MUCOPOLYSACCHARIDOSES (MPS)

Surgical Specialty:	Cardiac, Dental, General Surgery, Orthopedics, Otolaryngology, Neurology
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Background:

- General Considerations
  - The mucopolysaccharidoses (MPSs) are a group of rare genetic disorders of extracellular matrix catabolism. They are caused by a deficiency in the enzymatic activity required to break down glycosaminoglycan (GAG), leading to a build-up of GAG throughout the body. This leads to cellular damage and eventual multisystem organ failure and reduced life expectancy.[1-7]
  - There are seven major types of MPS categorized based on the specific enzyme deficit, with MPS I (Hurler syndrome) being the most severe.[1-7]
  - Due to the multisystemic manifestations of the syndrome, patients with MPS frequently require diagnostic and surgical interventions.
  - Anesthesia for patients with MPS is associated with high morbidity and mortality.

Table 1. MPS Classification

Type	Eponym	Main Clinical Features	Airway Manifestations	Anesthetic Risk
MPS IH	Hurler	Coarse facies, severe intellectual disability, hydrocephalus, joint stiffness, cardiac valve disease, corneal clouding	Macroglossia, obstructive sleep apnea, atlantoaxial instability, recurrent URIs, difficult airway that worsens with age	Very High
MPS IS	Scheie	Stiff joints, aortic valve disease, normal stature, normal intelligence, least severe, often diagnosed in adulthood.	Macroglossia	Mildly High
MPS I H/S	Hurler-Scheie	Intermediate phenotype, macrocephaly, mild cognitive impairment	Macroglossia, joint limitations	High
MPS II	Hunter	Severe course: similar to MPS IH. Milder course: manifests later with survival into adulthood with or without intellectual disability.	Adenotonsillar hypertrophy, difficult airway that worsens with age	High
MPS III A	Sanfilippo A	Behavioral problems, aggression	Adenotonsillar hypertrophy, may have difficult airway that worsens with age, but low risk.	Generally not increased
MPS III B	Sanfilippo B	Progressive dementia, seizures, living into the second or third decade		
MPS III C	Sanfilippo C	Interfamilial variability, mild dysmorphism		
MPS III D	Sanfilippo D	Rough hair, clear corneas, typically normal height		

MPS IV A	Morquio A	Short trunk dwarfism, fine corneal opacities, short stature with final height <125 cm, cardiac valve disease, normal intelligence, skeletal dysplasia	Atlantoaxial instability, adenotonsillar hypertrophy, otitis media	Very High
MPS IV B	Morquio B	Same as MPS IV A, but with final height > 125 cm		
MPS VI	Maroteaux-Lamy	Hurler phenotype with marked corneal clouding, normal intelligence, variable phenotypic expression, spinal cord compression from GAGs, progressive cardiac valve disease	Adenotonsillar hypertrophy, otitis media, progressive diffuse airway narrowing	High
MPS VII	Sly	Highly variable, macrocephaly, cardiac valve disease, short stature, possible odontoid hypoplasia	Unstable cervical spine, otitis media, adenotonsillar hypertrophy	High
MPS IX	Natowicz	Short stature, periarticular soft tissue masses, normal intelligence, painful joint swelling	N/A	Generally not increased

Table put together using information from references 1-4.

- Patient Considerations
  - Disease Specific Considerations
    - With the exception of MPS II (Hunter Syndrome), the MPSs have an autosomal recessive inheritance pattern and affect both males and females equally.
      - MPS II is an X-linked recessive disorder and therefore predominantly affects males.
    - Patients with MPS may initially show normal development, with abnormalities appearing in infancy or early childhood. The more severe forms of MPS (Hurler and Hunter) typically present in infancy, while the less severe forms may present later in life. Consequently, many procedures are performed prior to diagnosis[1,5], with 44% of MPS I patients having undergone at least two surgeries by four years of age.[6]
    - Operative risk is higher with MPS types I, II, IV, and VI, with an overall mortality rate of 20%.[2] As a general rule, MPS I presents the greatest anesthetic difficulty and has been described as "the worst airway problem in pediatric anesthesia".[2,3]
    - Intubation difficulty typically worsens with age due to increased accumulation of GAGs.[1-4,7]
    - Treatment for MPS is dependent on the specific enzyme deficiency.
      - Hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) are the preferred treatments for select MPS types, with earlier initiation showing improvement and/or stabilization of disease.[1,5-7]
      - The incidence of difficult intubation has been shown to be reduced in patients with MPS who receive HSCT.[1,4,5,7]
      - ERT is given as infusions throughout the entirety of the patient's life. ERT does not cross the blood-brain barrier and therefore does not demonstrate any neurocognitive benefit.[4,5]
    - Patients with MPS IV (Morquio's syndrome) have hypoplasia of the odontoid peg, causing them to be particularly high risk for spinal cord compression due to atlantoaxial subluxation.[2-4]

- Patients with Sanfilippo syndrome typically do not have severe anomalies or systemic involvement, with the exception of psychological and central nervous system disease.
- Not all MPS patients represent the same anesthetic risk. Therefore, the anesthetic plan must be tailored on a case-by-case basis.

- Associated Comorbidities/Syndromes
  - MPSs with the same mutations may not present with the same phenotypes due to differing amounts of residual enzyme activity. MPSs have a wide variety of physical manifestations, which often leads to a delay in the diagnosis.
  - The most commonly seen clinical features that are relevant to the anesthesia provider include:
    - Cardiac:
      - Cardiac valve disease, cardiomyopathy, bundle branch block, atrioventricular block, pulmonary hypertension, early-onset coronary artery disease due to intra-arterial GAG deposition
    - Pulmonary:
      - Restrictive pulmonary disease, central and obstructive sleep apnea, airway edema with recurrent infections, reactive airway disease
    - Airway:
      - Coarse facial features, prominent mandible, macroglossia, restricted jaw movement, narrow nasal passages, irregularly-shaped teeth, short neck with or without atlantoaxial instability, cervical spine stenosis, hypertrophic tonsils and adenoids, tracheal distortion, tracheomalacia, thickened copious secretions
    - Neurologic:
      - Developmental delay, mental retardation, epilepsy, increased intracranial pressure
    - Musculoskeletal:
      - Kyphoscoliosis, thoracic deformity, odontoid hypoplasia, joint stiffness, and contracture
    - General:
      - Inguinal/umbilical hernia, hepatosplenomegaly, glaucoma, sensorineural deafness [1-4,6,7]
  - The most common surgeries for MPS patients include:
    - Myringotomies, tracheostomy, adenotonsillectomy, nasal and sinus surgery
    - Corneal transplant, other eye interventions
    - Cardiac valve replacement/reconstruction, coronary artery bypass
    - Hernia repair, feeding tubes
    - Hydrocele repair, circumcision, and other urological procedures
    - Tendon release, carpal tunnel release, spinal decompression, scoliosis repair, correction of limb deformity, joint surgeries, including repair of hip dislocation
    - Hickman/Port placement for ERT and HSCT
    - Ventriculoperitoneal shunt placement
    - Dental rehabilitation[6]

Anesthetic Planning:

- Pre-Anesthetic Evaluation
    - Conduct a thorough preoperative evaluation and assessment
        - Particularly for cardiac disease, pulmonary disease, airway, and spine
    - Unless the case is emergent, an evaluation of the institution's facilities, resources, and available expertise is essential before assuming care.
    - Due to the variety of comorbidities that patients with MPS may have, there must be a multidisciplinary approach to the pre-anesthetic evaluation.
    - It should be noted that secondary to variable progression of disease (worsening of airway exam, and cervical spinal cord compression), regardless of recent anesthetic/surgical procedure, reevaluation is always necessary.
        - A thorough ear, nose, and throat assessment should occur, including the Mallampati score, head and neck range of motion, evaluation of tonsillar hypertrophy, nasopharyngeal obstruction, and supraglottic narrowing.
            - A pre-operative computed tomography scan (CT) is an excellent way to assess the trachea for possible tracheal abnormalities.[1-4]
        - Polysomnography to detect obstructive sleep apnea can assist with decision-making concerning the need for post-operative monitoring and ICU admission, as well as the likelihood of chronic hypoxemia and its consequences (e.g., pulmonary hypertension, right heart strain).[1-4]
        - Pulmonary function tests should be assessed, as there is a possibility of restrictive lung disease.[1-3]
        - Cervical spine x-rays/MRI with flexion and extension to assess for potential atlantoaxial instability.
        - A complete cardiac evaluation, including electrocardiography and echocardiography, is mandatory prior to surgery.
            - In some select patients, coronary angiography and cardiac stress test may be required to assess for coronary artery disease.[1-4]
            - Normal coronary angiography cannot rule out diffuse coronary disease. Sudden death in or outside the operating room remains a possibility.
        - CBC, electrolytes, liver function tests, and arterial blood gas should be assessed.[1-3,7]
    - Discussions to have with surgeon/family
        - Code Status
        - ECMO Candidate
        - Possible need for emergent surgical airway
        - In most severe cases, a discussion with family about possible fatal outcomes is essential.
- Specific or Unique Room Set-up Requirements
    - Airway
        - Anesthesia providers have reported a high incidence of difficult intubation (25%) and failed intubation (8%) in patients with MPS.[3]
            - Therefore, it is recommended that the first-line approach to intubation should be with indirect techniques performed by an experienced provider, including video laryngoscopy and fiberoptic bronchoscopy (FOB).

- Supraglottic airways (SGA) have also been used successfully in MPS patients.
- A combination of techniques can be utilized and may increase the chance of success.
    - To manage macroglossia, providers have intubated using video laryngoscopy and FOB together to move the tongue and improve the provider's view.
    - Intubation using FOB with a SGA as a conduit has also successfully ensured that the patient's tongue does not obstruct the provider's view.
- MPS patients often require the use of oral-pharyngeal airways and two-hand mask ventilation, as many are difficult, if not impossible, to ventilate.
- Ultimately, an adequate array of intubating tools should be at the provider's immediate disposal to ensure first-pass success, and there should be operating room staff and other anesthesiologists present should the need for help arise.[1-4,6,7]

- Nasal intubation is known to be difficult due to narrowed nasal passages and GAG infiltration of the adenoid tissue, which is often found in patients with MPS.
- The size of the endotracheal tube used is typically smaller than the size that would be predicted for the patient's age.
- Manual in-line stabilization may be necessary for those patients with known or suspected cervical spine instability.

- Drugs/Infusions
    - If premedication is needed, and the patient does not have an IV, intranasal dexmedetomidine can be given to ensure the continuation of spontaneous respiration.
    - Ketamine (2-3 mg/kg IV) should be considered for the induction of anesthesia to ensure that the patient remains breathing spontaneously until the airway can be secured, keeping in mind that secretions will increase.
    - Apneic doses of narcotics should be avoided before tracheal intubation. The same goes for paralytics, as there is a significant incidence of difficult mask ventilation.
    - Nasal decongestants (e.g., oxymetazolone spray) and anticholinergics can be administered preoperatively to reduce excessive mucus production and oral secretions.
    - High-dose dexamethasone (0.5 mg/kg IV, max of 20 mg) can be given to reduce laryngeal and subglottic edema.
- Monitors
    - Standard ASA monitors
    - An arterial line may be needed for those MPS patients who have known cardiac disease in order to more closely monitor intraoperative hemodynamic changes.
- Blood Availability (if indicated)
    - This is dependent on the type of surgery being performed, expected blood loss, and starting hemoglobin levels.
- PICU Bed Availability (if indicated)

        - Post-anesthetic ICU stay is often necessary for patients with MPS due to the increased risk of respiratory failure, hypoventilation, atelectasis, and pneumonia.[2]
    - Other Indicated Resources
        - Depending on the severity of the patient's airway exam, it may be necessary for ENT to be on standby in case need for an emergent surgical airway arises.
        - Tracheostomy may also be technically difficult due to GAG infiltration of neck tissues, leading to distortion and laxity of the trachea.[1,4]

Intraoperative Considerations:

- General
    - Narcotic premedication should be avoided.
    - If a benzodiazepine is administered, the patient should be monitored with pulse oximetry in the pre-operative area and on the way to the operating room.
    - At the time of intubation, a second or ideally a third anesthesiologist should be present. Ensure that other operating room staff are available to assist should the need arise.
    - With regard to spinal/epidural anesthesia, there have been several documented cases of spinal cord infarction after combined general and neuraxial anesthesia.
        - It was postulated that this was likely due to spinal cord compression or hypoperfusion.[1,4] These cases were reported to WakeUp Safe, resulting in a recommendation to avoid neuraxial anesthesia in patients with MPS.
    - Regional anesthesia can be used as an adjunct to decrease the amount of narcotics administered, but may be technically difficult secondary to the accumulation of GAGs in the tissues.
- Induction
    - The maintenance of spontaneous ventilation is the goal of induction of MPS patients prior to securing the airway.[1-3,7]
    - If no IV is in place, high-concentration volatile anesthetic with oxygen is commonly used, but a pre-induction IV is highly desirable.
- Positioning
    - Prior to intubation, placing the patient in a position of comfort is ideal, if possible (e.g., the child's favorite sleeping position).[1,3]
    - After intubation, ensure that the cervical spine is stabilized, particularly if the patient has known cervical spine instability.
    - Careful positioning of kyphotic patients is paramount to avoiding spinal cord compression or injury.[1,2,4]
- Maintenance
    - Standard maintenance drugs/volatile anesthetics can be utilized, depending on the type of surgery being performed and overall post-operative goals.
- Hemodynamic/Physiologic goals
    - Maintain spontaneous ventilation prior to successful intubation
    - Keep the patient well-hydrated to prevent the thickening of secretions.
    - In patients with known kyphoscoliosis, mean arterial pressure should be maintained within a normal range to ensure spinal cord perfusion.
- Surgical Considerations
    - If the patient has known/suspected cervical spine instability, it is recommended that somatosensory evoked potentials be monitored to assess spinal cord integrity during and after intubation and positioning.[1,2,4]

    - If muscle relaxation is required, administer paralytic only after securing the airway.
- Emergence/Disposition
    - Patients should be extubated when fully awake after a leak test has been performed to avoid emergent re-intubation or tracheostomy.
    - Transfer to the ICU should be initiated if the patient does not meet extubation criteria.
        - Even patients with MPS who have been extubated safely often require admission to the ICU for closer post-operative monitoring and aggressive pulmonary toilet.
- Post-operative Care
    - MPS patients should be monitored closely for post-operative airway complications, including apnea, bronchospasm, and respiratory failure.
        - Heliox may be considered for severe airway obstruction.[2]
    - CPAP/BiPAP may be necessary to ensure proper ventilation post-operatively.
    - Chest physiotherapy is often required to prevent infectious respiratory complications.

Case-Specific Complications/Pitfalls

- Failed intubation or extubation
    - MPS patients may be difficult to intubate regardless of the equipment available to the provider.
    - Failed intubations may be salvaged by using a laryngeal mask airway.[2,3,7]
    - Remote and out-of-OR anesthesia for patients with MPS is associated with a more than 5-fold increased odds of complications, namely airway/respiratory complications.[7]
    - Strongly consider inducing and extubating in a familiar and controlled area with appropriate assistance and equipment, like the operating room suite.
- Dangerous neck manipulation
    - All MPS patients with atlantoaxial instability and cervical spine stenosis need to be assessed and managed carefully.

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