

Review

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Review

Updates in Advances in Therapeutic Options for Pulmonary and Sleep Disorders in Mucopolysaccharidosis (MPS) Patients: A Narrative Review

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Abstract

Mucopolysaccharidosis (MPS) are a group of inherited lysosomal storage genetic disorders that affect the body's ability to break down glycosaminoglycans (GAGs) due to the deficiency of required enzymes. This leads to depositions of these GAGs in various tissues and organs resulting in multi-systemic manifestations including pulmonary and sleep related issues. In recent years, there have been significant advancements in therapeutic options and supportive management which has led to overall improvement in respiratory care culminating in improved quality of life for MPS patients. Management of pulmonary and sleep disorders in mucopolysaccharidosis requires a multidisciplinary approach due to the multi-systemic affection of the genetic disorders. Therapeutic options such as enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) have yielded varying success in mitigating respiratory complications. Emerging treatments such as gene therapies have shown exciting and promising results thus far. Supportive therapies such as airway clearance, regular vaccination and use of positive airway pressure devices are also essential. Pre-operative airway and anesthesia planning is critical to mitigate peri-operative and post-operative complications. Early diagnosis, close monitoring and a patient focused individualized approach are essential for respiratory optimization and overall improvement in clinical outcomes. This review article aims to discuss these advancements in a comprehensive format, making it accessible to medical providers who care for this subset of patients.

Keywords: mucopolysaccharidosis; pulmonary disorders; sleep disorders; advances in treatment

1. Introduction

Mucopolysaccharidosis (MPS) also known as lysosomal storage diseases (LSD) characterized by accumulation of GAGs in tissues and organs due caused by genetic disorders leading to deficiency in enzymes required for their degradation^{1,2}. GAGs are long chains of polysaccharides found in cells and tissues which are required in cellular functional processes such as cellular signaling and adhesion¹. Deposition of these GAGs in the lysosomes of cells is the primary cause of MPS resulting in multi-systemic manifestations including respiratory, airway and sleep related disorders³.

MPS were first described in 1917 by Charles Hunter when he observed the clinical manifestation of the disease in two brothers which was eventually recognized as MPS II (Hunter syndrome)⁴. In 1917, Gertrud Hurler, a German pediatrician described similar condition in another patient, now recognized as MPS I (Hurler syndrome). The biochemical basis of the disease was not hypothesized until the middle of the 20th century. Identification of GAGs in the urine and tissues of MPS patients helped in the pathogenesis of the disease^{1,5-8}. Subsequent studies on the quantity and types of GAGs accumulation helped with accurate classification of the disease types. Pierre Maroteaux and Maurice

Lamy made the first clinical description of MPS VI (Maroteaux-Lamy syndrome)⁹. MPS IX also known as Natowicz disease, was first noted in 1996¹⁰.

The several types of MPS are associated with peculiar enzyme deficiency and resultant characteristic symptoms (See Table 1).

This accumulation manifests as a spectrum of clinical features, including skeletal dysplasia, cardiac involvement, and neurological impairment, with pulmonary and sleep disorders emerging as critical complications that significantly impact morbidity and mortality. In MPS, GAG deposition in airway tissues, chest wall, and lungs results in upper and lower airway obstruction, restrictive pulmonary disease, and obstructive sleep apnea (OSA), often presenting early in life and exacerbating with disease progression. These multi-systemic issues are complicated by structural abnormalities like macroglossia, adenotonsillar hypertrophy, and chest wall deformities, which impair ventilation and sleep quality, ultimately affecting overall survival and health-related quality of life.

2. Methods

2.1. Search Strategy

A systematic search of major medical databases (PubMed, Embase, Cochrane Library) was conducted for articles published between January 1960 and October 2025 to identify studies, and review papers on diagnosis and management of pulmonary and sleep disorders in MPS disease. Keywords (e.g., ‘mucopolysaccharidosis’, ‘pulmonary disorders’, ‘sleep disorders’, ‘advances in treatment’) were combined using Boolean operators. Titles and abstracts were screened, followed by full-text review to ensure focus on therapeutic options for pulmonary and sleep disorders in MPS disease.

Initial database searching identified 400 records. After duplicate removal and relevance-based filtering, 200 records were screened against eligibility criteria. Of these, 100 papers were excluded, resulting in 100 papers being included in the final synthesis.

- Eligibility criteria included:
- MPS Focus:** Does the paper specifically address mucopolysaccharidosis
 - Pulmonary or Sleep Content:** Does the paper discuss pulmonary, airway, or sleep disorders in MPS?
 - Management Discussion:** Does the paper cover management, treatment, or interventions for pulmonary or sleep disorders in MPS?
 - Clinical Relevance:** Is the content clinically relevant (e.g., case studies, trials, reviews)
 - Outcome Reporting:** Does the paper report outcomes or efficacy of management strategies?
 - Review Type:** Is the paper a review, guideline, or consensus statement?

Table 1. MPS types and enzyme deficiency.

MPS type	Syndrome name	Enzyme deficiency	OMIM
1 (H, HS, S)	Hurler, Hurler-Scheie, Scheie	Dermatan sulphate, Heparan sulphate	607014, 607015, 607016
II	Hunter	Dermatan sulphate, Heparan sulphate	309900
III (A,B,C,D)	Sanfilippo	Heparan sulphate	252900, 252920, 252930, 252940
IVa	Morquio	Keratan Sulphate, Chondroitin sulphate	253000
VI	Maroteaux-Lamy	Dermatan sulphate, Chondroitin sulphate	253200
VII	Sly	Dermatan sulphate, Heparan sulphate, Chondroitin sulphate	253220

IX	Natowicz	Hyaluronidase	601492
X	MPS10	Mutation in gene ARSK	619698
MPS Plus Syndrome	MPSPS	Mutation in the VPS33A gene	617303

2.2. Relevant Section

Physiology of pulmonary and sleep complications in MPS

Sleep and pulmonary involvement are usually progressive and have varying manifestation depending on the specific type of MPS. The various mechanisms (see Figure 1) in which MPS causes sleep disordered breathing and pulmonary issues include:

Tracheal collapse and airway obstruction:

Pulmonary involvement in MPS is characterized by upper airway obstruction due to GAG deposition causing adenotonsillar hypertrophy, macroglossia, and tracheal narrowing. Functional and structural changes occur in the upper and lower airway due to deposition of GAGs¹¹⁻¹⁴. These results in tonsillar and adenoidal enlargement, macroglossia and tracheobronchomalacia. Resultant oropharyngeal, supraglottic airway collapse and tracheal changes (tracheal stenosis and tortuosity) can also lead to airway obstruction and collapse respectively¹⁵⁻¹⁹. In MPS I and II, these features manifest early, with neonatal respiratory distress in 32% of MPS II cases²⁰ and progressive multilevel obstruction in MPS II contributing to mortality via tracheal collapse. In adults, airway tortuosity and narrowing persist, quantified by the Salford MPS Airway Score correlating poorly with BMI¹⁶

Sleep disordered breathing (SDB)

Physiologic changes that occur during sleep lead to pharyngeal muscular relaxation leading to worsening airway obstruction. This causes obstructive sleep apnea, sleep hypoxemia and hypoventilation. Untreated significant SDB may lead to neuro-cardiac complications such as strokes, hypertension, coronary artery disease and pulmonary hypertension. SDB is highly prevalent in MPS patients with some studies reporting about 80%^{2,13,21,22}.The MPS types most affected include I and II^{11,22-24}. Pretreatment rates of OSA in a particular study was 81% with a mean apnea-hypopnea index (AHI) of 10.4 events/hour overall, escalating to 16.6 in MPS I where 75% experienced moderate-to-severe disease²⁵. Almost all MPS patients have adenotonsillar hypertrophy but the cause of OSA is usually multifactorial. Other causes of sleep disordered breathing include GAG deposition in upper airway, crowded retroglossal and retropalatal spaces, small chest wall, macroglossia and short neck^{26,27}.

Restrictive Lung Disease

Pulmonary involvement in MPS is characterized by restrictive lung disease from skeletal deformities and reduced chest wall compliance, leading to recurrent infections and impaired gas exchange. Restrictive patterns predominate, with reduced forced vital capacity linked to thoracic kyphosis in MPS I²⁸. Hurler Chest wall restriction caused by kyphoscoliosis, broad spatulate ribs with reduced intercostal space, pectus carinatum, spinal disorders are common in MPS patients. There can be complicated with ventilatory failure due to reduced lung volumes. Abdominal enlargement due to hepatosplenomegaly can cause diaphragmatic dysfunction due to compressive effects^{2,14,23,29}.

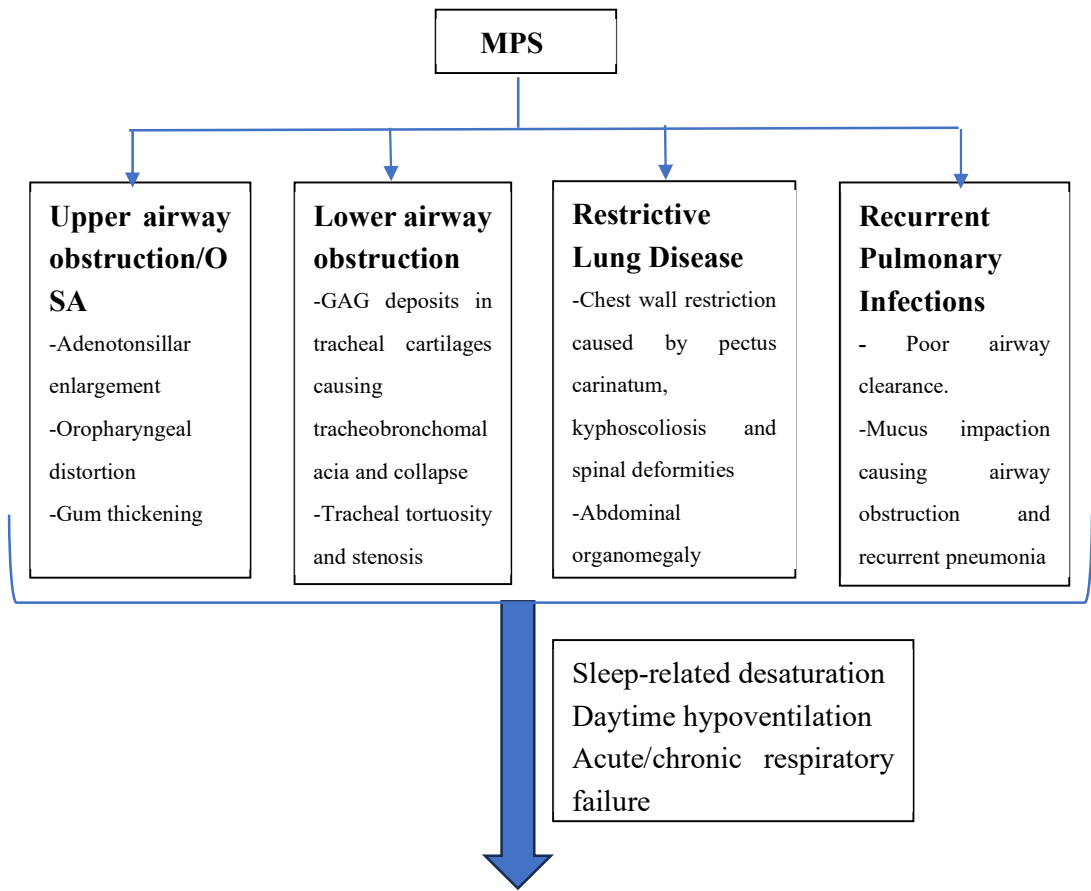


Figure 1. Pathophysiology of respiratory and sleep disorders in MPS.

2.3. Disease-Targeting Therapies

Enzyme replacement therapy (ERT): ERT can be an effective therapeutic option in MPS types 1, II, IVA, VI and VII^{30–34} (See table 2). It involves intermittent administration of intravenous recumbent enzymes to address the deficiency of lysosomal enzymes in these patients^{32,33,35}. This aims to reduce the GAG burden and accumulation in the tissues of the respiratory tract. ERT has shown varying levels of benefits in pulmonary function, sleep disordered breathing and airway obstruction^{31,34,36,37}. ERT can cause patients to develop anti-drug antibodies (ADA) in response to treatment. Some of these ADAs can be inhibitory and negatively affect the overall efficacy of ERT²⁵. A study showed that ERT improved obstructive sleep apnea in MPS patients with low levels of inhibitory antibodies²⁵. Another study showed no positive effect of ERT on OSA in MPS II³⁸. The effect of ERT on reducing adenotonsillar enlargement was negligible^{38–40}. Overall, there is a paucity of data available on the long-term effect of ERT on OSA in MPS patients.

Spirometry evaluations in MPS usually involve measurements of forced expiratory volume in 1s (FEV1) and forced vital capacity (FVC) in clinical and research settings^{23,24,41,42}. The 6 min-walk test (6MWT) is the most common respiratory parameter used to evaluate endurance in MPS patients^{7,31,32,43,44}. ERT also has varied and limited success in improving lung volumes, usually reaching a plateau within 2 years of starting therapy^{45,46}. Several studies have shown short term improvement in endurance after ERT, but long-term effects are limited^{30,31,34,39,47,48}. ERT with laronidase (100 U/kg weekly) improves pulmonary function in MPS I, increasing forced vital capacity by 11% and 6-minute walk distance by 38 meters over 26 weeks, alongside urinary GAG reductions from 63.4 mg/mmol creatinine baseline to 16.3 mg/mmol at 24 months⁴⁹.

In MPS 1 and IVA, ERT has shown some improvements in these measures up to 5%, usually limited to the first year of treatment⁵⁰. In other MPS types, there was no clinically significant

improvement^{31,51}. In prospective, longitudinal studies, the FVC and FEV1 overall changes in the long term were limited to less than 20%^{35,38,47,52}. Galsulfase ERT has been recommended as the first line treatment therapy for MPS VI for over 20 years. In a recent 15 year-analytic clinical surveillance program for MPS VI, ERT-treated patients demonstrated persistent decrease in urinary GAG levels with associated improvements in pulmonary function and endurance over a prolonged follow-up timeframe⁵³. Harmatz and colleagues demonstrated a sustained improvement in walking distance for an extended period in an open-label extension study in MPS VI patients³¹. In MPS II, idursulfase ERT showed limited improvement in pulmonary function, with function tests unhelpful due to disabilities, though growth dynamics indicate anabolic effects in <50% mild cases⁵⁴. Respiratory dysfunction in MPS is usually multi-factorial: GAG accumulation in the soft tissues of the pharyngeal and upper airway with resultant obstruction; tracheobronchomalacia and stenosis causing lower airway narrowing and collapse respectively; and restrictive thoracic disorders due to chest wall, rib and spinal deformities. Since the major principle for the therapeutic efficacy of ERT is based on the reduction in GAG deposition, therefore it appears to be relatively more effective on soft tissues and upper airway obstruction^{12,13,16,23,27}. Conventional ERT is largely ineffective in treating skeletal and cartilage abnormalities related to MPS due to poor circulation in these tissues which makes it less effective in chest wall and tracheal deformities. Additionally, structural changes in cartilages and bony structures are usually less reversible^{12,19,33,38,47,55}. Pre-clinical studies showed that using a long-circulating form of enzymes (Pert-GUS) significantly improved bone lesions due to enhanced circulation⁵⁶. Similarly, due to the inability of ERT to cross the blood-brain barrier (BBB), it is ineffective in treating neurological manifestations due to MPS. A recent therapy for MPS II - Hunter syndrome (Pabinafusp Alfa) using fusion of transferrin receptor antibody with idursulfase enzyme improves delivery across the BBB therefore improving efficacy for treatment of neurological symptoms⁵⁷.

In summary, these studies show that ERT significantly improves lung function with endurance, reduces AHI, and improves sleep quality. Early initiation of ERT is crucial, as it is most effective at reducing GAG storage in soft tissues and stabilizing pulmonary and sleep disorders before irreversible anatomical damage occurs.

Hematopoietic Stem Cell Transplantation (HSCT): HSCT is a proven long-term treatment for certain MPS types including MPS 1, MPS II, MPS IVA, MPS VI and MPS VII^{47,58-62} (See table 2). It involves transplanting matched donor stem cells to provide the deficient enzyme. The efficacy of HSCT is dependent on factors such as patient age, MPS type, donor selection and overall functional status. The age at which HSCT is performed affects the overall efficacy of treatment with outcomes vary by timing, with early HSCT (<2 years) improving survival^{58,60,63}. Several studies have shown that cord blood transplantation usually is more effective and has a relatively lower rate of graft versus host disease (GVHD) compared to traditional bone marrow transplantation (BMT)^{64,65}. The latter option may be more suitable for adult and older MPS patients due to less incidence of GVHD.

Unlike ERT where the infused deficient enzymes are unable to cross the BBB, donor stem cells in HSCT are able to cross the barrier hence providing neurologic improvements.

HSCT has shown promise in the treatment of respiratory and airway issues, especially in young patients with MPS 1. Walker et al revealed a significant reduction in the incidence of airway complications in MPS 1 patients treated with HSCT compared to ERT (14% vs. 57%)⁶⁶. A retrospective study reported no intubation failures in MPS 1 patients previously managed with HSCT⁵⁹. Another study showed improved respiratory outcomes in a small number of MPS 1H patients⁶⁷. These findings suggest that there is clinically significant improvement in airway management, intubation success as well as the overall safety of anesthesia.

Yabe and colleagues reported cessation of orthopnea, snoring and improved respiratory function in four MPS IVA patients after HSCT⁶⁸. Careful selection for MPS IVA patients is necessary as they have severely narrowed airway due to tracheobronchial distortion which leads to difficult intubation, peri-intubation respiratory complications and reduced success of ventilator liberation overall⁶⁹. In the largest non-pharmaceutically supported retrospective study, pediatric MPS 1 who

received either ERT or HSCT, serial spirometric evaluations demonstrated a universal degree of restrictive lung function irrespective of the therapeutic intervention. During the follow up, the level of restrictive lung disease stabilized in 67% of post HSCT and 57% in post ERT in MPS 1 patients⁴¹. There has been varying success in improvement in sleep disordered breathing, airway obstruction and lung function improved lung function in other MPS types.

In summary, early use of HSCT can diminish upper airway obstruction and reduce OSA, but late complications may still require additional treatments such as surgeries.

Gene and Cell Therapy: ERT and HSCT provide replacement enzymes exogenously however neither is fully effective and both have inherent challenges. Gene therapy is an emerging therapeutic option currently undergoing several studies in pre-clinical and clinical stages⁷⁰⁻⁷². Many of these trials have been designated as fast track, orphan drug emphasizing the much-needed therapeutic options for the disease. Each type of MPS is caused by a faulty gene and gene therapy may slow the progression of the disease. These faulty genes affect the production of needed enzymes for the breakdown of GAGs leading to accumulation. Gene and cell therapy involves the introduction of a gene into the cells needed for producing enzymes. The working version of the gene is introduced via a vector which are usually viral derivatives⁷³.

Investigational gene therapies for different MPS types are in various stages of development – RegenXbio (MPS1, MPS II), Orchard therapeutics (MPS III A and B), Magenta therapeutics (MPS1), Lysogene (MPS III A and B) and Abeona Therapeutics (MPS III A and B)⁷².

Gene editing with the help of CRISPR technology is also being researched in various stages of development⁷⁴. Gene editing involves removal and correction of faulty DNA within the gene unlike gene therapy which involves introduction of a new gene. A recent study using delivery of HSPC gene into a patient's own hematopoietic stem cells resulted in significant metabolic correction in peripheral tissues and central nervous system.⁷⁵

Gene therapy and editing hold the promise of sustained supply of the deficient enzymes and may address the limitations of pulmonary and airway involvement that current therapeutic options face.

2.4. Surgical Interventions

Surgical interventions play a fundamental role in managing upper and lower airway obstruction in MPS patients

Adenotonsillectomy (AT): Adenotonsillectomy is the first line treatment for OSA in pediatric MPS patients and about half of this subset of patients undergo the surgery⁷⁶. Few studies have reviewed the efficacy of AT and the outcomes are usually non-lasting likely due to the multifactorial pathogenesis, progressive nature of MPS disease as well as recurrence of adenoid hypertrophy. The recurrence rate of adenoid hypertrophy has been reported to be up to 56% versus 1.9% in healthy counterparts^{77,78}.

Lee et al showed more than 50% reduction in AHI in about a quarter of patients (15 patients)¹⁷.

Tracheostomy: Tracheostomy is a surgical intervention which can be feasible and helpful for isolated upper airway obstruction. Ten percent of MPS patients usually undergo tracheostomy for airway issues⁷⁹. 47% of cases of MPS II were reported to undergo tracheostomy which was the most frequent subtype of MPS⁷⁹. This underscores the fact that this subset of patients is at a higher risk of respiratory failure due to progressive airway obstruction secondary to GAG deposition. Patients may develop lower or multi-level airway obstruction which makes finding the right tracheostomy tube for a patient with MPS very challenging⁷⁹. AT and other surgeries are usually unsuccessful for permanently alleviating airway obstruction^{11,14,15,66}. It may be necessary to undergo tracheostomy when other surgeries have failed. Tracheostomy may be challenging in MPS patients due to peculiar anatomical features such as stiff short neck, low hanging cricoid ring, multi-level tracheal obstruction and large protruding mandible⁷⁹. Airway obstruction may persist despite tracheostomy due to airway collapse distal to the tip of the tube⁸⁰.

Tracheal resection and reconstruction: This is applicable in cases when there are significant narrowing and collapse of a segment of the trachea for which tracheostomy may not be applicable. MPS IVA can have very significant tracheal narrowing, and this procedure can significantly improve pulmonary function and quality of life in this subset of patients.^{6,12,18,58,62,69} Pizarro et al⁸¹ and Hack et al⁸² described tracheal resection via median sternotomy with post operative improvement in patient-reported outcomes and quality of life.

Kent et al evaluated sixteen patients with severe MPS IVA and radiological evidence of advanced airway obstruction who underwent tracheal resection with combined manubrial resection. Post operatively, there were significant spirometric improvements including a mean increase of 0.68 liters in forced expiratory lung volume in 1 second (FEV1)⁸³. There were no reported long-term complications. These findings highlighted the significant improvements in patient-reported outcomes and overall quality of life.

Tracheobronchial stents: The use of airway stents have been established in adult malignant airway disease. Pediatric use of these stents has been sparse but slowly increasing. Airway stent placement is usually performed in the United States by experienced interventional pulmonologists and thoracic surgeons. The reported use of airway stents in MPS patients are sparse with only a handful of cases⁸⁴. Stents are prone to accumulation of biofilms, mucus plugging, granulation formation and migration. Insertion and replacement of these stents are extremely challenging in MPS patients⁸⁴. Stents may be very beneficial with short-term success as a bridge to other permanent solutions such as tracheal resection⁸⁴. They are very feasible for palliative care given the short-term improvement in quality of life.

2.5. Supportive Therapies

Supportive therapies are crucial for optimizing respiratory function, endurance and overall wellbeing in MPS patients.

Prevention of Anesthetic and post-operative complications- As a result of the multi-systemic and complex nature of the disease, MPS patients usually require several procedures and surgical interventions. MPS patients carry the highest reported intra and peri-operative mortality because of airway, pulmonary, cardiac and neurologic issues^{11,47,66,85,86}. MPS I, II, IV have the highest rates of airway complication due to the relatively high prevalence of adenotonsillar hypertrophy, copious thick secretions, macroglossia, facial dysmorphism and airway collapse due to laryngomalacia. The airway mucosa is very friable with easy bleeding. MPS 1 and IV may have unstable atlanto-axial joint, short neck and decreased mobility of the temporo-mandibular joint which makes intubation very difficult with increased complications^{47,85-87}.

A team approach for anesthesia is essential for pre-operative assessment for MPS patients. A pre-operative evaluation with an individualized plan is important to reduce these risks. Patients deemed to be high risk should have a pre-operative evaluation jointly by the anaesthetic, ENT and pulmonary team and risks of the airway intervention should be discussed across the benefits of surgery. A collective multidisciplinary approach is strongly recommended.^{66,86} A thorough evaluation should be done by detailed history and where possible- nasal endoscopy, CT scans and PFTs should be obtained. Airway intervention risks can be based on previous anesthetics and holistic lip-to-lung assessments. Post-operative complications are reduced by staged extubation, optimal use of opiates, early physiotherapy and mucolytics^{66,88}. Patients with a history of difficult intubations should be flagged on electronic medical records for easy identification. Awake flexible fiberoptic airway examination and bronchoscopic intubations may lead to lesser airway injury compared to standard video laryngoscopy^{47,85}. 3D airway reconstruction, virtual endoscopy and the use of the Salford MPS airway score can also help mitigate airway intervention risks.¹⁶

Positive airway pressure devices- There are several therapeutic options for the treatment of OSA and sleep disordered breathing in MPS patients including adenotonsillectomy, ERT, HSCT and tracheostomy. Given the non-invasive approach and the likely sustained efficacy with multi-level upper airway obstruction, CPAP is advantageous compared to the other options^{21,25,27}. Tolerance may

be an issue particularly with MPS patients due to behavioral issues^{23,25,27}. PAP mask tolerance may be affected by facial dysmorphism, large tongue and oropharyngeal changes^{21,23,29}. Using a nasal mask may be better tolerable. Use of bi-level PAP devices may be needed if CPAP is unable to effectively treat nocturnal hypoventilation and desaturation. There is increasing use of 3D- printing to help with customized mask production for this sub-set of patients to improve adherence⁸⁹. Close team working with long term ventilation team and respiratory physiotherapists, pulmonologists and sleep specialists is important to find the right CPAP equipment which fits the MPS patients²¹.

3. Insomnia

Insomnia can lead to increased morbidity and reduced overall wellbeing of MPS patients⁹⁰⁻⁹². It may be related to circadian misalignment due to involvement of the retina and central nervous system. Melatonin has been used to treat sleep disturbance with significant success in MPS patients⁹⁰. It also has a superior side effect profile compared to other sleep aides such as benzodiazepine^{90,92}. Benzodiazepines are better avoided due to underlying complex airway and sleep disordered breathing.⁹³

Secretion Management and Airway Clearance Techniques- Due to excessive and thick lung secretions, airway clearance techniques such as manual chest physiotherapy, chest wall oscillatory percussion devices and mechanical devices may be needed to improve secretion mobilization as well as clearance⁶⁶. The use of nebulized mucolytics is also very helpful⁶⁶. Inhaled corticosteroids, bronchodilators, nasal decongestants may be used to address airway inflammation and associated symptoms such as nasal congestion, postnasal drip, chest congestion and wheezing^{14,47}. Mucolytics such as acetylcysteine, saline and hypertonic saline nebulization, steam inhalation are all other useful methods⁹⁴.

Regular vaccination- Vaccinations against respiratory syncytial virus (RSV), influenza, SARS-COV2 and pneumococcal are essential to reduce the risk of respiratory infections⁹⁵.

Aggressive management of respiratory infection and pneumonia- Timely diagnosis of respiratory infections and aggressive treatment is critical in preventing complications of respiratory failure¹⁴.

Pulmonary rehabilitation- MPS patients with chest wall disease, spinal deformities and neuromuscular weakness should be referred to pulmonary rehab programs to help maximize respiratory muscular strength and functionality⁹⁶.

Spinal Decompression Surgery- All MPS patients undergoing anesthetic intervention should be treated as unstable spine avoiding any hyper extension. MPS IV patients have odontoid dysplasia and hypermobility of the spine⁹⁷. MPS patients with critical spinal cord compression affecting respiratory muscular functionality should be referred for surgical decompression which may help improve pulmonary function⁹⁸.

Table 2. Types of pulmonary manifestations in MPS with management strategies.

Pulmonary Manifestation	Description	MPS types involved	Management Strategies
Upper airway obstruction	Adenotonsillar enlargement, oropharyngeal distortion, leading to sleep disordered breathing. Abnormal teeth protrusion, mouth opening, high Mallampati class affects airway.	MPS 1, II, IVA, VI, VII Minimal involvement in MPS III	Adenotonsillectomy, nasal steroid (more effective in young patients), tracheostomy (in recalcitrant cases), ERT, HSCT
Lower Airway Obstruction	GAG accumulation in tracheal cartilages causing collapse and tracheobronchomalacia. Tracheal stenosis and tortuosity MPS IVA has a peculiarity for severely narrowed airways due to tracheobronchial distortion.	MPS 1, 11, IVA Minimal involvement in MPS III and other subtypes of MPS IV	PAP therapy particularly at night, use of tracheal and bronchial stents in very selected patients, inhaled steroids (airway inflammation), ERT/HSCT (less effective compared to upper airway obstruction), tracheostomy (for severe cases)
Restrictive Lung Disease	Chest wall restriction caused by pectus carinatum, broad spatulate ribs, reduced intercostal space, kyphoscoliosis and spinal deformities. Reduced lung volumes due to abdominal organomegaly. Atelectasis with resultant hypoxemia	MPS IV, VI Minimal involvement in MPS III	Spinal and chest wall surgeries (if applicable), ERT, HSCT (less effective for chest wall disorders compared to upper airway obstruction).
Sleep Disordered Breathing	Obstructive sleep apnea (OSA) and sleep hypoxemia/hypoventilation	MPS I, II	Weight loss, adenotonsillectomy, CPAP or Bilevel PAP devices, supplemental oxygen (may worsen hypoventilation), ERT, HSCT. Tracheostomy (in severe cases)
Recurrent Pulmonary Infection	Poor airway clearance causing upper respiratory infections, bronchitis and pneumonia. Reduced immunity.	All MPS types	Appropriately recommended vaccinations, use of mucolytics and cough assistance devices and maneuvers.

Importance of a Multidisciplinary Approach- The MPS Team

The multi-systemic involvement, complex and progressive nature of the disease requires a dedicated multidisciplinary team including consultants in pulmonology, neurology, general pediatrics, genetics, otolaryngologist and anesthesia (See table 3). An MPS program is needed for collaborative care across specialties to address the individualized needs of MPS patients and to maximize the quality of life and overall long-term health^{99,100}.

This narrative review is subject to several limitations, primarily stemming from the rarity of the disease which results in a reliance on small study populations rather than large prospective randomized controlled trials. The therapeutic landscape, including ERT and HSCT, presents challenges in evaluating long-term efficacy due to the progressive nature of airway obstruction and the potential for treatment benefits to wane over time. Finally, as a narrative review, this does not provide a systematic meta-analysis, making it difficult to firmly establish the impact of new therapies on disease progression.

Table 3. MPS team members and roles.

MPS Team Member	Role in MPS Management
Pulmonologist	Provide respiratory care to MPS patients which may include positive airway pressure devices, airway clearance and cough assist devices, prescription of medications to address airway inflammation and help with secretion mobilization. Assessment and monitoring of lung function.
Otolaryngologist	Addressing complicated airway obstruction, performing adenotonsillectomy for sleep disordered breathing, airway planning prior to surgical interventions, management of recurrent otitis media and hearing issues
Anesthesiologist	Pre- and Peri-operative airway assessment plans and management
Neurologist	Evaluation and management of neurological complications, including and nerve impingement affecting overall mobility and functionality
Orthopedic/Spinal Surgeon	Management of skeletal deformities, chest wall and restrictive thoracic disorders, addressing spinal cord compression to improve functionality
Clinical Geneticist	Diagnosis of MPS type, understanding disease progression and implications for treatment
Cardiologist	Optimizing cardiac health to prevent complications particularly during vulnerable periods such as during anesthesia for surgical interventions

4. Limitations

This review has several limitations. Studies encompass predominant case series and retrospective data which are prone to selection bias, with small samples limiting generalizability; polysomnography metrics vary (e.g., AHI vs. desaturation index), hindering direct comparisons, and few address adult patients. Mechanistic insights are sparse beyond GAG deposition.

5. Conclusions

Therapeutic advances in the management of respiratory and sleep disorders have improved clinical outcomes in MPS diseases. The integration of early-stage ERT, improved HSCT techniques, and early surgical intervention for airway obstruction have significantly altered the disease course allowing patients to live longer and with better quality of life. However, management of advanced airway structural changes remains a critical challenge, requiring a multidisciplinary, long-term approach to minimize mortality and improve quality of life.

6. Gaps and Future Directions

Future clinical studies should conduct prospective, multicenter trials in exact MPS populations (e.g., severe vs. attenuated) using synchronized polysomnography and pulmonary function tests and modalities to quantify long-term intervention effects. Methodological advances like 3D airway imaging could strengthen subtype comparisons, while targeted research in underrepresented adults and low-resource contexts would address access biases.

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List of Abbreviations

MPS – mucopolysaccharidosis
 GAG- Glycosaminoglycans
 ERT – enzyme replacement therapy
 HSCT – hematopoietic stem cell therapy
 OSA- obstructive sleep apnea
 CPAP- continuous positive airway pressure
 PAP- positive airway pressure
 FEV1 – forced vital capacity in first second
 FVC – forced vital capacity
 6 MWT- 6-minute walk test
 BMT- bone marrow transplant
 AT - adenotonsillectomy
 LSD – lysosomal storage disease
 AHI- apnea hypopnea index
 SDB- sleep disordered breathing

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