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Infantile-Onset Pompe Disease (IOPD): From Standard ERT to the Evolving Therapeutic Landscape

Based on:

- My Child's Pompe Treatment – A Guide for Parents and Carers (Pompe Support Network, UK, 2025)
- MetabERN Clinical Pathway Recommendations for Pompe Disease (Parenti et al., Orphanet J Rare Dis, 2024)

What is Pompe Disease?

- **Lysosomal storage disorder & metabolic myopathy**
- Caused by deficiency of **lysosomal acid alpha-glucosidase (GAA / acid maltase)**
- GAA hydrolyzes 1,4 and 1,6 glucosidic bonds of glycogen → **glycogen accumulation in lysosomes**
- **Tissues affected:** cardiac, skeletal, and smooth muscle
- **Secondary feature:** accumulation of **autophagic material** in muscle fibers

Downstream effects: mitochondrial dysfunction, oxidative stress, disrupted cytoplasmic glycogen metabolism

Genetics:
Autosomal recessive

GAA located on chromosome 17q25.2–q25.3 (20 exons, 19 coding)
High allelic heterogeneity: >648 disease-associated variants reported (as of Dec 2020)

Epidemiology & Classification

Incidence:

- Estimated **1:40,000 – 1:146,000** (clinical diagnosis)
- Newborn screening (NBS) programs report **1:8,684 – 1:23,596**

Feature	IOPD (Classic)	Atypical IOPD	LOPD
Onset	Birth – first months	>6 months	Childhood – adulthood
Cardiomyopathy	Prominent	Less prominent	Usually absent
Progression	Rapid, fatal in 1st year untreated	Slower	Slow
Motor milestones	Not achieved	Delayed	Progressive loss

IOPD — Clinical Manifestations

Classic Infantile Form:

- Present at birth or within first few months
 - **Hypotonia**, feeding difficulties, respiratory problems
 - **Hypertrophic cardiomyopathy** — may develop in utero
- Without therapy: death within first year from **cardiorespiratory failure**
 - Patients do not achieve major motor milestones

Atypical Infantile Form (beyond 6 months):

- Generalized hypotonia, cardiac hypertrophy (less prominent)
 - Mild liver enlargement, macroglossia
 - Recurrent respiratory infections
- Delayed motor milestones — some achieve sitting/standing without therapy

Diagnosis — The Gold Standard

Newborn Screening (NBS): Essential for timely identification of IOPD

Limitations: screening test only (not diagnostic); cannot distinguish IOPD from LOPD

Confirmatory Diagnosis:

GAA enzyme assay in **leukocytes/lymphocytes, cultured fibroblasts, or muscle biopsy**

Gold standard: pathological GAA assay + genetic confirmation

Molecular analysis of GAA gene — for confirmation and genetic counseling

CRIM status (Western blot or DNA analysis) — critical prognostic and predictive factor

Complementary Tests: Elevated AST, ALT, CK, LDH, PAS-positive vacuoles in lymphocytes (rapid test) ,Biomarkers: BNP/pro-BNP, urinary Glc4, neurofilament light chain

Therapeutic Goals in IOPD Infants:

1. **Improve survival**
2. **Improve or normalize cardiorespiratory function**
3. **Improve or preserve normal motor skill acquisition**
4. **Normalize growth**
5. **Prevent need for ventilator support**

Treatment should be started **immediately after diagnosis, without delay**.
Early initiation contributes to better physical and developmental outcomes.

Enzyme Replacement Therapy (ERT) Mechanism:

- Provides working **recombinant human GAA (rhGAA)**
- Reduces glycogen accumulation in cells



Preparation	Approval	Indication	Dose
Alglucosidase alfa (Myozyme)	2006	IOPD + LOPD	20 mg/kg q2w (licensed); high-dose 40 mg/kg/week used in IOPD
Avalglucosidase alfa (Nexviazyme)	FDA 2021, EMA 2022	LOPD (IOPD: 40 mg/kg q2w may be considered)	20 mg/kg q2w
Cipaglucosidase alfa (Pombiliti) + miglustat	EMA 2023	LOPD	20 mg/kg q2w

Clinical Benefits (Alglucosidase alfa):

- Reduced heart muscle thickening
- Improved movement
- Delayed need for breathing support
- Prolonged survival vs. no treatment

Dosing Strategies

Standard Dose:

- Alglucosidase alfa **20 mg/kg every other week** (licensed)

High-Dose Regimens:

- Published studies: **20 mg/kg q2w → 40 mg/kg/week** Shown to be **clinically appropriate and safe** in IOPD

Improvements in:

Gross motor outcomes
Pulmonary function measures
Biochemical markers

40 mg/kg/week showed better effect on **survival** and **walking ability** than standard dose in classic infantile patients

Second-Generation Enzymes:

- Enriched in **mannose-6-phosphate** content
 - Improved **muscle-targeting** properties
- Avalglucosidase alfa: dose increase to **40 mg/kg q2w** may be considered in IOPD with insufficient response

administration & Practical Aspects

Administration:

- **Intravenous infusion** — 3 to 6 hours
- Started in **specialist centre** under monitoring
- May transition to **home infusion** once stable (family training or home care nurse)
 - **Portacath** may be fitted for easier access

Enzyme is gradually broken down → **regular intervals, lifelong treatment**

Missing infusions should be avoided — even during holidays

Effects may take **several months** to be seen

Monitoring:

Close monitoring in first year

At least **annual** specialist centre visits thereafter

Antibody status: baseline + every 6–12 months

Immunogenicity — The CRIM Paradigm

The Problem:

- Some children produce **antibodies against ERT** → reduced effectiveness
- **CRIM (Cross-Reactive Immunologic Material)** classification predicts response:

CRIM-Positive	CRIM-Negative
Produce some endogenous GAA	Produce no GAA protein
~2/3 of IOPD patients	~1/3 of IOPD patients
Less likely to develop high antibody titers	Higher risk of neutralizing antibodies
—	Require immunomodulation

Cross-reactive immunological material (CRIM) status affects IOPD prognosis

Cross-reactive immunological material (CRIM) status refers to the presence or absence of endogenous GAA protein with or without enzymatic activity.

A CRIM-positive status indicates that molecular forms of acid α -glucosidase could be detected.

CRIM is produced by patients with Pompe disease who have non-null GAA mutations
(eg, missense rather than nonsense mutations)

A CRIM- negative status indicates that these were undetectable.
CRIM- negative patients have two null GAA mutations and produce no GAA protein(no GAA protein expression) of their own.

CRIM-negative (CRIM–) patients have been reported to have a poorer prognosis than CRIM+ patients, along with:

- Increased incidence of ventilator dependency
- Less motor development than CRIM+ patients
- More profound and sustained antibody titers than CRIM+ patients
 - Reduced survival



CRIM status should be determined immediately upon IOPD diagnosis to allow prompt immune tolerance induction (ITI).

Whereas

CRIM⁺ patients can develop immunological tolerance of GAA protein
(alglucosidase alfa therapy)
but

CRIM⁻ patients are not tolerant of GAA protein.

CRIM⁻ patients who receive alglucosidase alfa therapy mount an immune response to it as “nonself”.

Thus

CRIM⁻ patients should be identified at diagnosis to allow treatment for immune

CRIM-negative patients experience an initial response to ERT before entering a phase of devastating clinical decline at rate that approximates that observed in untreated IPD.

This clinical decline in CRIM-negative cases is largely due to the development of high sustained anti-rhGAA antibody titers (HSAT).

While

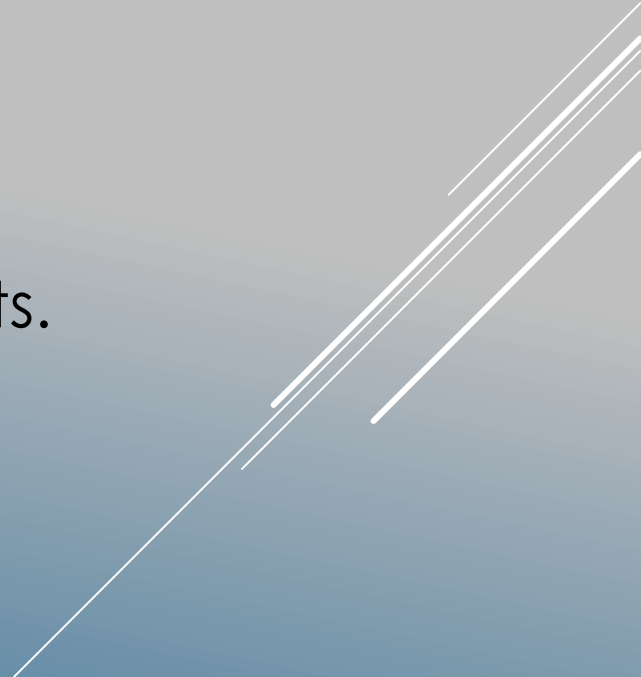
there are some exceptions in which CRIM positive patients develop HSAT and experience clinical decline similar to CRIM-negative patients

the majority of CRIM-negative patients with missense mutations and some residual GAA protein either do not mount an immune response or mount a transient low titer response, and exhibit a more favorable response to ERT monotherapy .

As a result, patients are classified into three subclasses according to anti-rhGAA IgG antibody titers :

- (1) High and sustained antibody titer, defined as antibody titer **> 51,200** on samples at least 6 months on ERT
- (2) sustained intermediate titer, defined as titers of **$\geq 12,800$ < 51,200** within 12 months on ERT
- (3) low titer, defined as antibody titers of **< 12,800** during 1 year on ERT.

It is demonstrated that after 52 weeks on ERT
5% of CRIM-positive IOPD patients died or were invasively
ventilated
compared to
around 50% of CRIM-negative IOPD patients.

Three parallel white lines of varying lengths are positioned in the bottom right corner of the slide, slanted upwards from left to right.

There are no apparent relationship between the titer and the dose of ERT, nor between the titer and the use of recombinant human acid α -glucosidase from either rabbit milk or CHO (Chinese hamster ovary) cell .

Immune Tolerance Induction (ITI)

Goal: Prevent or counteract neutralizing antibodies to rhGAA

When to Start:

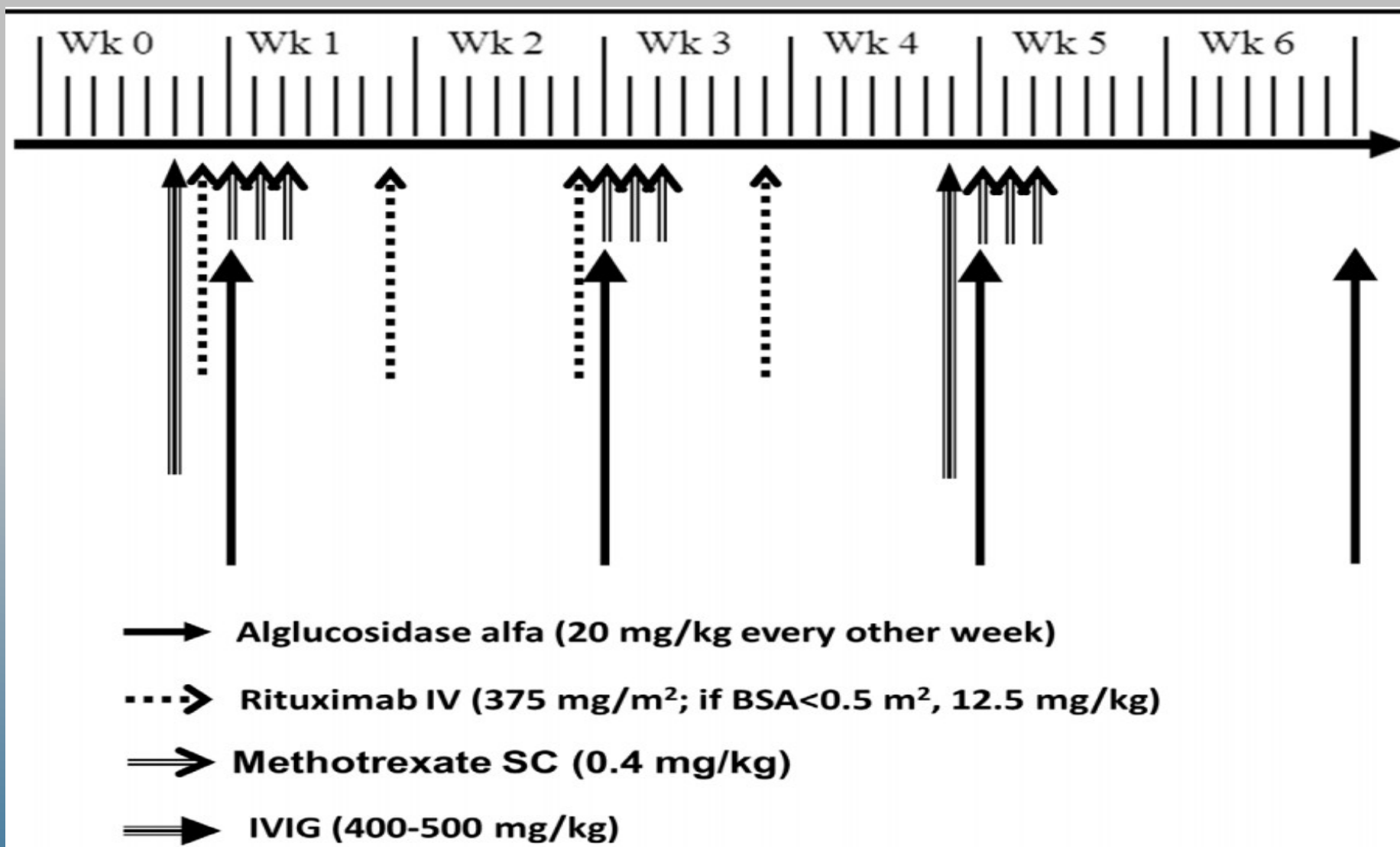
- **Prophylactic ITI must begin BEFORE the first rhGAA infusion**
 - Mainly indicated in **CRIM-negative** patients
- Also considered for CRIM-positive patients who develop HSAT

Protocols:

- Variable combinations of:
 - **Rituximab**
 - **Methotrexate**
 - **Bortezomib**
 - **Rapamycin (sirolimus)**
 - **Plasma exchange**
 - **Gamma globulin support**

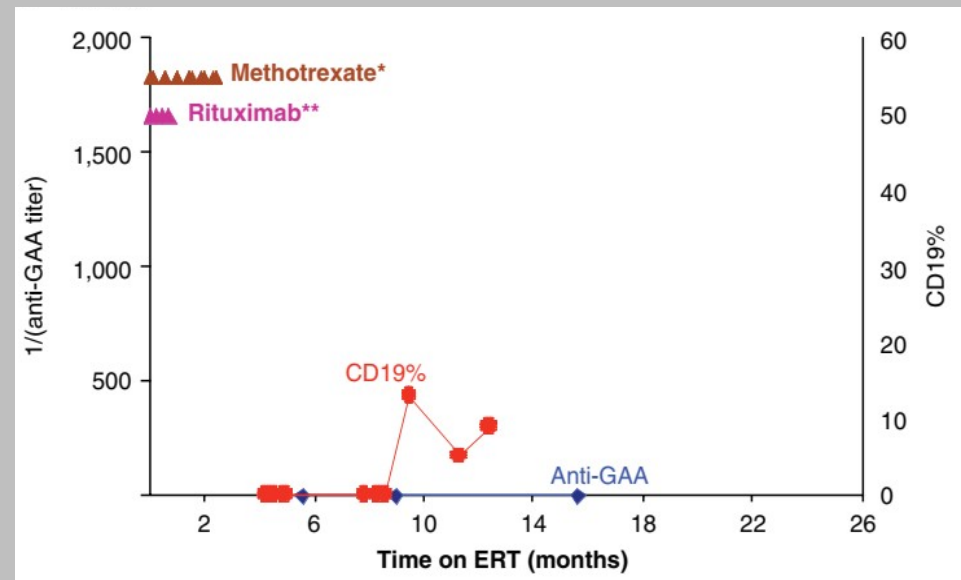
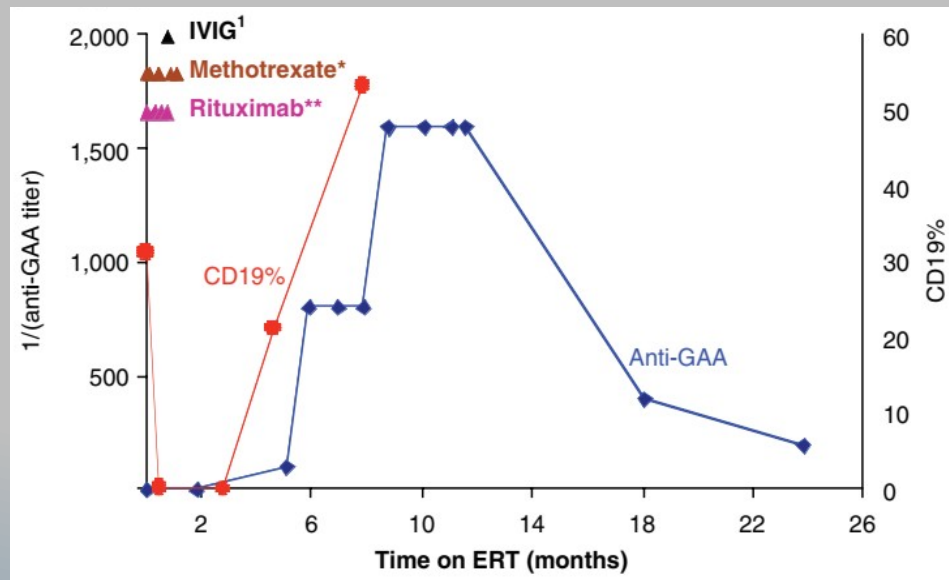
Monitoring:

- Antibody measurement at baseline and regular intervals (every 6–12 months)
 - More frequent if unexpected worsening



ITI treatment regimen which includes rituximab, MTX and IVIG. This short course of ITI regimen (5 weeks) needs to **be started together with the first dose** of ERT.

IVIG is administered on a monthly basis for a period of 5–6 months.



Prophylactic-treated patients. Tolerance-induction regimen, antibody levels, and B-cell percentage for patients treated prophylactically in the naïve setting with rituximab and methotrexate. Both patients are tolerant to ongoing enzyme replacement therapy, off immune therapy with B-cell recovery.

(a) Patient with remains with low-titer (1:200) antibody level, similar to CRIM-positive patients.

(b) Patient with negative antibody titer

When to Start, Switch, or Stop ERT

Starting ERT (IOPD):

- **Start immediately after diagnosis, without delay**
 - High level of evidence for early initiation

When ERT May Not Be Started / May Be Stopped:

- Extremely severe manifestations
 - Already invasively ventilated

No residual respiratory and skeletal muscle function

No beneficial effects expected

Only after extensive discussion with parents

Criteria under evaluation by European expert panel (EPoC)

Switching to Second-Generation ERT:

- No stabilization/improvement in skeletal muscle and/or respiratory function after ≥ 1 year on first-generation ERT

Severe infusion-associated reactions that cannot be managed

Dose

Adjustment:

Increasing dose or switching may be considered if muscle weakness and/or breathing has not stabilized/improved

Baseline & Follow-Up Assessments in IOPD

Before Starting Treatment:

- Medical history, medications
- Laboratory tests (urine, blood) — baseline
 - CRIM status
- Antibody status (baseline)

During First Year of ERT:

Close monitoring — frequency depends on needs

After 1 Year:

At least **annual** specialist centre visits

Domain	Tests
Hearing	Otoacoustic emissions, tympanometry, ABR/BAEP
Lung	Polysomnography, pulse oximetry, FVC sitting/supine
Heart	Chest X-ray, ECG, ECHO, 24-h Holter, blood pressure
Swallowing	Video fluoroscopy

Cardiac:

- Avoid **digoxin or inotropes** initially (may worsen LV outflow)
- ACE inhibitors, calcium antagonists, beta-blockers — with caution, by pediatric cardiologist

Respiratory:

- Oxygen supplementation and/or **NPPV** based on abnormalities
- FVC <40% → refer to home ventilation team
- Airway secretion clearance routines

merging Therapeutic Approaches

Beyond ERT:

- 1. Beta-2 adrenergic agonists** (e.g., albuterol) — add-on therapy to enhance lysosomal uptake of rhGAA
- 2. In vivo and ex-vivo gene therapy** — under clinical development
- 3. Substrate reduction therapy** — oral small-molecule GYS1 inhibitors (muscle glycogen synthase inhibitors)
- 4. Second-generation ERTs** — avalglucosidase alfa, cipaglucosidase alfa (enriched M6P, improved muscle targeting)