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An Overview of Pompe Disease and Clinical Manifestations

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Pompe Disease

- Deficiency of acid α-glucosidase (GAA), which leads to the accumulation of lysosomal glycogen
- Autosomal recessive disorder
- More than 300 mutations have been described
- Broad spectrum of illness

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Classification of Pompe Disease

Infantile: Most severe

- *Onset ≤12 months of age*
  - **Infantile Onset *with* Cardiomyopathy** ("Classic Form") – progressive hypotonia and cardiomyopathy; without treatment, death usually within the first year of life
  - **Infantile Onset *without* Cardiomyopathy** ("Nonclassic Form") – typically no cardiomyopathy; longer survival, but without treatment, death in early childhood

Late-onset: Variable Presentation

- *Clinical onset >12 months of age*
- *Most seek care for symptom onset in adulthood (>18 years)*
- *Diagnosis ~8-10 years later, and death ~27 years later*
- *May have mild weakness in childhood that can go unrecognized*
- *Slowly progressive myopathy*
- *Variable long-term outcomes without treatment (e.g., wheelchair dependence; ventilator assistance; respiratory failure)*

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Enzyme Replacement Therapy (ERT)

Treatment: Replace alglucosidase alfa (GAA) deficiency

FDA Approval	Pompe Disease Form (Indication)	Drug	Wholesale Acquisition Cost per 50mg vial
2006	Infantile-onset (ERT start ≤3.5 years)	Myozyme	$975
2010	Late-onset (≥ 8 years)	Lumizyme	$725

- *Not curative*
- *Infusion typically every two weeks with central line*
- *Typical dose is 20 mg/kg infused over 2 hours*
- *Adverse Effects: Infusion Associated Reactions, Antibody Formation*

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Factors that Affect Detection

Carriers

- *May have below normal GAA enzyme activity level and be identified through screening*

Pseudodeficiency

- *Low measured GAA enzyme activity level, but does not lead to Pompe disease*
- *High frequency in East Asian populations (3.9%)*
- *Can be identified by genotyping*

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Factors that Affect Treatment Response

CRIM+ vs. CRIM–

- *Cross-Reacting Immunologic material – individuals make some endogenous enzyme, which may or may not be functional*
- *CRIM- can develop high titers of antibodies that neutralize ERT, leading to poor outcome*
- *Standard CRIM status detection: Western blot, however mutation analysis is usually helpful*
- *CRIM+: ~25% of CRIM+ individuals can also develop antibodies to ERT, usually not as significant as antibody development among those who are CRIM-*

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Diagnosis

- Establish low functional GAA enzyme levels
- Genotyping
  - *Rule out pseudodeficiency*
  - *Identify carriers*
  - *Predict infantile-onset vs. late-onset*
  - *Predict CRIM status*

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Expected Epidemiology in the United States

- Overall Incidence ~1/28,000
- Infantile-onset Pompe disease
  - *~28% of cases are infantile-onset Pompe disease*
    - ~85% of infantile cases are classic Pompe disease
      - ~75% of cases of classic infantile-onset Pompe disease are CRIM+
- Late-onset Pompe disease
  - *~72% of cases are late-onset*
- Pseudodeficiency occurs in <1% of births

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Clinical Course Before ERT Availability: Infantile-Onset Pompe Disease

	Symptom Onset *Median Age*	Diagnosis *Median Age*	Mechanical Ventilation Assistance *Median Age, %*		Death *Median Age*	% Survival [% Ventilator-Free]		
	Mos (range)	Mos (range)	Mos (range)	%	Mos (range)	12 mos	18 mos	24 mos
Infantile-onset	**2.0** (0- 12)	**4.7** (<0–84.2)	**5.9** (0.1–39.5)	**29**	**8.7** (0.3–73.4)	**25.7** [16.9]	**14.3** [8.5]	**9.0** [4.9]
WITH cardiomyopathy	**2.9**	**6.0**						
WITHOUT cardiomyopathy	**4.4**	**15.6**						

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Clinical Course Before ERT Availability: Late-Onset Pompe Disease

	Symptom Onset (med. consult) *Median Age*	Diagnosis *Median Age*	Death *Median Age*	Estimated Survival Post-Diagnosis (%)			
				+5 yrs	+10 yrs	+20 yrs	+30 yrs
Late-onset	28 years	38 years	+27 years post-dx	95	83	65	40

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Effectiveness of ERT – Infantile Onset

- Compared to historical controls, ERT at 52 weeks (first infusion by 6 months of age)
  - *Reduced the risk of death by 95%*
  - *Reduced the risk of death or invasive ventilation by 87%*
- Overall survival at 36 months: 72%
- Overall ventilator-free survival at 36 months: 49%
- CRIM- status associated with worse outcomes
- Lower survival if ERT begun after 6 months of age

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Pre-symptomatic Detection of Late-Onset Pompe Disease

- No trials of pre-symptomatic ERT for late-onset disease
- Treatment decisions based on presence of weakness or muscle damage (e.g., elevated CK). MRI can also show muscle damage.
- Recommendations for follow-up not standardized
- Potential harms of early identification include treatment with ERT, central line placement, economic cost of lifelong treatment, and psychosocial harm.
- There is evidence from an RCT of ERT for symptomatic individuals (mean age in the 40s) that ERT can improve respiratory status and motor function.

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Pre-symptomatic Detection of Late-Onset Pompe Disease

- The effect of treatment begun after symptom development might be limited because muscle damage is irreversible. Treatment begun before symptom development might avoid muscle damage.
  - *Biologic plausibility for pre-symptomatic treatment*
    - Muscle damage cannot be reversed by ERT
    - Autophagic inclusion bodies persist after ERT even after reduction of glycogen in muscle cells
- Testing this hypothesis would require a prospective study that would take many years.

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Summary

- About 1/28,000 have Pompe disease
- Most cases are late-onset
- There is good evidence that early identification of infantile-onset Pompe compared to clinical detection improves outcomes.
- There is no direct evidence that pre-symptomatic treatment leads to better outcome; however, there is biologic plausability.
- Most cases of infantile-onset Pompe disease are CRIM+.
  - *CRIM- is associated with worse outcomes*
  - *Immunomodulation appears to improve outcomes, and early immunomodulation may be more effective*

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Diagnostic issues in Pompe Disease

APHL Webinar
February 19, 2014

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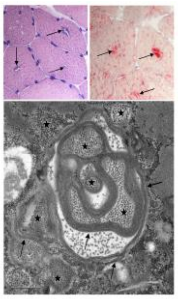
Case report Pompe Disease

- Female, 18 years
- Presented with progressive proximal myopathy
- Elevation of CK (670 U/L)
- Muscle biopsy showed vacuolar myopathy
- Late-onset Pompe Disease confirmed by enzyme analysis in fibroblasts followed by molecular analysis of *GAA* gene

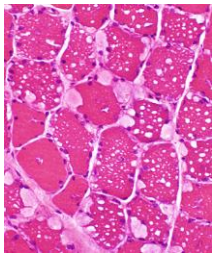


Diagnostic avenues Pompe Disease

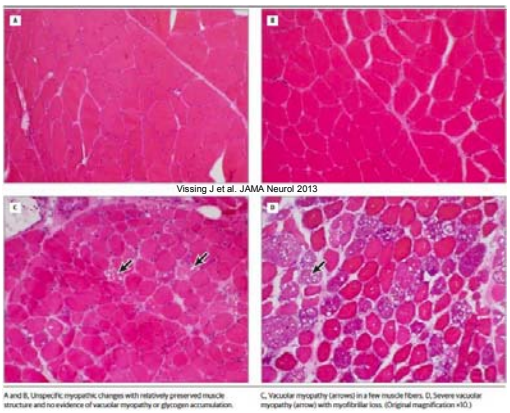
- Clinical symptoms
- General laboratory abnormalities
- Histology/histochemistry in muscle
- Analysis of α-glucosidase activity
- Molecular analysis of the *GAA* gene

Histology/histochemistry in muscle

- Vacuolar myopathy
- Vacuoles contain PAS(+), PASD(-), acid phosphatase
- Degree of pathologic change varies with disease severity, and with different muscles
- Analysis of acid maltase in muscle tissue feasible



- **Muscle biopsy may miss diagnosis!**



Vissing J et al. JAMA Neurol 2013

A and B, Unspecific myopathic changes with relatively preserved muscle structure and no evidence of vacuolar myopathy or glycogen accumulation. C, Vacuolar myopathy (arrows) in a few muscle fibers. D, Severe vacuolar myopathy (arrow) with myofibrillar loss. (Original magnification ×10.)

General laboratory abnormalities

- Elevation of CK (400-1000 U/L)
- Elevation of aldolase, AST and ALT (ratio=1)
- Elevations of AST and ALT may be misinterpreted as liver disease

General laboratory abnormalities-ctd

Disease	Genes Involved	Age at Onset, y	Pattern of Weakness	CK Level, ×ULN[a]	Respiratory Involvement	Cardiac Involvement[b]
LGMD1A	*MYOT*	20-40	Proximal/distal	N to <5×	No	A, CM
LGMD1B	*LMNA*	4-35	Proximal/distal	N to 5×	Yes	A, CM
LGMD1C	*CAV3*	15-40	Proximal/distal	5-25×	No	No
LGMD1D	*DNAJB6*	20-60	Proximal	N to 5×	No	No
LGMD2A	*CAPN3*	2-40	Proximal	10-20×	No	No
LGMD2B	*DYSF*	10-30	Proximal/distal	10-50×	No	No
LGMD2C-F	*SGCG, SGCA, SGCB, SGCD*	3-20	Proximal	5-25	Yes	CM (not LGMD2D)
LGMD2I	*FKRP*	3-40	Proximal	10-50×	Yes	CM
LGMD2L	*ANO5*	20-50	Proximal/distal	5-50×	No	No
LGMD2M	*FKTN*	0-15	Proximal	10-25×	Yes	CM
DMD	*DYS*	2-5	Proximal	10-50×	Yes	CM
BMD	*DYS*	5-30	Proximal	5-50×	Rare	CM
Childhood and adult Pompe disease	*GAA*	1-60	Proximal and axial	N to 5×	Yes	Rare

Abbreviations: A, arrhythmia; BMD, Becker muscular dystrophy; CK, creatine kinase; CM, cardiomyopathy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; N, normal; ULN, upper limit of normal.

[a] The ×ULN indicates the serum CK level at diagnosis reported as multiples of the ULN.

[b] Arrhythmia and cardiomyopathy.

Vissing J et al. JAMA Neurol 2013

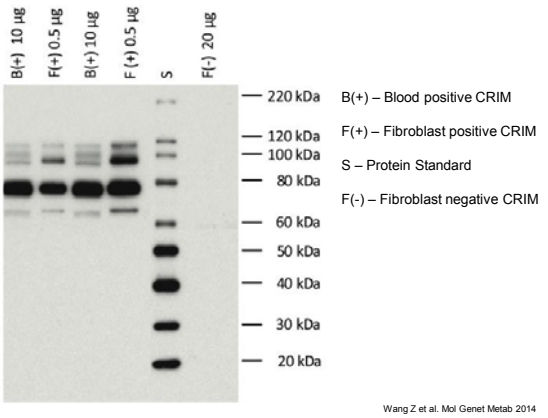
Analysis of α-glucosidase activity

- Fluorometric assay
  - singleplex, high throughput
  - ideal for dried blood spots and leukocytes
- Tandem mass spectrometry
  - multiplex capabilities, high throughput
  - ideal for dried blood spots
  - 24-36 hour assay time
- Inhibition of maltase-glucoamylase by arcabose needed to avoid false negative results

Cross Reacting Immunological Material

- CRIM negative infants with Pompe disease mount an immune response against recombinant enzyme
- CRIM status can be determined in fibroblasts or peripheral blood mononuclear cells using Western Blot
- CRIM status may be predicted based on genotype in the majority of CRIM (-)

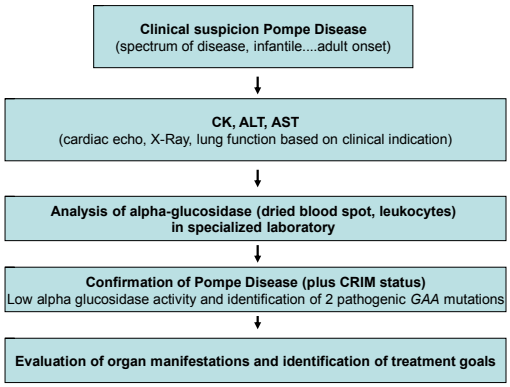
Bali DS et al. Am J Med Genet 2012
Wang Z et al. Mol Genet Metab 2014



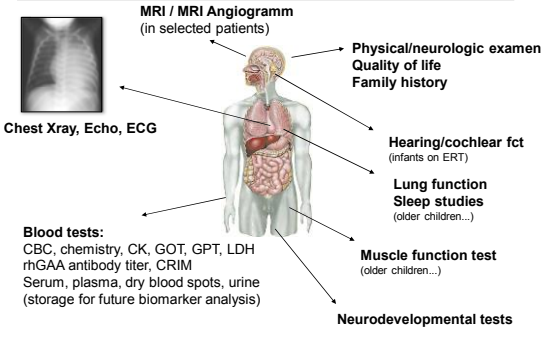
Wang Z et al. Mol Genet Metab 2014

Molecular analysis of the *GAA* gene

- *GAA* gene spans 28kb on 17q25.3; 20 exons
- >250 pathogenic mutations (www.pompecenter.nl)
- Common pathogenic mutations include:
  - c.-32-13T>G (Caucasian)
  - p.R854X (African-American)
  - p.D645E (Chinese)
- Pseudodeficiency variant p.G576S (20% enzyme activity)



Pompe Disease staging



Summary and conclusions

- Diagnosis of Pompe disease has to be timely to maximize the benefit of therapy
- Laboratory abnormalities include moderately elevated CK and transaminases in most patients
- Muscle biopsy is obsolete for the diagnosis of Pompe disease
- Diagnostic test of choice is analysis of α-glucosidase activity in dried blood or leukocytes followed by molecular analysis of the *GAA* gene (cave pseudodeficiency!)
- Diagnostic testing should be done in CLIA/CAP certified laboratory with high sample load

Contact information

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Pompe Disease: Treatment

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Medical Biochemical Geneticist
Director, Metabolic Treatment Program
February 19, 2014

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Treatment Targets for Pompe Disease

Glycogen

α-glucosidase

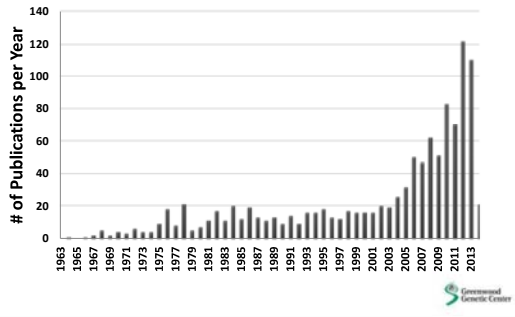
Glucose

Substrate Reduction Therapy

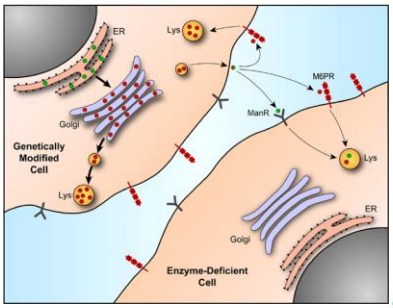
Enzyme Replacement Therapy (ERT)
Chaperones
Gene Therapy

Supportive Care For:
- Heart Function
- Respiratory Function
- Muscle Function
- Improved Quality of Life

PubMed Articles on Treatment for Pompe Disease



Treatment Strategies



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Mol Ther. 2006 May;13(5):839-49.

Initial Clinical Trials with rhGAA

4 patients treated for 36 weeks with rhGAA from Rabbit Milk[1]	**3 patients treated for 1 year with rhGAA from CHO cells[2]**
Clinical Outcomes	Clinical Outcomes
• Cardiac function – improved	• Cardiac function – improved
• Motor function – improved	• Motor function – variable
• Respiratory function – variable	• Respiratory function – variable
• Survival beyond 1 year – all	• Survival beyond 1 year – all
Muscle Biopsy	Muscle Biopsy
• α-glucosidase activity – normalized	• α-glucosidase activity – improved
• Glycogen material – decreased	• Glycogen material – variable

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1. J Inherit Metab Dis. 2001 Apr;24(2):266-74.
2. Genet Med. 2001 Mar-Apr;3(2):132-8.

ERT for Infantile-Onset Pompe Disease (IOPD)

- Multiple clinical trials demonstrated:
  - Survival rate - improved
  - Invasive ventilation-free survival rate – improved
  - Cardiac function – improved
  - Motor function – improved
- Treatment response is variable and correlates with:
  - Age at onset of symptoms
  - Stage of disease at ERT initiation
  - CRIM status

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Pediatrics 2004; 113:e448-57, Neurology 2007;68:99-109, Genet Med. 2009;11:210-219, Pediatr Res 2009;66: 329-335.

CRIM Status in Pompe Disease

- Cross-reacting immunologic material (CRIM)
  - Negative status: 20% of infantile-onset form
    - No endogenous GAA enzyme produced
    - Develop high-sustained antibody titers (HSAT)
    - Reduced survival
    - Reduced invasive ventilator-free survival
    - Decreased cardiac response
    - Regression/loss of motor development

Mol Genet Metab. 2010;99:26-33.
Genet Med. 2011; 3:729-736.

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Immune Toleration Induction (ITI)

- Prevent or eliminate immune response to rhGAA
- Immune modulation with:
  - Rituximab
  - Intravenous immune globulin (IVIG)
  - Methotrexate
  - Gene Therapy?

N Engl J Med. 2009;360(2):194-195.
Mol Genet Metab. 2010;99:26-33.
Genet Med. 2012; 14:135-142.
Am J Med Genet Part C Semin Med Genet. 2012;160C:30-39.

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Impact of Early ERT for IOPD

- NBS in Taiwan: Oct. 2005 – Dec. 2007
  - 206,088 newborns screened
  - 6 cases IOPD diagnosed and treated with ERT
  - After 14-32 months of treatment
    - Normal cardiac size
    - Normal respiratory status
    - Normal motor development

Pediatrics.2009;124:e1116-e1125.

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ERT for Late-Onset Pompe Disease (LOPD)

- Respiratory function –stabilized or improved
- Muscle function – stabilized or improved
- Quality of life – improved
- Treatment response is variable and correlates with:
  - Age at onset of symptoms
  - Stage of disease at ERT initiation

J Neurol. 2010;257:91-97.
N Engl J Med.2010;362:1396-1406
Muscle & Nerve. 2012; 45(3): 319-333.

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ERT for LOPD

- Recommended for symptomatic LOPD
  - Decreased pulmonary function
  - Demonstrable muscle weakness
- Efficacy should be assessed after 1 year to determine if symptoms have been
  - Slowed
  - Reversed
  - Stabilized
  - Prevented

Muscle & Nerve. 2012; 45(3): 319-333.

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Impact of Early Diagnosis/ERT for LOPD

- NBS in Taiwan: 2005 –2009
  - 344,056 newborns screened
  - 13 cases LOPD diagnosed (no cardiomyopathy)
  - 4 cases started on ERT (at 1.5 month to 3 years) due to:
    - Low muscle tone
    - Developmental delays
    - Elevated creatine kinase
  - 9 untreated cases monitored every 3-6 months

J Pediatr. 2011; 158: 1023-7.

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FDA Approved ERT

- Myozyme® - 2006
  - Approved for Infantile Pompe
  - 20 mg/kg IV every 2 weeks
  - 50 mg vial = $975*
  - Annual Cost: $50 – 400 K

www.myozyme.com

- Lumizyme® - 2010
  - Approved for ≥ 8 years old without cardiac hypertrophy
  - 20 mg/kg IV every 2 weeks
  - 50 mg vial = $725*
  - Annual Cost: $300 – 600 K

www.lumizyme.com

*Commercial cost per Genzyme – February 2014

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ERT Considerations/Limitations

- Infusion-related reactions
- Antibody formation
- Unsatisfactory access to muscle cells
- New emerging neurological phenotype
- Life-long treatment
- Cost

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Second Generation ERT

- BMN-701 (BioMarin)
  - Alternative lysosomal targeting with IGF-2 linked to GAA
  - Phase 1/2 clinical trials
- Neo-GAA (Genzyme)
  - Synthetic bis-M6-P linked to GAA
  - Phase 1 clinical trials

Mol Ther. 2009;17(6):954-963.
J Biol Chem. 2013 Jan 18;288(3):1428-38.
http://www.clinicaltrials.gov/

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Chaperones

- Stabilize/rescue misfolded or unstable proteins
- N-butyldeoxynojirimycin (NB-DNJ)
  - Improved GAA transport from ER to lysosomes
  - Increased GAA activity
- Phase 2 Clinical Trial – Duvoglustat Hydrochloride (Amicus)
  - Administered 1 hour prior to ERT

Mol Ther. 2007;15:508–514.
Mol Ther. 2009;17(6):964-971.

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Gene Therapy
Adeno-Associated Virus (AAV)

- Trials in GAA-KO mice
  - Target: Skeletal muscle
    - Limited systemic effects
  - Target: Liver
    - Efficient production, secretion and uptake in multiple tissues
    - Neutralization by anti-hGAA antibodies
  - Target: Diaphragm
    - Increased phrenic nerve activity and improved ventilatory function
- Phase I/II Clinical Trial– in progress

Proc Natl Acad Sci USA.1999;96:8861-8866. Mol Ther. 2002;6:601-608.
Mol Ther. 2010;18:502-510. Hum Gene Ther. 2013 Jun;24(6):630-40.

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Other Adjunct Therapies

- Nutrition and Exercise
  - Low-Carbohydrate, High Protein Diet
    - Minimize glycogen accumulation
    - Increase muscle protein synthesis
- Daily Aerobic Exercise
  - Increase ratio of type I to type II muscle fibers

Muscle Nerve 2007;35:70 –77.

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Supportive Treatments

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Genet Med 2006;8(5) 267-287.
Muscle & Nerve 2011;45 (3) 319-333.

Patient/Family Support

amda
Acid Maltase Deficiency Association
www.amda-pompe.org

IPA
International Pompe Association
www.worldpompe.org

POMPE REGISTRY
www.pomperegistry.com

United Pompe Foundation
www.unitedpompe.com

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