An Emerging Approach to Managing Infant Malnutrition in the US: Real World Evidence and Case Studies

Presenter: Thomas Wallach, MD – SUNY Downstate Health Sciences University – Assistant Professor of Pediatrics

Live event date: August 1st, 2023 - *Recording on NutriciaLearningCenter.com*

Learning Objectives:

- Review newly published global consensus paper on Catch up growth in infants and young children with faltering Growth
- Review real-world evidence from an ENDF early experience program
- Discuss case studies using an Energy and Nutrient Dense Formula (ENDF) in clinical practice

Notes:

Nutricia North America supports the use of breast milk wherever possible.

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An Emerging Approach to Managing Infant Malnutrition in the US: Real World Evidence and Case Studies

Thomas Wallach MD
SUNY Downstate Health Sciences University – Assistant Professor of Pediatrics

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Disclosures- Dr. Thomas Wallach

- Nutricia Early Experience Program Contributor
- Nutricia Speaker
- Advisory Board – Kiwi Biosciences
- PI – IBS trial – Ardelyx Pharmaceuticals
- ***None pose any conflict of interest for this presentation***

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

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We are not all the same size.

For example, I'm the very large guy at a festival in Vietnam in 2011.

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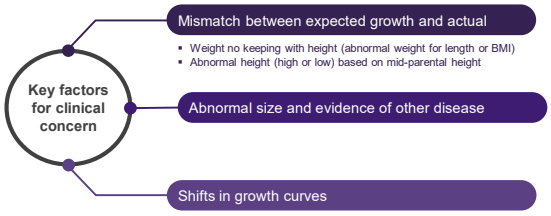
When does that matter?

There are a wide range of perfectly normal sizes in humanity.



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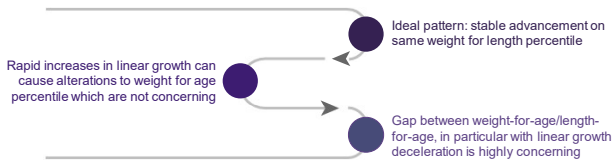
Percentile Determinism

The best type of growth trajectory does not believe in changing direction.



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Failure to Thrive (FTT)

- Commonly used term with a lot of possible meanings
- Most common:
  - Weight-for-length <5th percentile
  - BMI <5th percentile
  - Alteration of growth velocity downward by >2 major percentile markers
- While the ICD10 still likes it as a search term, not a great clinical term

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Recent Global Consensus Statement

Catch-up Growth in Infants & young children with Faltering Growth: Expert Opinion to Guide General Clinicians
Cooke R, Goulet O, Huysentruyt K, Joosten K, Khadilkar AV, Mao M, Meyer R, Prentice AM, Singhal A.
J Pediatr Gastroenterol Nutr. 2023.

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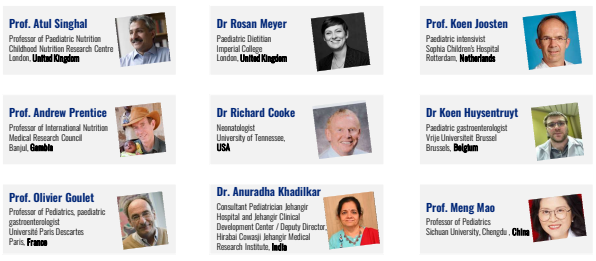
Global representation from Europe, Americas, India, Africa & Asia



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Agreed Statement:

"Growth faltering is a fall in weight for age Z-score of ≥1.0 that occurs over a period of one month or more and does not include the first 2 weeks after birth"

Cooke R, Goulet O, Huysentruyt K, et al. Catch-up Growth in Infants and Young Children with Faltering Growth: Expert Opinion to Guide General Clinicians [published online ahead of print, 2023 Mar 28]. *J Pediatr Gastroenterol Nutr*. 2023;10.1097/MPG.0000000000003784. doi:10.1097/MPG.0000000000003784

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Growth Faltering

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Primarily occurs in the first 2 years of life

Does not demonstrate durable complications if remediated by 2 years of age

Cooke et al, *JPGN*, 2023

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Impact of Growth Faltering

- Impaired linear growth
- Impaired educational and cognitive outcomes
- Decreased socioeconomic success

Mehta et al. *Journal of Parenteral and Enteral Nutrition*, 2013.

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Agreed Statement:

"Faltering growth in low- and middle-income countries (LMICs) commonly occurs together with numerous health and social outcomes, including poor brain development and delayed cognitive performance; delayed attainment of milestones; greater susceptibility to some infections; higher overall and disease-specific mortality in childhood; lower physical work capacity in adulthood; poorer earnings; and diminished human capital."

Cooke R, Goulet O, Huysentruyt K, et al. Catch-up Growth in Infants and Young Children with Faltering Growth: Expert Opinion to Guide General Clinicians [published online ahead of print, 2023 Mar 28]. *J Pediatr Gastroenterol Nutr*. 2023;10.1097/MPG.0000000000003784. doi:10.1097/MPG.0000000000003784

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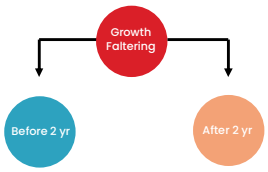
Growth Faltering is Time Sensitive



Alderman et al, *PLoS One*, 2018

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Causes of Growth Faltering

1. Inadequate caloric intake — Non-ORGANIC
2. Excess energy requirements — ORGANIC
3. Impaired absorption — ORGANIC

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What's the most common cause of growth faltering?

A. Inadequate Intake

B. Impaired Absorption

C. Excess Energy Needs

D. All of the above

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Inadequate caloric intake

~80-95% of all growth faltering in the US is secondary to inadequate intake as the primary cause

(Peppers are not an amazing source of calories little guy.)

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Agreed Statement:

"For most children with faltering growth the primary cause is nutritional."

Cooke R, Goulet O, Huysentruyt K, et al. Catch-up Growth in Infants and Young Children with Faltering Growth: Expert Opinion to Guide General Clinicians [published online ahead of print, 2023 Mar 28]. *J Pediatr Gastroenterol Nutr*. 2023;10.1097/MPG.0000000000003784. doi:10.1097/MPG.0000000000003784

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But why?

In pictures: a non-exhaustive list of many things toddlers would rather do than sit and eat

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Other risk factors for poor caloric intake

- Restrictive diets:
  - Vegetarian/Vegan
  - Elimination diets (gluten, dairy, EoE, etc.)
  - Religious restrictions
- Reflux
  - Patients with severe reflux (or parental adaptations to reflux limiting intake

(Schurmann et al, *European Journal of Nutrition*, 2017)

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Other risk factors for poor caloric intake

- Socioeconomic:
  - Some studies associate income strata with risk of faltered growth
  - Low caregiver education level and low socioeconomic status associated with increased mixing errors
    - Formula packaging reading level is 9th grade to college level (Wallace et al, Maternal and Child Health, 2015)

(Altazan et al, *Pediatric Obesity*, 2019), (Kachi et al, *Frontiers in Pediatrics*, 2018), (Ellison et al, *Journal of Nutritional Educational Behavior*, 2017)

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Formula Mixing

Minimally studied, but evidence shows prevalence of over and under concentration:

Observational studies have shown high rates of errors and absent education

- 77% of parents did not receive instructions on mixing or storage
- 30% did not read instructions themselves
- Reading level well above 4-6th grade recommendations

Labiner-Wolfe et al, *Pediatrics*, 2008

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Agreed Statement:

"Nutritional management of faltering growth should consider the cause of the growth faltering and intervention should be tailored towards the underlying problem"

Cooke R, Goulet O, Huysentruyt K, et al. Catch-up Growth in Infants and Young Children with Faltering Growth: Expert Opinion to Guide General Clinicians [published online ahead of print, 2023 Mar 28]. *J Pediatr Gastroenterol Nutr*. 2023;10.1097/MPG.0000000000003784. doi:10.1097/MPG.0000000000003784

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Diagnosis

History History History
History History History
History History History

Lezo et al, *Nutrients*, 2020

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Diagnosis

Less than 1% of lab evaluations in growth faltering generate diagnostic utility

Should only perform if major concerning symptoms:
- severe watery diarrhea,
- respiratory/neurologic/cardiac disease etc)

Labs for micronutrient deficiencies can be indicated in more significant cases/older children (not for diagnosis)

Lezo et al, *Nutrients*, 2020

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Basic evaluation approach

If needed, go by history

Feeding Intolerance
Consider cardiac eval, metabolic eval

Abnormal Linear Growth
Consider endocrine referral, TSH/T4

Malabsorption
Stool PH, reducing substance, elastase.

Abnormal features
Consider genetic referral

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Basic evaluation approach

If not improving with appropriate care….

- Consider inpatient hospitalization and monitored feeding
- SLP eval

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Organic Management Approach

1. Fix the problem (if possible)
2. Increase calories to meet needs
   - If unable to tolerate oral feeding, consider gastrostomy
3. TPN if unable to tolerate PO

ORGANIC

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Non-Organic Management Approach

1. Infant < 1 year of age
   - Review formula mixing, ensure adequate intake
   - Increase formula caloric density
   - Consider ready to feed liquid
   - If reflux, smaller more frequent feeds
2. Toddler > 1 year of age
   - Consider addition of supplemental formula
   - Calorie dense foods (oil, butter, cheese, etc)
   - Consider addition of periactin

Non-ORGANIC

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Biggest Hurdles for Littlest People

Big Hurdles!

Infant

- Poor tolerance of increased feeding volume → increase formula density
- Reflux
  - Smaller more frequent feedings
  - Formula thickening agents

Toddler

- Low appetite → consider periactin
- Restrictive feeding patterns
- Consider supplementary formula
- Referral to feeding therapy

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Caloric supplementation

- Key to maintain protein:energy ratio
  - Per WHO guidelines: 9-12% of energy from protein for catch up growth
- Addition of fat/carbohydrate along is suboptimal
  - Impacts ratio of lean:fat mass in catch up growth
  - Increases osmolar concentration of feeds

World Health Organization/Food and Agriculture Organization of the United Nations, 2007

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Agreed Statement:

"In formula fed infants ready to use energy dense therapeutic feeds with proven efficacy should be used, where available; if these are not available suitable locally available powdered feeds can be used, applying WHO hygiene safety for mixing.

Modular additions of only fat and carbohydrates to feed and food should be avoided, as this reduces the protein energy ratio"

Cooke R, Goulet O, Huysentruyt K, et al. Catch-up Growth in Infants and Young Children with Faltering Growth: Expert Opinion to Guide General Clinicians [published online ahead of print, 2023 Mar 28]. *J Pediatr Gastroenterol Nutr*. 2023;10.1097/MPG.0000000000003784. doi:10.1097/MPG.0000000000003784

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Catch-up Growth

Definition: Increased growth velocity following recovery from caloric restriction.

- Expected to see increased growth velocity during recovery from growth faltering
- Should slow at original weight for age Z-score (if available)

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Catch up vs. Accelerated Growth

Recent focus on obesity → concern for incidence of accelerated growth with growth faltering

- A: Accelerated growth: Upward-centile crossing for weight for age w/o preceding faltering
- B: Associated with increased risk of obesity and metabolic syndrome

Necessary to be cognizant of overcorrection, but these are different phenomena and rapid weight gain in growth faltering (catch up growth) is not concerning

Druet et al. *Paediatric Perinatal Epidemiology*, 2012

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Agreed Statement:

"**Catch up growth** is increased growth velocity following recovery from illness or starvation. It is a physiologic increase in weight ZS after a period of 'growth faltering', ideally to original weight ZS.

Accelerated or **Rapid growth** is upward crossing of centiles in weight or length (e.g. an increase in weight ZS of ≥ 1.0) the is not preceded by growth faltering. It can occur both spontaneously (e.g. in infants born SGA) and can be promoted (e.g. as a consequence of overfeeding or formula-feeding compared to breast-feeding)."

Cooke R, Goulet O, Huysentruyt K, et al. Catch-up Growth in Infants and Young Children with Faltering Growth: Expert Opinion to Guide General Clinicians [published online ahead of print, 2023 Mar 28]. *J Pediatr Gastroenterol Nutr*. 2023;10.1097/MPG.0000000000003784. doi:10.1097/MPG.0000000000003784

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Formula Composition

Standard infant formula: 20 kcal/oz (matches human breast milk roughly)

Enriching caloric density classically meant more dense mixture of powder

Osmotic cap: exceeding 400 mOsm/L (~450 mOsm/kg) creates a hard limit on formula enrichment (~27 kcal/oz)

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ENDF Formula

Energy and Nutrition Dense Formulas

- Nutritionally complete infant formula at 30 kcal/oz

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ENDF Formula

Energy and Nutrition Dense Formulas

- Nutritionally complete infant formula at 30 kcal/oz
- Appropriate protein:energy ratio

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ENDF Formula

Energy and Nutrition Dense Formulas

- Nutritionally complete infant formula at 30 kcal/oz
- Appropriate protein:energy ratio
- Tolerable osmolarity (<400) achieved typically with polymeric linkage of core nutritional components (glucose, etc)

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ENDF Formula

Energy and Nutrition Dense Formulas

- Nutritionally complete infant formula at 30 kcal/oz
- Appropriate protein:energy ratio
- Tolerable osmolarity (<400) achieved typically with polymeric linkage of core nutritional components (glucose, etc)
  - Lowers osmolarity without making digestion more challenging

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Are you familiar with an ENDF?

A. Yes, very familiar and have used an ENDF

B. Yes, very familiar but have NOT used an ENDF

C. I have heard of ENDF

D. No, I am not familiar with ENDF

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ENDF Formula Supplementation

Real World Experience

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Early Experience Program

Multicenter Program: 4-week observation
- Institutions: n=19
- Healthcare Providers (HCP): n=22

Inclusion Criteria for Infants: n=73
- Term infants
- 0-18 months of age
- Weight up to 9kg
- With or at risk of poor growth, increased energy requirements, and/or fluid restrictions

Data Collection:
- Pre-survey: HCP
- Post-survey: HCP & Caregiver

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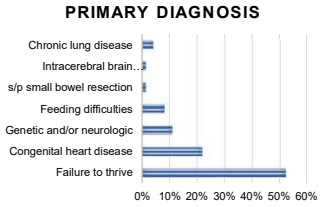
Early Experience Program



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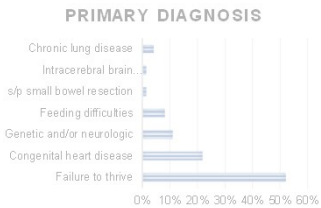
Early Experience Program



Additional reported indications for ENDF:
- Increased energy needs (27.4%)
- Risk of poor growth (8.2%)
- Fluid restrictions (5.5%)

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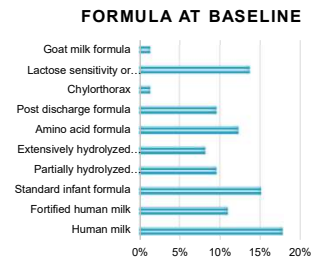
Early Experience Program



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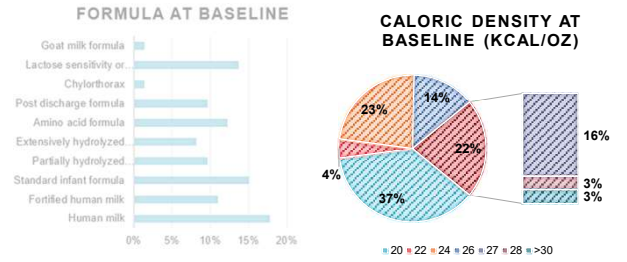
Early Experience Program



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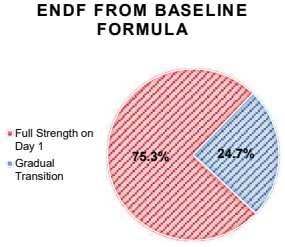
Early Experience Program



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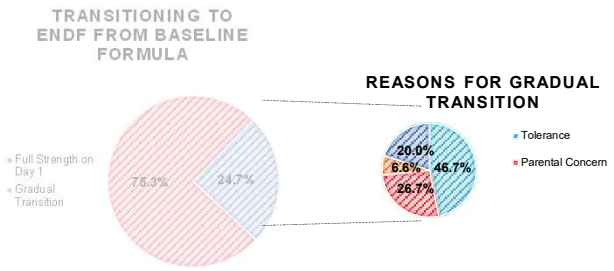
Early Experience Program



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Early Experience Program

1. **ENDF can be used as a short-term intervention**: 10% of infants discontinued ENDF early as achieved growth goals
2. **ENDF was well tolerated**: <7% of infants discontinued ENDF due to poor tolerance, AND among infants on a wide range formula prior to transitioning to ENDF
3. **HCPs recommended initiated ENDF at full strength**: gradual transition was recommended if infants had a history of poor tolerance or were <12 weeks of age

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Growth Faltering and ENDF: Case Studies

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Case 1

- 10-month-old female, full term, presents to your office for failure to thrive
  - Taking 110 kcal/kg daily of formula alone (standard 20 kcal, powder)
  - Eating solids, appropriate for age
  - Normal stools, ROS negative
- On Exam:
  - Well appearing but small for age
  - Weight <3rd percentile
  - Weight for length <3rd percentile

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Case 1 - Continued

What do you want to know?

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Case 1

Further history elicited family using inaccurate mixing ratio, resulted in highly dilute formula

- Plan?

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Case 1: What's your plan?

A. Keep same formula, enrich to 24 kcal/oz

B. Lab evaluation

C. Start Periactin

D. ENDF 30kcal/oz formula

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Case 1

Plan:

- Initiated on ENDF at 8 oz 3x daily. (105.8 kcal/kg/day formula alone)
- Encourage addition of more solids. Suggested formula feed to follow solids (solids increase sensation of satiety)

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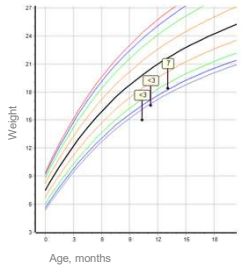
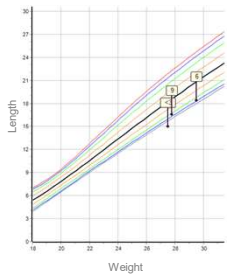
Case 1





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Case 2

7 mo M born to recent immigrant parents w/ known genetic abnormality c/w possible Russel-Silver Syndrome

- Referred for growth failure

History

- Initially breastfed → Formula at 5 months
- Taking 3.5 oz 5x daily of 27 kcal/oz formula and pureed baby foods BID
- Exam c/s RS syndrome, abnormal facies, small for age
- Inappropriately low fat deposition for age

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Case 2: How do I know if a child with a genetic abnormality has growth faltering?

A. Assess weight for length and weight trajectory

B. Determine if disease specific growth chart exists

C. Review OMIM entry

D. All of the above

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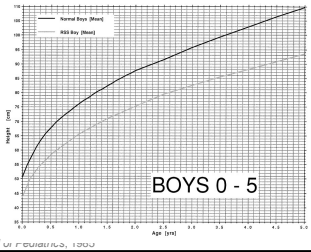
Case 2: Russel Silver Growth Chart

1 publication assessing height (not weight)



Wollmann et al, *European Journal of Pediatrics*, 1993

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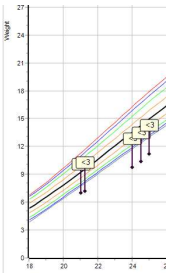
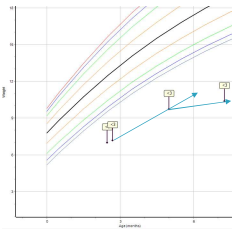
Case 2: Weight for Length/Trajectory

- Length consistent w/ published growth chart data
- WFL low
- Weight trajectory slowed





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Case 2: Russell-Silver

Russel-Silver: (AKA Silver-Russell depending if you are asking Russell or Silver)

- Clinically heterogenous condition characterized by IUGR (often severe), poor growth (sparing head growth mainly), abnormal craniofacial features, broad forehead, and body asymmetry.
- No association with malabsorption, and should not have significant increased energy needs

So… is this young man having growth faltering and caloric undersupply, or is he just genetically small?

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Case 2: Can't it be both?

Russel-Silver: (AKA Silver-Russell depending if you are asking Russell or Silver)

- Expected to have poor growth
- Standard weight charts are not available, disconnect between height trajectory and weight trajectory, as well as delta of weight trajectory, highly suggest a component of growth faltering.

It helps to note he was only gaining 5 g/day

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Case 2: Management

- Initial intake:
  - Only 87 kcal/kg/day
- Recommendations:
  - Increase of feeding on 27 kcal formula (15 to 22 oz) for total 128 kcal/kg/day to incorporate catch up (~50% increase in calories)

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Case 2: Management

- At follow up 4 weeks later:
  - 107 kcal/kg/d
  - Gaining 18 g/day
- Recommendations:
  - Increased feedings to 25 oz daily → 133 kcal/kg/d

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Case 2: Management

- At next f/u- 10 months old:
  - Despite:
    - increased calories (124 kcal/kg/day formula alone)
    - increased solid PO intake
    - only gaining 6 g/day.
  - Strong concerns about mixing.
- Recommendations:
  - Decision made to convert to 30 kcal/oz RTF ENDF at same volume. (138 kcal/kg/day)

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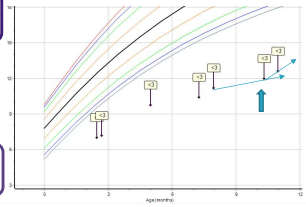
Case 2: Outcome

At next visit:

- Weight gain improved, markedly → 16 g/d
- Remained inadequate for catch up
- Reflects likely component of mixing issues, as weight gain inc 3x with a 10% increase in nominal intake



Converted to toddler formula (30 kcal/oz

- Ultimately required conversion to 1.5 strength formula and periactin initiated to support solid PO intake

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In Summary…

1. Managing infants with growth faltering is challenging, and has consequences if it is not addressed in a timely manner
2. Addressing and correcting growth faltering includes adequate history, diagnosis, and nutrition management with the correct balance of macro and micronutrients
3. An ENDF provides the correct macro- and micro- nutrient content to manage term infants with growth failure
4. ENDF has been successfully used across the United States to manage infants with growth faltering

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