress, vascular adhesion, and blood coagulation. Studies by Rayman<sup>31</sup> and Diggs<sup>32</sup> have shown that red blood cells containing hemoglobin S (HbS) can undergo sickling and block blood flow at altitudes below 10 000 feet (3048 m). However, most sickle cell patients are unlikely to develop red blood cells at altitudes below 21 000 feet (6400 m).

In addition to hypoxia, the role of dehydration should be emphasized as one of the factors involved in the occurrence of SCD complications during air travel. Ambient air in the cabin at cruising altitudes is about 10%-20% humidity, which is low compared to buildings (ranging from 40%-50%). According to some research, the low humidity of the aircraft cabin does not lead to dehydration. However, it leads to fluid loss of around 150 mL on an 8-hour flight, without any change in plasma osmolality and which would be easily compensated by normal homeostatic mechanisms.<sup>11</sup> In addition, this low humidity can cause dry mucous membranes of the lips and tongue, leading to a feeling of thirst and may also cause problems for contact lens wearers due to dry eyes in a healthy subject traveling by air.<sup>33</sup> In a sickle cell patient, however, this fluid loss would be greater than normal and could lead to dehydration, which would contribute to the installation of vascular occlusions. These vascular occlusions are responsible for tissue ischemias and pain in the body.

Based on the above, it is concluded that the most important factors in determining the fitness of sickle cell patients to fly are: (i) the functional severity of the disease; (ii) the hemoglobin level; (iii) the extent of any deficiency in the exchange of gas; (iv) basic PaO<sub>2</sub> at ground altitude; and (v) the availability of oxygen in reserve to provide supplementation when necessary.<sup>34</sup> Systematic assessment of these factors can

help the physician determine which sickle cell patients will fly safely, which may need additional oxygen in flight, or which will not.

### **Risk Assessment of Sickle Cell Disease Complications in Air Travel**

The sickle cell produces abnormal hemoglobin, which induces fragility in red blood cells, which lyse easily (anemia), the rigidity of the red blood cells which adhere to the walls of the vessels and cause in certain situations (cold, stress, infection, dehydration) their closure (vaso-occlusive crises), which causes pain often severe in bones, chest, and abdomen. In general, anyone with a hemoglobin level of less than 8.5 g/dL deserves special attention because, at such low levels, passengers may experience dizziness and even loss of consciousness during flight (often due to physical efforts such as going to toilets).<sup>11</sup> Sickle cell air travelers are exposed to considerable medical risks such as hypovolemia and VOC.<sup>35</sup> Although the literature speaks very little about the risks that sickle cell patients face when traveling by air, the few published case reports and case series studies report complications of SCD ranging from painful VOC<sup>18,36</sup> to severe splenic complications requiring splenectomy,<sup>37-40</sup> and even sudden death from a pulmonary embolism on the flight.<sup>41,42</sup> During flights, VOC may occur in up to 8.7% of sickle cell patients.<sup>43</sup> In addition, it is established that long-haul flight is one of the risk factors for venous thromboembolism.<sup>44</sup> Spleen infarction in sickle cell patients (and even those with a sickle cell trait generally asymptomatic) occurs during exposure to low partial oxygen pressure at high altitudes, including air travel.<sup>17,37,42,45,46</sup>

### **Prevention of Complications and Recommendations to Sickle Cell Patients During Air Travel**

Sickling of erythrocytes and, therefore, complications of SCD may, however, be induced by mild hypoxemia. Air travel that maintains cabin pressure at approximately 6000 to 8000 feet is associated with a decrease in PaO<sub>2</sub> that may affect Sickle cell patients.<sup>18</sup> Knowing that reduced oxygen pressures can worsen SCD, these patients are advised not to travel by air without medical oxygen as it has been shown that a sickle cell crisis could be fatal on-air travel.<sup>17,41</sup> Oxygen therapy is recommended for sickle cell patients on board aircraft at altitudes above 2135 m (7600 feet), especially if they have splenomegaly and have a relatively higher blood viscosity.<sup>47</sup> Although air travel is a probable risk factor for VOC, there is no universal consensus on additional oxygen recommendations.<sup>48</sup> Further research is needed to determine the need for additional oxygen to prevent flight-related complications in sickle cell patients.

In addition, sickle cell patients are advised to have their anemia corrected before traveling by air.<sup>11</sup> Flying in pressurized aircraft is generally not a problem for sickle cell patients when the recommendations are correctly met.<sup>35</sup> The most important considerations are to move around the aircraft cabin as often as possible, to drink plenty of fluids, and to dress warmly.<sup>49</sup>

## Review Highlights

### What Is Already Known?

SCD is a hereditary hemoglobin disease that causes abnormal expression of hemoglobin. In sub-Saharan Africa, this disease affects approximately 12 to 15 million people. Sickle cell patients have an increased risk of complications during air travel. Prolonged hypoxia, dehydration, temperature changes, and stress contribute to the occurrence of complications in these patients.

### What Does This Study Add?

Through this literature review, we highlight the existence of an increased risk of complications in sickle cell air travelers, particularly VOC. In addition, this review reviews the epidemiology and pathophysiology of these complications and proposes preventive options to follow. This paper is intended not only for physicians who provide pre-travel and post-travel advice but also for sickle cell patients and their families to know the risk involved when traveling by air.

Although they are often overlooked, the advice from the physician to patients is essential before any air travel.<sup>50</sup> The pre-travel health consultation provides an opportunity to assess the health risks of travel for an individual and provide education and advice to promote healthy travel. A key component of the pre-travel consultation is an individualized health risk assessment based on traveler demographics and details of the planned trip (including itinerary, duration, and planned activities).<sup>51</sup> Before traveling by air, sickle cell patients should follow the following recommendations<sup>34</sup>:

- combat relative hypoxemia: no unpressurized airplane flight, careful treatment of asthma and airway obstruction;
- correct anemia if Hb is below 8.5 g/dL;
- folic acid supplementation (to compensate for secondary needs of bone marrow regeneration) and zinc supplementation (pre-pubertal);
- maintain adequate hydration (amount to be adapted in case of diarrhea or a dry atmosphere);
- no undue exertion, no tramping, no sudden or prolonged standing;
- combat cold (warm clothes);
- combat circulatory slowdown (watch for postures, tight clothes).

Thus, preventive measures against complications of SCD during air travel can be summarized in two categories:

- Individual prophylaxis with general recommendations is for all travelers and specific measures for sickle cell patients. The general rules are to avoid sitting long, walking short in the aisle every 2-3 hours, drinking lots of water, and avoiding alcohol consumption.
- Environmental protection includes maintaining the pressure in the aircraft cabin under hypobaric conditions (altitude 1800 to 2500 m). In addition, the prevention of dehydration by providing adequate moisture via air conditioners and encouraging passengers to drink water or non-alcoholic beverages; movement and easy walking

in the aisles are possible. Similarly, oxygen support may be useful in some patients with SCD.

A trained travel medicine specialist should evaluate all sickle cell patients planning to travel by air. These visits are productive when they are made well in advance of the trip.

### Conclusion

Air travel may be associated with higher risks (especially for long-term flights) and require detailed preparation. However, there are no absolute contraindications to air travel, except for certain situations such as severe anemia that require correction prior to flight. Therefore, a clinical and functional assessment of the fitness to fly is recommended to identify patients who require oxygen and fluid supplements and reduce the risk of health complications during flight.

### Authors' Contributions

SOW and OM designed the study. SOW, OM, PML, and DSM carried out the literature search. SOW and OM wrote the first draft of the manuscript. SOW and LMT have edited the manuscript. All authors read and approved the final version of the manuscript.

### Conflict of Interest Disclosures

No conflicts of interest to declare.

### Ethical Approval

Not Applicable.

### Funding/Support

None.

### References

1. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561-1573. doi:10.1056/NEJMra1510865.
2. Pleasants S. Epidemiology: a moving target. *Nature*. 2014;515(7526):S2-3. doi:10.1038/515S2a.
3. Aygun B, Odame I. A global perspective on sickle cell disease. *Pediatr Blood Cancer*. 2012;59(2):386-390. doi:10.1002/pbc.24175.
4. Agasa B, Bosunga K, Opara A, et al. Prevalence of sickle cell disease in a northeastern region of the Democratic Republic of Congo: what impact on transfusion policy? *Transfus Med*. 2010;20(1):62-65. doi:10.1111/j.1365-3148.2009.00943.x.
5. Tshilolo L, Aissi LM, Lukusa D, et al. Neonatal screening for sickle cell anaemia in the Democratic Republic of the Congo: experience from a pioneer project on 31 204 newborns. *J Clin Pathol*. 2009;62(1):35-38. doi:10.1136/jcp.2008.058958.
6. Mukuku O, Sungu JK, Mutombo AM, et al. Albumin, copper, manganese and cobalt levels in children suffering from sickle cell anemia at Kasumbalesa, in Democratic Republic of Congo. *BMC Hematol*. 2018;18:23. doi:10.1186/s12878-018-0118-z.
7. Sungu JK, Mukuku O, Mutombo AM, Mawaw P, Aloni MN, Luboya ON. Trace elements in children suffering from sickle cell anemia: a case-control study. *J Clin Lab Anal*. 2018;32(1):e22160. doi:10.1002/jcla.22160.
8. Borhade MB, Kondamudi NP. Sickle cell crisis. In:

- StatPearls. Treasure Island, FL: StatPearls Publishing; 2020.
9. Novelli EM, Gladwin MT. Crises in sickle cell disease. *Chest*. 2016;149(4):1082-1093. doi:10.1016/j.chest.2015.12.016.
  10. Connes P. Physiopathologie de la drépanocytose. In: de Montalembert M, Brousse V, Marchetti MT, Allali S. La drépanocytose de l'enfant et l'adolescent. Paris: Elsevier Masson; 2020.
  11. Aerospace Medical Association Medical Guidelines Task Force. Medical guidelines for airline travel, 2nd ed. *Aviat Space Environ Med*. 2003;74(5 Suppl):A1-19.
  12. Sand M, Morrosch S, Sand D, Altmeyer P, Bechara FG. Medical emergencies on board commercial airlines: is documentation as expected? *Crit Care*. 2012;16(2):R42. doi:10.1186/cc11238.
  13. Silverman D, Gendreau M. Medical issues associated with commercial flights. *Lancet*. 2009;373(9680):2067-2077. doi:10.1016/s0140-6736(09)60209-9.
  14. Parker S, Mahomed O. Epidemiology of medical events on a commercial African national airline carrier between 2009 and 2011. *Int J Travel Med Glob Health*. 2019;7(2):53-56. doi:10.15171/ijtmgh.2019.12.
  15. Nable JV, Tupe CL, Gehle BD, Brady WJ. In-flight medical emergencies during commercial travel. *N Engl J Med*. 2015;373(10):939-945. doi:10.1056/NEJMra1409213.
  16. Guiu G, Monin J, Perrier E, Manen O. Epidemiology of in-flight medical events. *Int J Travel Med Glob Health*. 2019;7(1):10-12. doi:10.15171/ijtmgh.2019.03.
  17. Padda A, Corriveau-Bourque C, Belletrutti M, Bruce AAK. Supplemental oxygen therapy recommendations in patients with sickle cell disease during air travel: a cross-sectional survey of North American health care providers. *Paediatr Child Health*. 2020;25(2):107-112. doi:10.1093/pch/pxz049.
  18. Claster S, Godwin MJ, Embury SH. Risk of altitude exposure in sickle cell disease. *West J Med*. 1981;135(5):364-367.
  19. Tzani P, Pisi G, Aiello M, Olivieri D, Chetta A. Flying with respiratory disease. *Respiration*. 2010;80(2):161-170. doi:10.1159/000313425.
  20. Mohr LC. Hypoxia during air travel in adults with pulmonary disease. *Am J Med Sci*. 2008;335(1):71-79. doi:10.1097/MAJ.0b013e31815f1e35.
  21. Sheffield PJ, Heimbach RD. Respiratory physiology. In: DeHart RL, ed. *Fundamentals of Aerospace Medicine*. Philadelphia: Lea & Febiger; 1985:72-109.
  22. Boussemart T, Port-Lis M, Bonardi JM. [Medical aspects of commercial air travel]. *Arch Pediatr*. 2006;13(8):1160-1168. doi:10.1016/j.arcped.2006.06.002. [French].
  23. Ward MP, Milledge JS, West JB. Ventilatory response to hypoxia and carbon dioxide. In: *High Altitude Medicine and Physiology*. 3rd ed. London: Arnold; 2003:50-64.
  24. Marotte H. Le transport aérien: conséquences physiologiques et physiopathologiques de l'exposition de l'Homme à l'altitude, moyens de protection. In: Obadia E, Cha O. *Le Rapatriement Sanitaire par Transport Aérien Medicalisé, à Usage Civil et Militaire*. Paris: Elsevier Masson; 2020. doi:10.1016/B978-2-294-76875-0.00005-6.
  25. British Thoracic Society Standards of Care Committee. Managing passengers with respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax*. 2002;57(4):289-304. doi:10.1136/thorax.57.4.289.
  26. Muhm JM, Rock PB, McMullin DL, et al. Effect of aircraft-cabin altitude on passenger discomfort. *N Engl J Med*. 2007;357(1):18-27. doi:10.1056/NEJMoa062770.
  27. Akerø A, Edvardsen A, Christensen CC, Owe JO, Ryg M, Skjønsberg OH. COPD and air travel: oxygen equipment and preflight titration of supplemental oxygen. *Chest*. 2011;140(1):84-90. doi:10.1378/chest.10-0965.
  28. Martin-Gill C, Doyle TJ, Yealy DM. In-flight medical emergencies: a review. *JAMA*. 2018;320(24):2580-2590. doi:10.1001/jama.2018.19842.
  29. Bazex J, Cabanis EA. [Health risks of long-distance air travel. Role of the general practitioner]. *Bull Acad Natl Med*. 2010;194(6):1045-1069. [French].
  30. Pianosi P, D'Souza SJ, Esseltine DW, Charge TD, Coates AL. Ventilation and gas exchange during exercise in sickle cell anemia. *Am Rev Respir Dis*. 1991;143(2):226-230. doi:10.1164/ajrccm/143.2.226.
  31. Rayman RB. Sickle cell trait and the aviator. *Aviat Space Environ Med*. 1979;50(11):1170-1172.
  32. Diggs LW. The sickle cell trait in relation to the training and assignment of duties in the Armed Forces: I. Policies, observations, and studies. *Aviat Space Environ Med*. 1984;55(3):180-185.
  33. Ghafari F, Izadi M, Pazham H. Traveling guides for patients suffering from thyroid disorders; a narrative review. *Int J Travel Med Glob Health*. 2015;3(4):149-152. doi:10.20286/ijtmgh-0304146.
  34. Wembonyama SO, Mukuku O, Lukusa PM, Malekani DS, Tshilolo LM. Voyage aérien et drépanocytose: revue de littérature. *Journal of Medicine, Public Health and Policy Research*. 2021;1(1):20-26.
  35. Willen SM, Thornburg CD, Lantos PM. Travelers with sickle cell disease. *J Travel Med*. 2014;21(5):332-339. doi:10.1111/jtm.12142.
  36. Ware M, Tyghter D, Staniforth S, Serjeant G. Airline travel in sickle-cell disease. *Lancet*. 1998;352(9128):652. doi:10.1016/s0140-6736(05)79607-0.
  37. Cooley JC, Peterson WL, Engel CE, Jernigan JP. Clinical triad of massive splenic infarction, sicklemia trait, and high altitude flying. *J Am Med Assoc*. 1954;154(2):111-113. doi:10.1001/jama.1954.02940360009003.
  38. Doenges JP, Smith EW, Wise SP 3rd, Breitenbucher RB. Splenic infarction following air travel and associated with the sickling phenomenon. *J Am Med Assoc*. 1954;156(10):955-957. doi:10.1001/jama.1954.02950100031010a.
  39. Green RL, Huntsman RG, Serjeant GR. The sickle-cell and altitude. *Br Med J*. 1971;4(5787):593-595. doi:10.1136/bmj.4.5787.593.
  40. Murano T, Fox AD, Anjaria D. Acute splenic syndrome in an African-American male with sickle cell trait on a commercial airplane flight. *J Emerg Med*. 2013;45(5):e161-165. doi:10.1016/j.jemermed.2013.05.009.
  41. Nadesan K, Nagaratnam M. Sudden death during long distance air travel in an Hb S/C disease patient. *J Clin Forensic Med*. 2001;8(3):151-155. doi:10.1054/jcfm.2001.0476.
  42. Abdool K, Ramcharan K, Reyes AJ, Lutchman N, Alexander A. Bilateral pulmonary embolism after a short-haul flight in a man with multiple risk factors including sickle cell trait. *Case Rep Emerg Med*. 2017;2017:4316928. doi:10.1155/2017/4316928.
  43. Naik RP, Streiff MB, Lanzkron S. Sickle cell disease and

- venous thromboembolism: what the anticoagulation expert needs to know. *J Thromb Thrombolysis*. 2013;35(3):352-358. doi:10.1007/s11239-013-0895-y.
44. Philbrick JT, Shumate R, Siadat MS, Becker DM. Air travel and venous thromboembolism: a systematic review. *J Gen Intern Med*. 2007;22(1):107-114. doi:10.1007/s11606-006-0016-0.
45. Franklin QJ, Compeggie M. Splenic syndrome in sickle cell trait: four case presentations and a review of the literature. *Mil Med*. 1999;164(3):230-233.
46. Sheikha A. Splenic syndrome in patients at high altitude with unrecognized sickle cell trait: splenectomy is often unnecessary. *Can J Surg*. 2005;48(5):377-381.
47. Samuels MP. The effects of flight and altitude. *Arch Dis Child*. 2004;89(5):448-455. doi:10.1136/adc.2003.031708.
48. Padda A, Corriveau-Bourque C, Belletrutti MJ, Bruce A. Supplemental oxygen during air travel in sickle cell disease-common clinical practices. *Blood*. 2017;130(Suppl 1):2079. doi:10.1182/blood.V130.Suppl\_1.2079.2079.
49. National Heart, Lung, and Blood Institute (NHLBI). Division of Blood Diseases and Resources. *The Management of Sickle Cell Disease*. 4th ed. Bethesda: NHLBI; 2002.
50. Bellinghausen AL, Mandel J. Assessing patients for air travel. *Chest*. 2021;159(5):1961-1967. doi:10.1016/j.chest.2020.11.002.
51. Torresi J, McGuinness S, Leder K, et al. Principles of pre-travel healthcare. In: *Manual of Travel Medicine*. Singapore: Springer; 2019:1-17. doi:10.1007/978-981-13-7252-0\_1.