Inhalation Dornase Alfa – Adult/Pediatric – Inpatient Clinical Practice Guideline

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Executive Summary

Guideline Overview

This document is intended to provided recommendations and guide appropriate therapeutic use of inhaled dornase alfa in cystic fibrosis and other pulmonary disease states which may result in production of viscous pulmonary or sinus secretions.

Key Practice Recommendations

1. Inhalational dornase alfa demonstrates benefit for the symptomatic management of cystic fibrosis in patients 6 years of age and older. (*Class I, Level A*)
2. Inhalational dornase alfa may be a reasonable treatment to improve rhinosinusitis symptoms through vibrating sinonasal inhalation in cystic fibrosis patients. (*Class IIa, Level B*)
3. Inhalational dornase alfa may be considered for the management of pulmonary atelectasis following congenital heart surgery in neonatal and pediatric patients if other standard therapeutic modalities fail. (*Class IIb, Level C*)
4. Once-daily dornase alfa has been shown to be as effective in airway clearance as twice-daily dosing for most cystic fibrosis patients. (*Class I, Level A*)
5. For patients maintained on twice-daily dornase alfa prior to admission, it is reasonable to dose dornase alfa twice daily during the inpatient stay. (*Class IIa, Level C*)
6. Short-term increases in dornase alfa frequency are not recommended. (*Class III, Level C*)
7. A small population of cystic fibrosis patients may benefit from twice-daily dornase alfa administration when administered for a duration of longer than14 days. These patients include those older than 21 years of age or with a baseline FVC greater than 85%. (*Class IIa, Level B*)

Companion Documents

Aerosolized Respiratory Drugs - Adult/ Pediatric - Inpatient/ Ambulatory

Scope

Disease/Conditions:

- Cystic fibrosis (CF)
- Atelectasis
- Oropharyngeal secretions (OPS) with head-and-neck (H&N) cancer
- Asthma
- Idiopathic Bronchiectasis
- Chronic Bronchitis
- Chronic Obstructive Pulmonary Disease (COPD)
- Acute Bronchiolitis

Clinical Specialty/Intended Users:

- Physicians, Advanced Practice Providers, Pharmacists, Respiratory Therapists, Nurses

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Objective:
To maximize dornase alfa use in alignment to evidence-based medical practice or expert opinion when no evidence is available.

Target Population:
- Adult and pediatric patients with cystic fibrosis
- Other pulmonary diseases requiring airway clearance

Interventions and Practices Considered:
This guideline identifies the use of dornase alfa for the clinical management of cystic fibrosis patients and other pulmonary disease requiring airway clearance, including the dosing, timing of administration, device and medication compatibility, and adverse effects.

Major Outcomes Considered:
- Pulmonary Exacerbation Frequency
- Hospitalizations
- Mortality
- Pulmonary Function Tests (FEV_1 and FVC)
- Oxygenation
- Chest Radiograph Scores
- Coughing Frequency
- Subjective Dyspnea Symptoms
- Rhinosinusitis symptoms
- Quality of life measures
- DNA content

Methodology

Methods Used to Collect/Select the Evidence:
A systematic search and review of available evidence through September 2015. Searches were extended to studies, reviews, and other evidence that were conducted in human subjects and accessible via PubMed, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. The search included combinations of the following key terms: dornase, dornase alfa, Pulmozyme, rhDNase, cystic fibrosis, atelectasis, asthma, bronchiectasis, chronic bronchitis, chronic obstructive pulmonary disease (COPD), nebulized. Systematic reviews, randomized control trials, cohort studies, case studies, and expert opinion were evaluated for the development of this guideline.

Methods Used to Assess the Quality and Strength of the Evidence:
A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Appendix 1) was used to assess the quality and strength of the evidence and recommendations.[1]

Recognition of Potential Health Care Disparities: None identified.

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Introduction

Dornase alfa is a solution containing recombinant human deoxyribonuclease. This enzyme is an endonuclease that nonspecifically cleaves DNA in the sputum and mucous thereby decreasing viscosity. Cystic fibrosis (CF) patients have high amounts of DNA in their secretions derived from the disintegration of inflammatory cells.[2] By decreasing the viscosity of the sputum, the sputum clearance is increased, ultimately resulting in improved lung function (PFT scores) and reduced pulmonary exacerbation events.[3] There is a paucity of clinical evidence for dornase use in other non-CF, pulmonary-related indications.

Recommendations

Indications where inhalation of dornase alfa is recommended or is useful

1. **Cystic Fibrosis**. Inhalation with dornase alfa shows benefit for the symptomatic management of CF in patients 6 years of age and older.[4-8] *(Class I, Level A)*
    a. In CF patients with an FVC of 40% or greater, inhalation of dornase alfa can reduce the risk of respiratory tract infections requiring parenteral antibiotics.[4]

Indications where inhalation of dornase alfa may be reasonable

1. **Cystis Fibrosis Rhinosinusitis**. Inhalational dornase alfa may be a reasonable treatment to improve rhinosinusitis symptoms through vibrating sinonasal inhalation in cystic fibrosis patients.[9] *(Class IIa, Level B)*
2. **Pediatric Congenital Heart Surgery Atelectasis**. Inhalational dornase alfa may be considered for the management of pulmonary atelectasis following congenital heart surgery in neonatal and pediatric patients if other standard therapeutic modalities fail for clearance of mucous secretions and improvement of atelectasis scores, pO_2, heart rate, and respiratory rate.[10,11] *(Class IIb, Level C)*
        a. Dornase alfa use in this patient population should be considered only if: (1) atelectasis is unresponsive to 24 to 48 hours of airway clearance techniques (chest physiotherapy, IPV, suctioning, etc.) and (2) there evidence of white blood cells in tracheal Gram stain samples. (*Class IIb, Level C*)
3. **Neuromuscular Disorders**. In patients with neuromuscular disorders which cause neuromuscular weakness (e.g. spinal muscular atrophy, muscular dystropy, congenital or acquired myopathies) requiring airway clearance, the inhalation of dornase alfa may be reasonable.[12,13] *(Class IIb, Level C)*
    a. There were no published clinical trials identified that demonstrate reduced morbidity with use of inhalational dornase alfa in these patient populations.

Indications where use of dornase alfa is not recommended or may be harmful

1. **Atelectasis**. Inhalational dornase alfa is not indicated for atelectasis and is no more effective than normal or hypertonic saline at improving oxygenation or chest radiograph scores.[14,15] *(Class III, Level A)*
2. **Oropharyngeal secretions (OPS) with head-and-neck (H&N) cancer**. Inhalation of dornase alfa is not recommended for decreasing OPS in patients with H&N cancer and is no

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more effective than placebo on quality of life measures, clinical improvement, and DNA content of thick OPS.[16] *(Class III, Level B)*

3. **Asthma.** For refractory asthmatics in the emergency department and patients with stable, persistent asthma, dornase alfa is no more effective than placebo at increasing FEV_1 percent predicted and decreasing subjective dyspnea symptoms or hospitalizations.[17-19] *(Class III, Level A)*
4. **Idiopathic (Non-CF) Bronchiectasis.** Inhalational dornase alfa may be harmful and showed no benefit when compared to placebo for treatment of idiopathic (non-CF) bronchiectasis (more frequent pulmonary exacerbations, greater FEV_1 decline).[12,20,21] *(Class III, Level B)*
5. **Chronic Bronchitis**. Inhalational dornase alfa is not recommended and is no more effective than placebo in reducing mortality.[22] *(Class III, Level B)*
6. **Chronic Obstructive Pulmonary Disease**. Inhalational dornase alfa is not indicated for COPD and has not been shown to reduce mortality.[23] *(Class III, Level B)*
7. **Acute Bronchiolitis**. Inhalational dornase alfa is not recommended for the treatment or management of patients with acute bronchiolitis.[24] *(Class III, Level C)*

Dosing and Administration

1. The FDA-approved inhalational dornase alfa dose is 2.5 mg/2.5 mL inhaled once daily via nebulizer.
   a. Once-daily dornase alfa has been shown to be as effective as twice daily dosing for most cystic fibrosis patients.[4] *(Class I, Level A)*
   b. A small population of CF patients may benefit from twice daily administration when administered for a duration of longer than 14 days and include patients older than 21 years of age or those with a baseline FVC greater than 85%.[4] *(Class IIa, Level B)*
   c. For patients maintained on twice-daily dornase alfa prior to admission, it is reasonable to dose dornase alfa twice daily during the inpatient stay. *(Class IIa, Level C)*
   d. Short-term increases in dornase alfa frequency are not recommended. *(Class III, Level C)*
      1. Dornase alfa accumulates in the sputum, with peak and trough levels increasing over two weeks.[3] Therefore, it is unlikely that a temporary increase in dornase alfa dose to twice daily will provide a significant benefit during the time the patient is hospitalized.

2. Timing
   a. Inhalation of dornase alfa in people with CF can be based on practical reasons or individual preference with no preference for before or after mechanical airway clearance or the time of day.[25] *(Class I, Level A)*

3. Do not mix or dilute dornase alfa with other medications or in the nebulizer.[4] *(Class I, Level C)*

4. Recommended devices with dornase alfa
   a. Nebulizers[4] *(Class I, Level C)*
      - Hudson T Up-draft II® (Pulmo-Aide® compressor)

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- Marquest Acorn II ® (Pulmo-Aide ® compressor)
- PARI LC® Plus (PARI PRONEB® compressor)
- PARI BABY™ (PAR PRONEB® compressor)
- Durable Sidestream® (MOBILAIRE™ compressor)
- Durable Sidestream® (Porta-Neb® compressor)
- eRapid™ Nebulizer System (eRapid™ Nebulizer Handset with eBase™ Controller)

b. Sinus Systems[9] *(Class I, Level C)*
- Pari LC-Sprint StarTM (Pari-Sinus™ compressor)

5. Dornase alfa monitoring for recommended indications[4]
   a. Efficacy (*Class I, Level C)*
      - Improvement in subjective symptoms (coughing frequency, ease of sputum expectoration, improvement in dyspnea)
      - Improvement in pulmonary function tests (FEV_1 and FVC)
   b. Toxicity *(Class I, Level C)*
      - Voice changes, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, fever, dyspepsia, dyspnea

UW Health Implementation

Potential Benefits:

Provide a standardized, evidence-based approach to the use of dornase alfa.

Potential Harms:

Treatment with dornase alfa may result in outcomes listed under *Dornase alfa monitoring for recommended indications* of this guideline related to toxicity of the medication.

Pertinent UW Health Policies and Procedures:

1. Patient Care Policy 2.27: Aerosolized Medication Treatment via Small Volume Nebulizer

Patient Resources

1. Nebulized Dornase Alfa or Pulmozyme
2. Lexicomp Online: Patient Care – Dornase Alfa

Guideline Metrics:

This guideline will be used to measure and assess the clinical and financial improvements resulting from the implementation of this guideline by reviewing the incidence of dornase alfa prescribing for indications with no evidence of benefit and improper escalation of once daily dosing to twice daily dosing.

Implementation Plan/Clinical Tools

1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Clinical pharmacists will be educated about this guideline through pharmacy team meetings.

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3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations (such as the dornase alfa medication record) will be reviewed for consistency and modified as appropriate.

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Appendix 1. Evidence Grading Scheme: Modified Grading of Recommendations Assessment, Development and Evaluation

SIZE OF TREATMENT EFFECT →

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

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References

1. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol.* May 10 2011;57(19):e215-367.
2. Chernick WS, Barbero GJ. Composition of tracheobronchial secretions in cystic fibrosis of the pancreas and bronchiectasis. *Pediatrics.* Nov 1959;24:739-745.
3. Wagener JS, Kupfer O. Dornase alfa (Pulmozyme). *Curr Opin Pulm Med.* Nov 2012;18(6):609-614.
4. Pulmozyme [package insert]. South San Francisco, CA: Genentech, Inc; 2005.
5. Mogayzel PJ, Jr., Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* Apr 1 2013;187(7):680-689.
6. Ballmann M, von der Hardt H. Hypertonic saline and recombinant human DNase: a randomised cross-over pilot study in patients with cystic fibrosis. *J Cyst Fibros.* Mar 2002;1(1):35-37.
7. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med.* Sep 8 1994;331(10):637-642.
8. Ramsey BW, Astley SJ, Aitken ML, et al. Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis.* Jul 1993;148(1):145-151.
9. Mainz JG, Schien C, Schiller I, et al. Sinonasal inhalation of dornase alfa administered by vibrating aerosol to cystic fibrosis patients: a double-blind placebo-controlled cross-over trial. *J Cyst Fibros.* Jul 2014;13(4):461-470.
10. Ozturk E, Tanidir IC, Haydin S, Onan IS, Odemis E, Bakir I. The use of dornase alpha for post-operative pulmonary atelectasis after congenital heart surgery. *Cardiol Young.* Oct 2014;24(5):807-812.
11. Thornby KA, Johnson A, Axtell S. Dornase Alfa for Non-Cystic Fibrosis Pediatric Pulmonary Atelectasis. *Ann Pharmacother.* May 8 2014;48(8):1040-1049.
12. Strickland SL, Rubin BK, Haas CF, Volsko TA, Drescher GS, O'Malley CA. AARC Clinical Practice Guideline: Effectiveness of Pharmacologic Airway Clearance Therapies in Hospitalized Patients. *Respir Care.* Jul 2015;60(7):1071-1077.
13. Crescimanno G, Marrone O. Successful treatment of atelectasis with Dornase alpha in a patient with congenital muscular dystrophy. *Rev Port Pneumol.* Jan-Feb 2014;20(1):42-45.
14. Youness HA, Mathews K, Elya MK, Kinasewitz GT, Keddissi JI. Dornase alpha compared to hypertonic saline for lung atelectasis in critically ill patients. *J Aerosol Med Pulm Drug Deliv.* Dec 2012;25(6):342-348.
15. Zitter JN, Maldjian P, Brimacombe M, Fennelly KP. Inhaled Dornase alfa (Pulmozyme) as a noninvasive treatment of atelectasis in mechanically ventilated patients. *J Crit Care.* Apr 2013;28(2):218 e211-217.
16. Mittal BB, Wang E, Sejpal S, Agulnik M, Mittal A, Harris K. Effect of recombinant human deoxyribonuclease on oropharyngeal secretions in patients with head-and-neck cancers treated with radiochemotherapy. *Int J Radiat Oncol Biol Phys.* Oct 1 2013;87(2):282-289.
17. Bakker EM, van der Wiel-Kooij EC, Mullinger B, Kroneberg P, Hop WC, Tiddens HA. Small-airways deposition of dornase alfa in children with asthma and persistent airway obstruction. *J Allergy Clin Immunol.* Aug 2013;132(2):482-485 e410.
18. Silverman RA, Foley F, Dalipi R, Kline M, Lesser M. The use of rhDNAse in severely ill, non-intubated adult asthmatics refractory to bronchodilators: a pilot study. *Respir Med.* Aug 2012;106(8):1096-1102.
19. Boogaard R, Smit F, Schornagel R, et al. Recombinant human deoxyribonuclease for the treatment of acute asthma in children. *Thorax.* Feb 2008;63(2):141-146.
20. Crockett AJ, Cranston JM, Latimer KM, Alpers JH. Mucolytics for bronchiectasis. *Cochrane Database Syst Rev.* 2001(1):CD001289.
21. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. *Chest.* May 1998;113(5):1329-1334.
22. Thompson A, Fuchs H, Corkery K. Phase II trial of recombinant human DNase for the therapy of chronic bronchitis [abstract]. *Am Rev Respir Dis.* 1993;147(4 pt 2):A318.
23. Bone R, Fuchs H, Fox N, al. e. The chronic obstructive pulmonary disease mortality endpoint trial [abstract]. *Chest.* 1995;108 (Suppl.:R).
24. Nebot MS, Teruel GC, Cubells CL, Sabadell MD, Fernandez JP. [Acute bronchiolitis clinical practice guideline: recommendations for clinical practice]. *An Pediatr (Barc).* Oct 2010;73(4):208 e201-210.
25. Dentice R, Elkins M. Timing of dornase alfa inhalation for cystic fibrosis. *Cochrane Database Syst Rev.* 2013;6:CD007923.

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