Updates in Pompe Disease: Overview and Emerging Treatment Strategies

A Resource for Clinicians

Overview[1-3]

Pompe disease (aka glycogen storage disease type II [GSD II] or acid maltase deficiency [AMD]) is a rare autosomal recessive genetic disorder[1,2]

Description

- Caused by **deficiency** in **acid α-glycosidase** (GAA)[1,2]
- Accumulation of lysosomal glycogen, primarily affecting skeletal and cardiac muscle tissue[1,2]

Epidemiology

- Globally, prevalence of **~1** in every **40,000** people[1]
- **Three-quarters** of these are late onset and **one-quarter** are infantile[1]
- African Americans and East Asians appear to be at higher risk[1]

Onset

- Infantile onset Pompe disease (IOPD) – **before 1 year** of age[2]
- Late onset Pompe disease (LOPD) – **between 1 year and adulthood**[2]

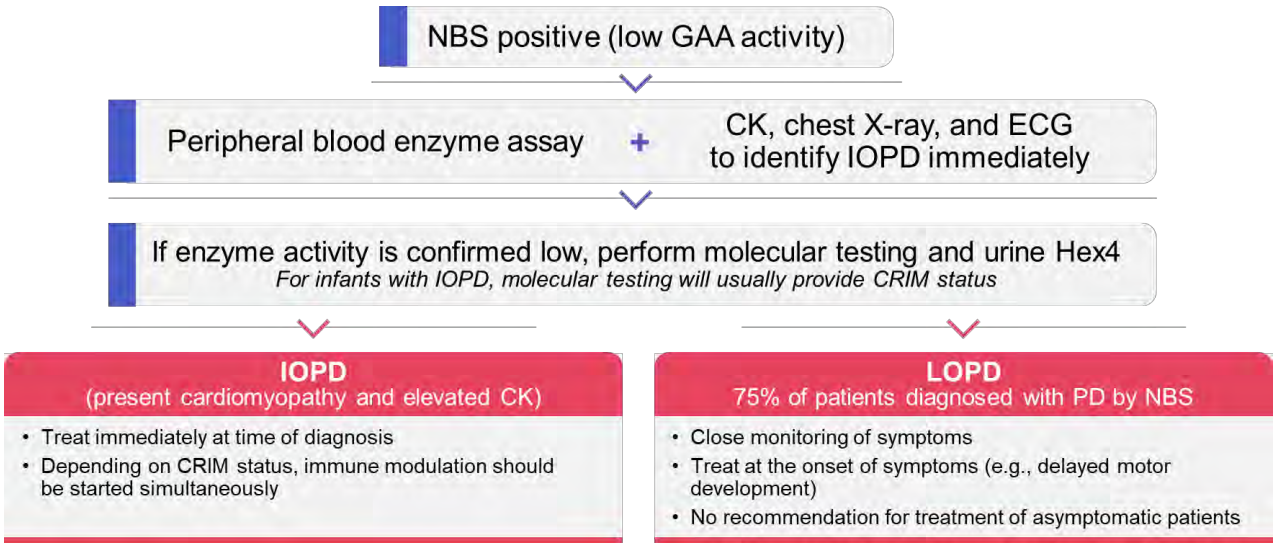
Prognosis

- Varies based on onset[1,3]
- Life expectancy of infants with **IOPD** is often **<1 year,** if untreated[1,3]
- **LOPD** progresses slowly, with a life expectancy into **late adulthood***[1,3]

ECG, electrocardiogram; GAA, acid alpha-glucosidase; GE, gastroesophageal; MDT, multidisciplinary team.
Kishnani PS, et al. *Genet Med.* 2006;8(5):267-288.

Diagnosis of Pompe Disease

Evaluation and Management of Infants With a Positive NBS for Pompe Disease[1-3]



CK, creatine kinase; CRIM, cross-reactive immunologic material; ECG, electrocardiogram; IOPD, infantile onset Pompe disease; LOPD, late onset Pompe disease; NBS, newborn screening; PD, Pompe disease.
1. Burton BK, et al. *Int J Neonatal Screen.* 2020;6(1):4. 2. Bali DS, et al. *Mol Genet Metab Rep.* 2015;5:76-79. 3. Stevens D, et al. *Curr Treat Options Neurol.* 2022;24(11):573-588.

Developed with the expertise of Barbara K. Burton, MD, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Illinois.

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Pompe Disease: Overview and Emerging Treatment Strategies (cont.)

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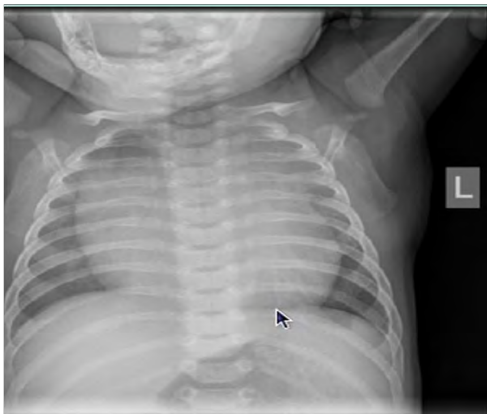
Clinical Features

Infantile Onset Pompe Disease (IOPD)

Symptoms: Present at birth or first few months
Rapidly progressing and often fatal by 1 year of age, when untreated[1]

- **Cardiomegaly**[2]
- **Hypotonia** and rapidly progressive **muscle weakness** (skeletal, smooth muscles)[2-4]
  - Cardiomyopathy and respiratory failure that can lead to death in absence of treatment[3,5]
  - Treated patients who survive show skeletal muscle involvement similar to people with LOPD
- **Hepatomegaly**[2,5]
- Feeding difficulties[2,5]
- Failure to thrive[5]

Infant with IOPD presenting with cardiomegaly*



Diagnostic delay of ~2.5 months†,6
- Quicker diagnosis when presenting with musculoskeletal/respiratory symptoms

* Photos courtesy: Dr. Ficicioglu.
† Data as per US Pompe Registry study.
LOPD, late onset Pompe disease.
1. Toscano A, et al. *Ann Transl Med.* 2019;7(13):284. 2. Marsden D. *Genet Med.* 2005;7(2):147-150. 3. Hahn A, et al. *Ann Transl Med.* 2019;7(13):283. 4. Stevens D, et al. *Curr Treat Options Neurol.* 2022;24(11):573-588. 5. Kishnani PS, et al. *Genet Med.* 2006;8(5):267-288. 6. Lagler FB, et al. *JIMD Rep.* 2019;49(1):89-95.

Late Onset Pompe Disease (LOPD)

Symptoms: Slow progressing with variable clinical presentation

Birth — Infancy ← Symptoms develop → **>60 years**

Musculoskeletal presentation[1-3]
- Proximal lower limb and para spinal trunk **muscles weakness**
- **Scoliosis/scapular winging**
- **Gait abnormalities**, muscular pain, frequent falls

Respiratory presentation[4,5]
- **Diaphragm muscle weakness**
  - Reduced vital capacity/respiratory insufficiency
  - Dyspnea, impaired airway clearance

Cardiac presentation[5]
- **Less common in adults**
- Arrhythmia, cardiac hypertrophy

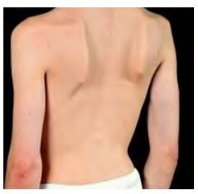
Gastrointestinal presentation[3,6]
- **Poor weight gain/maintenance**
- Chewing/swallowing difficulties
- Lingual weakness

Diagnostic delay of 12 months[7]
- Variable symptom presentations and differential diagnosis
- Common misdiagnoses and referrals: limb-girdle muscular dystrophy

Patients with LOPD presenting with (a) Gower's sign (b) Scapular winging*

a.

b.



*Photos courtesy of Dr. Herman FM Busch, Erasmus MC, Rotterdam, the Netherlands.
1. Alejaldre A, et al. *Neuromuscul Disord.* 2012;22 suppl 2:S148-S154. 2. Hobson-Webb LD, et al. *Clin Neurophysiol.* 2011;122(11):2312-2317. 3. Cupler EJ, et al. *Muscle Nerve.* 2012;45(3):319-333. 4. Sixel BS, et al. *J Bras Pneumol.* 2017;43(1):54-59. 5. Toscano A, et al. *Ann Transl Med.* 2019;7(13):284. 6. Hobson-Webb LD, et al. *Neuromuscul Disord.* 2013;23(4):319-323. 7. Lévesque S, et al. *Orphanet J Rare Dis.* 2016;11:8.

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MDT to Address Multisystem Manifestation of Pompe Disease

Cardiology	Respiratory	Physiotherapy and Neurology	Gastroenterology and Nutrition	Genetic Counselors
• Periodic X-ray/ECG • Monitor fluid status • Monitor arrhythmias	• Respiratory function assessment asleep and awake • Airway clearance • Supplemental oxygen	• Screen for osteopenia • Monitor cardiorespiratory status • Enhance muscle function • Motor and functional assessments	• Evaluate for GE reflux • Oral stimulation for nonoral feeder infants • Monitor growth and provide adequate nutrition care	• Genetic counseling to all parents with a child with Pompe disease • Determine the *GAA* mutations

ECG, electrocardiogram; GAA, acid alpha-glucosidase; GE, gastroesophageal; MDT, multidisciplinary team.
Kishnani PS, et al. *Genet Med*. 2006;8(5):267-288.

Current Treatments: ERT

Alglucosidase alfa[1,2]

Approved in 2006
Indicated **for patients with Pompe disease**

Patients with IOPD:
- Improvement in cardiac function and stabilization or improvements in growth parameters
- Moderate improvement in mobility and pulmonary function for first 1-2 years of treatment, followed by variable period of stability and slow decline thereafter
- Patients who develop high and sustained IgG antibody titers, including CRIM-negative patients may experience reduced clinical alglucosidase alfa treatment efficacy

Patients with LOPD:
- Moderate improvement in mobility and pulmonary function

CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; IgG, immunoglobulin G; IOPD, infantile onset Pompe disease; LOPD, late onset Pompe disease.
1. Myozyme® (alglucosidase alfa) [summary of product characteristics]. Amsterdam, the Netherlands: Sanofi B.V; February 2011. 2. Lumizyme (alglucosidase alfa) [product information]. Cambridge, MA:
Genzyme Corporation; May 2022

Pompe Disease: Overview and Emerging Treatment Strategies (cont.)

New Treatments

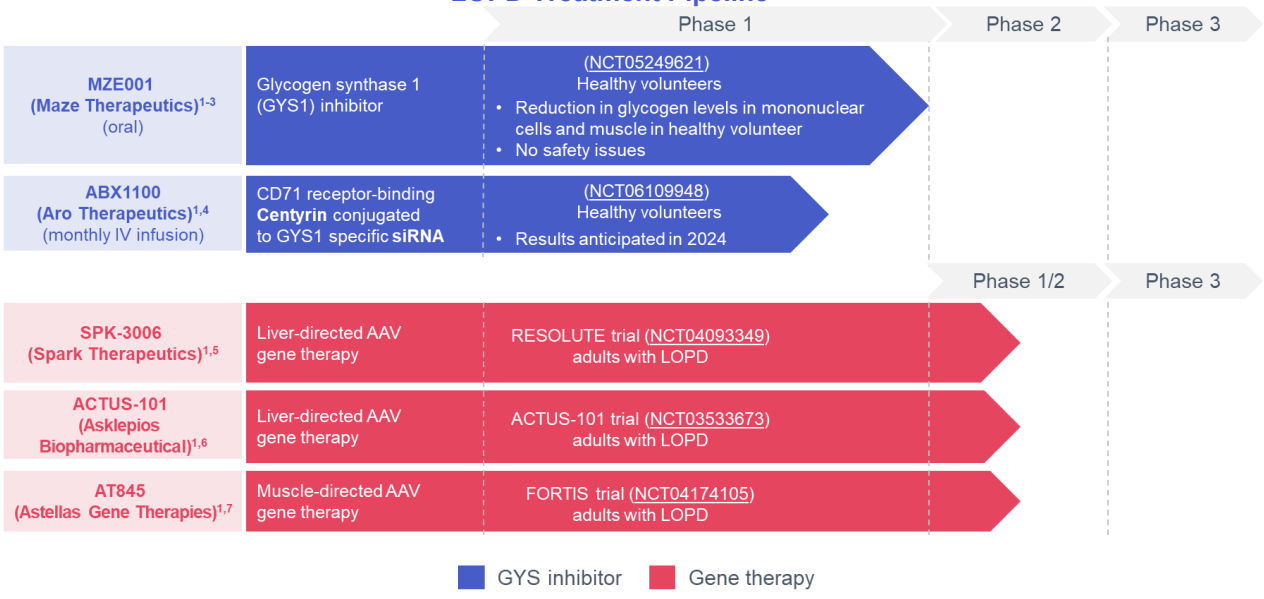
Enriched glycosylation (i.e., bis-M6P) allowing **greater entry into skeletal muscle through M6P receptors**[1,2]

Avalglucosidase alfa[1]	**Approved in 2021** Indicated for patients with **LOPD ages ≥1 year**	**COMET**, a phase 3 randomized, double-blind clinical trial, followed by OLE assessing safety and efficacy of avalglucosidase alfa vs. rhGAA (NCT02782741) • **Patients diagnosed with LOPD, ERT-naïve**, and ≥3 years old, (N=100, median age: 49 years [range 16-78])
Cipaglucosidase alfa[2] **+ miglustat***[,3] *chaperone designed to prolong half-life in circulation[3]	**Approved in 2023** Indicated for **adults with LOPD who are not improving on their current ERT**	**PROPEL**, a phase 3 randomized, double-blind clinical trial, followed by OLE assessing safety and efficacy of cipaglucosidase alfa plus miglustat vs. rhGAA plus placebo (NCT03729362) • **Patients diagnosed with LOPD, ERT- experienced or -naïve**, and ≥18 years old, (N=123, mean age: 47 years old [range 19-74 years old])

Avalglucosidase alfa, and cipaglucosidase alfa in combination with miglustat are currently evaluated in clinical trials for the treatment of patients with lOPD (NCT03019406 - Mini-COMET, NCT04910776 - Baby-COMET, NCT04808505 - ROSSELLA)[4-7]

ERT, enzyme replacement therapy; lOPD, infantile onset Pompe disease; LOPD, late onset Pompe disease; OLE, open-label extension; rhGAA, recombinant human acid alpha-glucosidase.
1. NEXVIAZYME® (avalglucosidase alfa-ngpt) [prescribing information]. Cambridge, MA: Genzyme Corporation; September 2023. 2. POMBILITI™ (cipaglucosidase alfa-atga) [prescribing information]. Philadelphia, PA: Amicus Therapeutics US, LLC; September 2023. 3. OPFOLDA™ (miglustat) [prescribing information]. Philadelphia, PA: Amicus Therapeutics US, LLC; September 2023. 4. https://www.sanofi.com/en/our-science/our-pipeline. 5. https://clinicaltrials.gov/study/NCT03019406. 6. https://clinicaltrials.gov/study/NCT04910776. 7. https://clinicaltrials.gov/study/NCT04808505.

LOPD Treatment Pipeline[1-7]



1. Bolano-Diaz C, et al. *Ther Clin Risk Manag*. 2022;18:1099-1115. 2. https://pompediseasenews.com/news/pompe-disease-treatment-mze001-shows-promise-phase-1-trial/. 3.. https://clinicaltrials.gov/study/NCT05249621. 4. https://clinicaltrials.gov/study/NCT06109948. 5. https://clinicaltrials.gov/study/NCT04093349. 6. https://clinicaltrials.gov/study/NCT03533673. 7. https://clinicaltrials.gov/study/NCT04174105. 8. https://resolutestudy.com/pompe-healthcare-providers.html.

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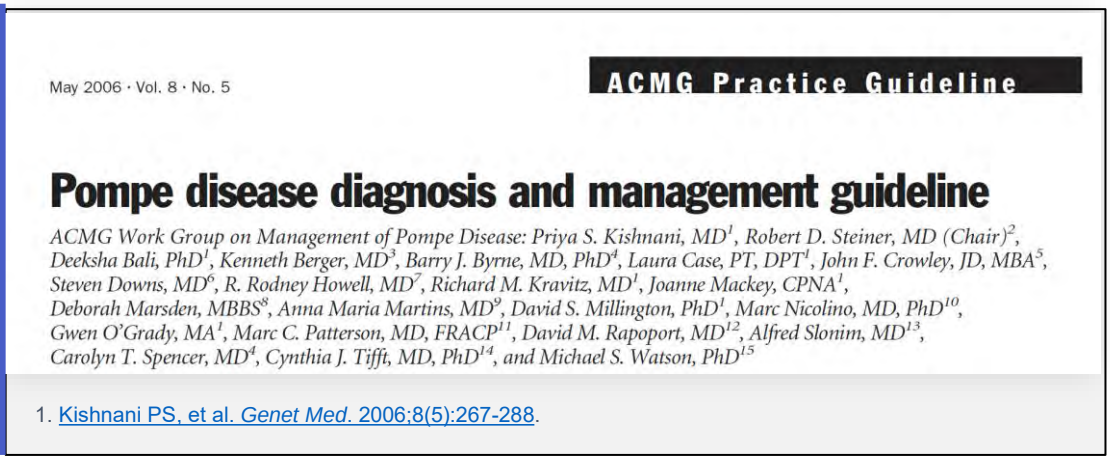
Resources and Additional Reading

Management Guidelines[1]



May 2006 · Vol. 8 · No. 5

ACMG Practice Guideline

Pompe disease diagnosis and management guideline

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1. Kishnani PS, et al. *Genet Med*. 2006;8(5):267-288.

Health Organizations

International Pompe Association

Association for glycogen storage disease

GARD

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View the companion mini-webinar here

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