

Anaesthesia recommendations for **Hermansky-Pudlak syndrome**

Disease name: Hermansky-Pudlak syndrome

ICD 10: E70.3

Synonyms: /

Disease summary: Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease characterised by abnormal intracellular vesicle formation and trafficking [7,17]. It was first described in 1959 [11]. There are a few hot spots of HPS in many regions of the world [6]. Generally, there is a lack of data regarding the disease's real frequency. Its prevalence is estimated with 1 in 500,000 to 1 in 1,000,000 [14,21]. For unknown reasons, in north-western Puerto Rico, there has been identified an unusual high incidence of up to 1:1,800 persons [6].

There are 11 known genetically distinct subtypes of HPS (HPS-1 to HPS-11) [6,7]. Mutations result in defects in intracellular protein trafficking and in the biogenesis of lysosomes as well as the biogenesis of lysosome-related organelles (BLOCs), such as melanosomes and platelet dense granules [6,23].

Oculocutaneous albinism (OCA) is characterised by hypopigmentation of hair, skin retina and iris in different degrees. A decline in visual acuity may be accompanied by retinal hypopigmentation, horizontal nystagmus, photophobia, and strabismus [2,6,21,23]. HPS-2 patients may also result in immunodeficiency from severe neutropenia, often treated with G-CSF [10].

In addition, HPS-1 and HPS-4 are at high risk to develop pulmonary fibrosis in adults as well as HPS-2 in children. Fibrosis is supposed to be promoted by lysosomal accumulation of ceroid-lipofuscin in alveolar macrophages, disruption of type II pneumocytes and a consecutive inflammation cascade [1,7,23,28]. In adults, interstitial, irreversible and progressive lung diseases usually develop in the third decade of life.

Due to dysfunction in platelet aggregation in HPS, anamnesis often reveals history of i.e., bruising, nose bleeding, menorrhagia or (unexpected) prolonged bleeding after dental extractions or further surgical procedures [6,20,22,23]. However, the severity of bleeding tendency may widely vary between patients with HPS [5]. In the absence of dense bodies, bleeding time may be prolonged although a regular number of platelets and inconspicuous coagulation factors [5,12,18,29].

Moreover, in about 15 % of HPS (type 1–4) patient's phenotypic presentation may include granulomatous colitis with crampy abdominal pain, weight loss, malabsorption, and frequent watery, bloody diarrhoea [6,9,12,23]. Cardiomyopathy and renal glomerular dysfunction secondary to ceroid deposition have been reported as rare complications of HPS [12].

Diagnosis is based on clinical features including the typical triad of OCA accompanied by a bleeding disorder due to platelet dysfunction [6,11]. The latter one is demonstrated via absence

of platelet dense bodies (δ granules) on whole-mount electron microscopy of platelets, which represents the “gold standard” test for platelet abnormality in HPS [6,7,28].

Molecular genetic analysis is recommended to determine the specific subtypes of HPS to plan follow-up and to better estimate prognosis in affected patients [6]. However, detailed diagnostic is complex and i.e. genetic testing and confirmation is expensive and usually only available on a research basis [2]. Furthermore, diagnosis of intestinal lung disease is established with a high-resolution computed tomography of the chest (HRCT), which also provides a good radiologic monitor of disease status and progression [1]. Lung biopsy is not necessary for diagnosis and may merely provoke bleeding complications [6,28].

There are currently no definitive therapeutic or even preventative approaches for HPS [6]. Therefore, therapy is solely symptomatic.

Prognosis in HPS usually depends on the progression of lung fibrosis and in patients with HPS-2 on the immunological defect. The course of pulmonary fibrosis is variable but universally progressive and a major cause of mortality in adults, especially in HPS-1 [7,8,9]. Generally, because of absent efficacy, a corticosteroid or immunosuppressive therapy is not recommended in HPS patients with pulmonary fibrosis [28]. Administration of pirfenidone as a new therapy approach is assumed to slow the progression of fibrosis, but its use is controversial and not generally recommended yet [8,15]. Patients with HPS-1, HPS-2 and HPS-4 may be referred for lung transplant evaluation to prolong life expectancy [6,7]. Finally, lung transplantation is the only curative therapy for pulmonary fibrosis now [17]. However, treatment of Crohn’s disease-like gastrointestinal disorder in HPS is reported to respond well to immunosuppressive therapy [9]. Unfortunately, the average life expectancy of patients with HPS is 40–50 years (especially in cases of pulmonary impairment) [28].

Medicine is in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong



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Emergency information

	AIRWAY / ANAESTHETIC TECHNIQUE	no definite recommendation for either GA or RA, but GA may be preferred (TIVA / balanced) – however, be aware of difficult mask ventilation and rapid desaturation because of restrictive pulmonary dysfunction (high risk for pulmonary fibrosis of variable course in HPS-1, -2, -4) – (modified) RSI in case of gastrointestinal affection – perform lung-protective ventilation – avoid neuraxial RA (bleeding complications!) or only use it with extreme caution
B	BLOOD PRODUCTS (COAGULATION)	increased bleeding tendency due to qualitative platelet disorder (platelet number and routine haematology tests may be normal!) – prematching of RBCs and 24h-availability of haematologic / coagulation monitoring recommended – consider perioperative haematologic consultation – inform your local transfusion specialist in advance for sufficient storage of blood products, especially platelets! – consider perioperative DDAVP, PPSB, TXA, rFVIIa or platelet transfusion and cell saving strategies to prevent (life-threatening!) bleeding complications
C	CIRCULATION	No specific recommendations
D	DRUGS	no risk for MH – consider malabsorption of oral medication (gastrointestinal affection) – avoid NSAIDs (bleeding complications)
E	EQUIPMENT	ambulatory anaesthesia not recommended – patient positioning / mobilisation with caution (easy bruising), strive for optimal padding – use neuromuscular monitoring and ultrasound for vessel cannulation / peripheral RA – be aware of perioperative respiratory complications due to fibrotic lung disease (up to VV-ECMO necessity) and delayed bleeding complications – help might be necessary due to visual impairment

Typical surgery

Lung transplantation [7,24], video-assisted thoracic surgery (VATS) [14,15,16], bronchoscopies for routine surveillance or to receive transbronchial biopsies, any kind of lung biopsy (even if not routinely recommended for diagnosis – see above) [7].

Intestine surgery as a last resort in inflammatory bowel disease (resembling Crohn's colitis clinically) [6,23].

Ophthalmologic surgery like frequently necessary strabismus correction [3].

Type of anaesthesia

Despite reports of successful performance in pregnant women with HPS, spinal or peridural anaesthesia should be avoided or only be used with extreme caution in affected patients due to the risk of bleeding complications [2,19,21,25,27]. Besides, there are reports of local infiltration with anaesthetics for dental surgery without complications [18]. No reports were made for the performance of ultrasound guided peripheral nerve blocks. There is no definite recommendation for either general or regional anaesthesia. Basically, general anaesthesia may be preferred in patients with HPS due to varying bleeding tendency in these patients. Any neuraxial anaesthesia (e.g., spinal or epidural) should be decided individually for each patient and surgery weighing the risks and benefits of these procedures. Peripheral regional anaesthesia might be performed in patients with bleeding disorders with adequate ultrasound guidance and approaches with low risks for vessel puncture.

General anaesthesia can be performed as balanced anaesthesia with volatile anaesthetics or as total intravenous anaesthesia (TIVA). Monitoring of neuromuscular block is advised before emergence of the anaesthesia, especially in patients with known pulmonary impairment due to HPS.

Using ultrasound visualisation of correct wire localisation within the blood vessel for placement of central venous line in V. jugularis interna / externa or V. subclavia is strictly recommended to avoid vascular damage (e.g., dissection) accidental pneumothorax or lung injury with respect to widespread pulmonary impairment in these patients.

Adequate prophylaxis of post-operative nausea and vomiting is recommended as usual.

Intra-operative patient positioning should focus on optimal padding of the patient to avoid easy bruising in patients with known bleeding tendency.

Necessary additional pre-operative testing (beside standard care)

As usual, the clinical condition and (pulmonary) status of patients with HPS is most important pre-operative (i.e., exercise intolerance via walking test for 6 minutes or other exercise testing). A chest X-ray may reveal extensive bilateral interstitial disease in patients with pulmonary involvement. Computed tomography can be performed when X-ray results remain unclear [1,6,17]. Spirometry may quantify the current degree of pulmonary impairment.

Moreover, thorough anamnesis should focus on bleeding and haematological complications. Evaluating platelet count and coagulation parameters may be performed pre-operatively. Nevertheless, one should be aware that despite affected platelets in HPS this is a qualitative platelet dysfunction and that the total number of platelets as well as routine haematology tests (i.e., prothrombin time, activated partial thromboplastin time, von Willebrand factor) are usually within normal ranges [6,7,17]. There are numerous reports of a typically prolonged bleeding time, an impaired secondary platelet aggregation and a reduction in platelet nucleotides

associated with an increased ATP/ADP ratio [19,21,27]. Highly specialised laboratory tests with screening platelet aggregation and ATP secretion in response to various platelet stimulatory agents is probably not everywhere available [13]. However, an abnormal platelet aggregation is neither pathognomonic for HPS, nor is the finding of a normal aggregation a definite proof of its absence [23]. Whenever practical and possible, it is recommended to perform most surgical procedures in a hospital with 24 hours of post-operative haematologic and coagulation monitoring [23].

With respect to minimise intra-operative fluid requirement in cases of pulmonary impairment and as a prophylaxis against bleeding, there are reports of preventive platelet administration and / or peri-operative intravenous infusion of desmopressin (DDAVP), whereby the clinical response to DDAVP can be variable [7,14,17,18,20,21,27]. Moreover, there is one case report about the successful use of tranexamic acid as well as recombinant activated factor VII (rFVIIa) to prevent bleeding in a patient with HPS [5].

Like other patients with lung diseases, patients with pulmonary fibrosis due to HPS should be provided with influenza immunisation and pneumococcal vaccination, in the absence of contraindications [6,23].

Particular preparation for airway management

As far as known, there are no anatomic peculiarities due to HPS itself. Nevertheless, a standardised approach for airway examination and detection of airway challenges is recommended. A thorough preparation for airway management should be based on the examination results.

However, mask ventilation may be difficult due to the patient's decreased pulmonary compliance [14]. Due to typically low pulmonary reserves in patients with HPS, one should be aware of a high risk of rapid desaturation in case of complications in airway management [14].

HPS may also affect the gastrointestinal tract by a granulomatous colitis with inflammatory bowel disease [6,9]. In case of associated gastrointestinal reflux, a rapid sequence induction may be considered. Due to the above mentioned pulmonary morbidities, a modified RSI approach might be better than a classic RSI approach.

Particular preparation for transfusion or administration of blood products

Due to a disease-associated bleeding tendency, prematching of RBCs is advised for patients with HPS. Inform your local transfusion specialist in advance for storage of sufficient numbers of blood products, especially platelets. Depending on the type of surgery, acute bleeding may occur and an aggressive haemostatic therapy is advisable i.e. with platelet transfusion, prothrombin complex concentrate, desmopressin or tranexamic acid [7]. Furthermore, cell saving strategies might be advisable.

There is a lack of data without any general recommendation in the management for bleeding in patients with HPS and individualised therapeutic plans for management of potential peri-operative bleeding are appropriate for affected patients [7]. With respect to a perspective transplantation a restrictive transfusion approach may help to avoid alloimmunisation. For the same reason, only HLA-matched leucodepleted platelet concentrates should be used whenever possible, although random platelets may be needed in a critical emergency [7,29].

Particular preparation for anticoagulation

Prophylactic or therapeutic anticoagulation should be performed weighing the risks and benefits of possible thromboembolic and bleeding complications. Thorough evaluation of bleeding history helps better than laboratory tests in identifying patients at risk for bleeding. Regarding the functional platelet defect in HPS, a comprehensive haematologic consultation is recommended for assessment of bleeding risk that may be associated with utilising extracorporeal membrane oxygenation (ECMO) in affected patients [7,24].

Particular precautions for positioning, transportation and mobilisation

Be aware of easy bruising in patients with known bleeding tendency during positioning, transport or mobilisation.

Interactions of chronic disease and anaesthesia medications

Not reported.

Anaesthetic procedure

Pre-operative evaluation: see details above.

Premedication: might be performed weighing the benefits and risks in individual patients. Patients with granulomatous colitis may have malabsorption of oral medications – premedication may be given intravenous in these patients [16]. Sedative premedication should be avoided in pulmonary compromised patients.

Patient positioning: no specific recommendations. Thorough padding is helpful to avoid bruises in patients prone to these complications.

IV line: no specific recommendations for peripheral IV line. Using ultrasound visualisation of correct wire localisation within the blood vessel for placement of central venous line in V. jugularis interna / externa or V. subclavia is strictly recommended to avoid accidental pneumothorax or lung injury with respect to widespread pulmonary impairment in these patients.

Invasive blood pressure measurement: facilitates frequent arterial blood gas analysis, especially in case of pulmonary impairment.

(Mechanical) Ventilation: a restrictive pulmonary dysfunction is characteristic in patients with HPS; moreover, ventilation should be performed lung-protective with adequate low tidal volumes to avoid baro- / volutrauma [14,17]. Single-lung ventilation during lung surgery may be challenging due to recurring hypoxaemia with need for intermittent bilateral lung ventilation [16].

Anaesthesia: total intravenous or balanced anaesthesia using volatile anaesthetics can be performed safely. There are no absolute or known relative contraindications for anaesthesia-related drugs just because of the disease HPS. There is no specific risk for malignant hyperthermia.

Local / regional anaesthesia can be performed as described above. With respect to potentially increased bleeding risk, regional anaesthesia should be primarily considered in pulmonary severe impaired patients for reducing the patient's work of breathing [14]. Despite reports of successful performance in patients with HPS, neuraxial (spinal or peridural) anaesthesia should be avoided or only performed with extreme caution in affected patients with positive bleeding anamnesis due to bleeding complications [2,19,21].

Particular or additional monitoring

Extended haemodynamic monitoring may help to optimise intra-operative fluid management, especially if in case of significant blood loss requires differentiated and careful transfusion and fluid administration. Hypervolaemia can be detrimental in patients with severe pulmonary dysfunction [14].

Possible complications

Severe respiratory failure / hypoxaemia.

Life-threatening bleeding complications.

Post-operative care

Post-operative care should focus on respiratory failure due to fibrotic lung disease which may complicate post-operative care [14]. Respiratory function should be monitored in an appropriately extended stay in PACU, IMC or ICU before transfer to the normal ward (or discharge at home) is acceptable.

Furthermore, the development of bleeding and haematoma at the operation site should be concerned closely.

Providing adequate analgesia is an important challenge in the anaesthetic management in patients with HPS because of its value and influence on respiratory function. Analgesic medications such as nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided due to possible bleeding complications [6,14,23,28]. Weighing the risks (thromboembolic events) and benefits (sufficient analgesia) selective COX-2 NSAIDs may be alternatively considered [23]. There are no HPS-specific contraindications for opioid agents [23]. In case of pulmonary impairment, one should be aware of impaired spontaneous breathing and consecutive respiratory acidosis [14].

A thorough dermatologic assessment and aggressive skin and eye protection are essential in the pre-transplant and post-transplant periods, given the increased risk of squamous cell carcinoma of the skin, basal cell carcinoma and melanoma due to hypopigmentation and peri-operative immunosuppressive therapy [6,7,17,23].

Disease-related acute problems and effect on anaesthesia and recovery

Emergency-like situations: life-threatening bleeding complications, recurrent / acute

pneumothorax, acute exacerbations of pulmonary fibrosis up to severe respiratory failure and necessity of veno-venous ECMO (often as a bridging therapy for final lung transplantation) [7,24,26].

Differential diagnostics: i.e. idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), pulmonary fibrosis due to a variety of other causes, Chediak-Higashi syndrome, Griscelli syndrome [6,27].

Ambulatory anaesthesia

We strongly encourage to operate patients with HPS in centres with haematologists / haemostaseologists as well as ICU facilities available 24 hours due to risk for bleeding / respiratory complications in the post-operative setting. Careful follow-up after discharge is also prudent to observe for delayed bleeding [17].

Obstetrical anaesthesia

Patients with HPS are fertile, thus the obstetrical anaesthetist might face women with HPS for labour analgesia. Pulmonary manifestation, frequently in the women's fertile age, may aggravate pregnancy and labour.

Besides, bleeding complications are the main problems during delivery. Despite reports of successful performance in pregnant women with HPS, spinal or peridural anaesthesia should be avoided or only be used with extreme caution in affected patients due to bleeding complications [2,19,21,25,27]. Therefore, anamnesis should focus on former episodes of epistaxis, easy bruising, gastrointestinal bleeding, prolonged bleeding during menstruation or tooth extraction as well as prolonged post-operative bleeding or even post-partum haemorrhage [2,4]. The mode of delivery must be decided individually [27]. Many authors recommend a vaginal birth in the aim to minimise bleeding complications [2]. Nevertheless, even in vaginal delivery bleeding may complicate post-partum period and moreover, there is a report of uneventful caesarean section in a woman with HPS receiving i.a. preventive platelets [19]. Referring to these issues, decision making and preventive administration of i.e., tranexamic acid, DDAVP or platelet transfusion may be facilitated with consideration of haematologists / haemostaseologists, especially in view of frequently normal test results for i.e. platelet count, prothrombin time and partial thromboplastin time in patients with HPS [2,4,25,27,29].

Women with HPS must be considered to be at risk of serious bleeding during labour. Therefore, an early predefined interdisciplinary schedule when peri-operative carrying pregnant women with HPS is recommended to act safe and preconceived, especially in emergency situations.

In summary, pregnant women with HPS should be supervised in specialised centres following a multidisciplinary approach. A well-considered peri-partum decision-making and management is indispensable in the setting of rare HPS. A multidisciplinary team including obstetricians and anaesthesiologists together with haematologists / haemostaseologists should discuss an individual patient-specific approach for an optimal and maximum safe peri-partum management [2].

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Please note that this recommendation has not been reviewed by an anaesthesiologist and a disease expert but by two specialists instead.
