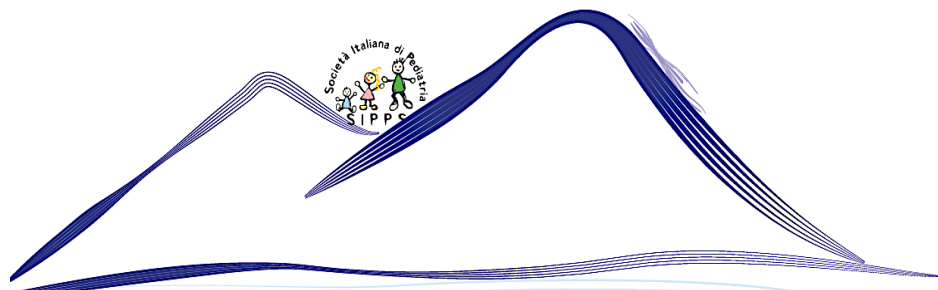


Napule è...

PEDIATRIA PREVENTIVA E SOCIALE



SOCIETÀ
AFFILIATA ALLA SIP



LUCI OMBRE ABBAGLI

Prevenzione

Allergologia

Gastroenterologia

Nutrizione

Dermatologia

***“Il rigurgito tra l’allergia e il reflusso,
il ruolo dei latti speciali”***

Salvatore Cucchiara

**Unità Complessa di Gastroenterologia e Epatologia Pediatrica
Sapienza - Policlinico Universitario Umberto I**



SAPIENZA
UNIVERSITÀ DI ROMA



Background

- **INFANTILE REGURGITATION**: does not require drug treatment but only parenteral reassurance and dietary management.
- **THICKENED FORMULAS**: indicated in infants formula-fed and with persistent regurgitation and poor weight gain or marked distress
- **DIFFERENT ANTI-REGURGITATION FORMULAS** (AR-F)
AVAILABLE ON THE MARKET

Thickened infant formula: What to know



❖ **CLINICAL EFFICACY RELATED TO THE CHARACTERISTICS OF THE FORMULA AND OF THE INFANT.**

➤ **COMMERCIAL THICKENED FORMULAS PREFERRED OVER THE SUPPLEMENTATION OF STANDARD FORMULAS WITH THICKENER (BETTER VISCOSITY, DIGESTIBILITY, AND NUTRITIONAL BALANCE).**

✓ **RICE AND CORN STARCH, CAROB BEAN GUM, AND SOY BEAN POLYSACCHARIDES AS THICKENING AGENTS.**

Thickened infant formula: What to know



THICKENED FORMULAS REDUCE THE FREQUENCY AND SEVERITY OF REGURGITATION AND ARE INDICATED IN FORMULA-FED INFANTS WITH PERSISTING SYMPTOMS DESPITE REASSURANCE AND APPROPRIATE FEEDING VOLUME INTAKE

VISCOSITY AND DIGESTIBILITY OF ANTIREGURGITATION FORMULAS

- WHEAT, TAPIOCA, CORN, RICE, OR POTATO STARCH
 - Precooked or gelatinized starches added to the formula up to **2 g/100 ml**

Remarks:

- *wheat, tapioca, corn, rice, or potato starch that is cooked for 10 min in water are all digested and efficiently (>98%) absorbed when the concentration is 1.6 g to 1.9 g/100 mL at 1 mo and 3.1 g to 3.5 g/100 mL at 3 mo of age. However, at 5 g to 6 g/100 mL, fermentative diarrhea has been reported in 2 of 5 infants who were tested*
- LOCUST BEAN GUM (FARINA SEMI DI CARRUBA)
 - From the endosperm seed of the locust/carob tree of the plant family of leguminosae (high molecular weight polysaccharides of which at least 75% are galactomannans). Resistant to human digestive enzymes and excreted unchanged in the feces or fermented by the gut microbiota.

HOME THICKENING COMPARED WITH ANTIREGURGITATION FORMULAS

- **MODERN COMMERCIAL AR-F:** controlled composition with thickening components (< 2 gr/100ml for starch; carob bean gum usually between 3 and 4 gr/100 gr of formula), caloric content similar to SF.
- **HOME-BREWED THICKENED STANDARD FORMULAS (SF)**, due to higher (1.5-2 times) cost of AR-F: effects of home-thickened feeding may differ from AR-F due to a heterogeneous composition (the added starch can be above the regulatory limit for starch)
- *In a prospective, case-controlled study (100 infants), regurgitation disappeared after 3 month in a slightly higher % of infants (52% vs 40%) fed AR-F vs homemade.*

CLINICAL EFFECTS OF ANTIREGURGITATION FORMULAS

GASTRIC EMPTYING

- *Thickening agents may delay gastric emptying, potentially worsening postprandial GER and symptoms, but its effect depends on viscosity and concentration as well as protein content.*
- *Several RCTs demonstrated an accelerated gastric emptying after feeding infants with partial HF and extensive HF with a combination of thickeners*

REGURGITATION

- *Several RCTs have reported a reduction in the daily number of episodes of regurgitation per day in infants who were fed rice, corn, and locust bean gum AR-F.*
- *No particular thickened AR-F decreased was shown to be more effective than another.*

CHARACTERISTICS AND EFFECTS OF DIFFERENT THICKENERS

THICKENER AGENT	viscosity	digestion	gastric emptying	regurgitation	GER/pH results
Carob/locust bean gum	↑↑	=	↓	↓	↓ n ↓ RI%
Corn starch	↑	=	=	↓	↓ all
Rice starch	↑	=	=	↓	↓ n = RI%

REGULATION AND ADVERSE EVENTS

Thickener agent	Concentration (max limit)	Adverse effect
Carob/locust bean gum	3 - 4 g/100 gr powder	Diarrhea, colics, bloating, meteorism
Corn starch	2 g/100 ml (13%)	-
Rice starch	2 g/100 ml (13%)	Cough Constipation Arsenic load

SAFETY OF THICKENERS

JPGN • Volume 66, Number 3, March 2018

Cereal based

CONCERNS ABOUT THE SAFETY OF RICE CEREAL AS A THICKENING AGENT

FOR INFANTS AND CHILDREN, (elevated levels of **inorganic arsenic** in all forms of rice including infant cereals (linked to **neurotoxicity and long-term cancer risk** in areas with environmental arsenic contamination).

USA FDA: limit of 100 parts per billion for inorganic arsenic in infant rice cereal, which corresponds to a level proposed by the European Commission for rice destined for the production of food for infants and young children.

Whenever possible, using rice cereal with low or no arsenic is recommended.

SAFETY OF THICKENERS

Commercial thickeners

The search did not identify any studies on the efficacy of thickening of **BREAST MILK**.

THICKENING OF HUMAN MILK by precooked starch in reducing GER in preterm infants: no significant reduction in the number of pH-MII detected reflux episodes with thickened feeds when compared to un-thickened feeds (Corvaglia et al.)

For babies with significant reflux, breastmilk can be thickened with xanthum gum or carob bean based thickeners (not with cereal, that is digested by the amylases in breast milk).

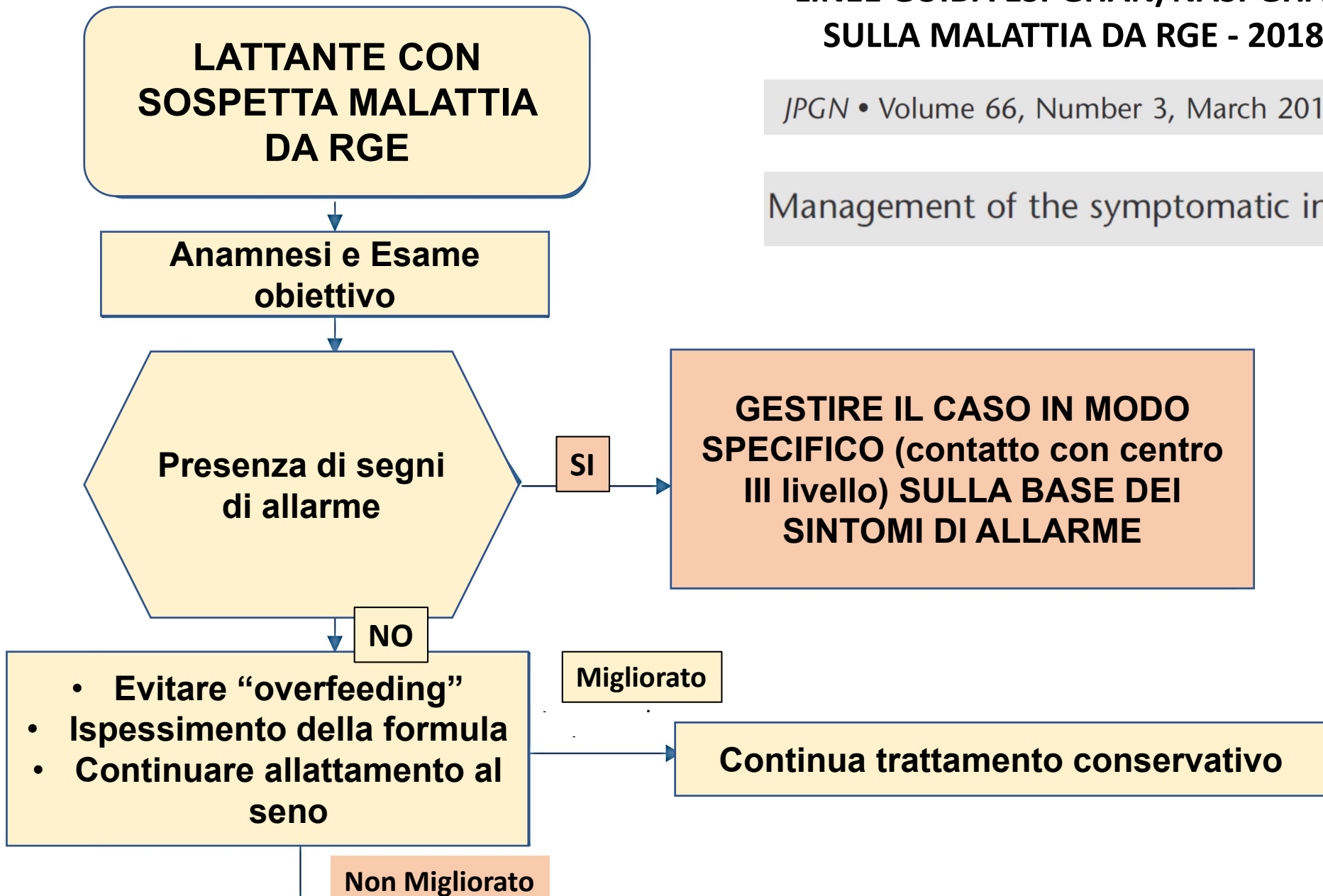
Carob bean thickeners are approved for use in infants after 42 weeks gestation.

Xanthum gum thickeners are approved for infants > 1 year old

LINEE GUIDA ESPGHAN/NASPGHAN SULLA MALATTIA DA RGE - 2018

JPGN • Volume 66, Number 3, March 2018

Management of the symptomatic infant.



segue...

LINEE GUIDA ESPGHAN/NASPGHAN SULLA MALATTIA DA RGE - 2018

JPGN • Volume 66, Number 3, March 2018

segue....

Non Migliorato

Migliorato

Considera 2-4 sett di idrolizzato o formula aminoacidica o, negli allattati al seno, eliminazione di PLV dalla dieta materna

Continua trattamento e programma reintroduzione delle PLV

Non Migliorato

Non possibile

Fai riferimento ad un gastroenterologo pediatrico (centro III livello)

Considera trial di 4-8 settimane con un acido-soppressore, poi sospendi se i sintomi migliorano

Invio al centro

I sintomi non migliorano o recidivano

Considera la diagnosi differenziale, i test diagnostici i e/o trial terapeutici di breve durata

Miglioramento stabile

Nessun ulteriore trattamento

Recommendations:

4.1 The working group suggests to use thickened feed for treating visible regurgitation/vomiting in infants with GERD (Algorithm 1).

Voting: 6, 7, 7, 8, 8, 8, 9, 9, 9, 9. (weak recommendation)

4.2 Based on expert opinion, the working group suggests to modify feeding volumes and frequency according to age and weight to avoid overfeeding in infants with GERD (Algorithm 1).

Voting: 7, 7, 8, 8, 8, 8, 8, 9, 9, 9. (weak recommendation)

4.3 Based on expert opinion, the working group suggests a 2 to 4 week trial of formula with extensively hydrolyzed protein (or amino-acid based formula) in formula fed infants suspected of GERD after optimal non-pharmacological treatment has failed (Algorithm 1, or see ESPGHAN 2012 CMPA guidelines).

Voting: 4, 6, 7, 8, 8, 8, 8, 9, 9, 9. (weak recommendation)

- **THICKENERS MAY IMPROVE SLIGHTLY OVERT REGURGITATION/VOMITING AS SYMPTOMS OF GER IN INFANTS. *It is uncertain whether food thickeners improves other signs of GER and whether their use leads to side effects***
- **NO EVIDENCE SUPPORTING MODIFICATION OF FEEDING VOLUMES OR INTERVALS**
- ***NO EVIDENCE TO SUPPORT EXTENSIVELY HYDROLYZED FORMULA (EHF) OR AMINO ACID–BASED (AAF) FORMULA FOR THE TREATMENT OF GERD IN INFANTS AND CHILDREN WHO DO NOT HAVE CMPA***
- **EHF OR AAF INDICATED IN PATIENTS WHO HAVE NOT RESPONDED TO CONVENTIONAL GERD THERAPIES.**

CONCLUSIONS

- *The approach for regurgitating infants consists of parental reassurance and education about position and feeding.*
- *AR-F reduced regurgitation with an effect depending on the thickening agent, concentration, protein ratio, and hydrolysis.*
- *Although locust bean gum increases viscosity more than other thickening agents, there is no evidence that one thickener is clinically better than another.*
- *AR-F offers the advantage of a balanced composition, controlled viscosity, and calories compared with the addition of thickening agents to a SF.*
- *Recent data suggest that thickened HF may also reduce regurgitation and accelerate gastric emptying.*



CMA
COW'S MILK ALLERGY

GENERAL CHARACTERISTICS OF INFANT FORMULAS FOR CMA

ENERGY	Similar to human milk (HM)
PROTEINS	Within normal recommended ranges, but CMP are hydrolysates, or whole proteins different than human milk proteins; some supplemented with lysine, threonine or tryptophan
FATS	Only 15 % have α-linolenic acid in similar amounts than HM; 31 % have more linoleic acid than HM; 46 % do not include DHA
CARBOHYDRATES	70 % of special formulae are without lactose; all have a content of carbohydrates higher than HM

GENERAL CHARACTERISTICS OF INFANT FORMULAS FOR CMA

MICRONUTRIENTS	Fe \leq than in HM (risk of iron-deficiency). Content of other minerals should be reviewed considering other factors.
VITAMINS A, E, D	Need to be reviewed the doses depending on other factors (<i>>25 % of children consumed <2/3 of the RDI of Ca, Vitamins D and E</i>).
NUCLEOTIDES	77 % have nucleotides
CHOLINE	Big variability in choline levels between different formulae.
TAURINE	92 % have taurine
CARNITINE	92 % have carnitine
PREBIOTICS	15 % include FOS/GOS
PROBIOTICS	8 % include probiotics

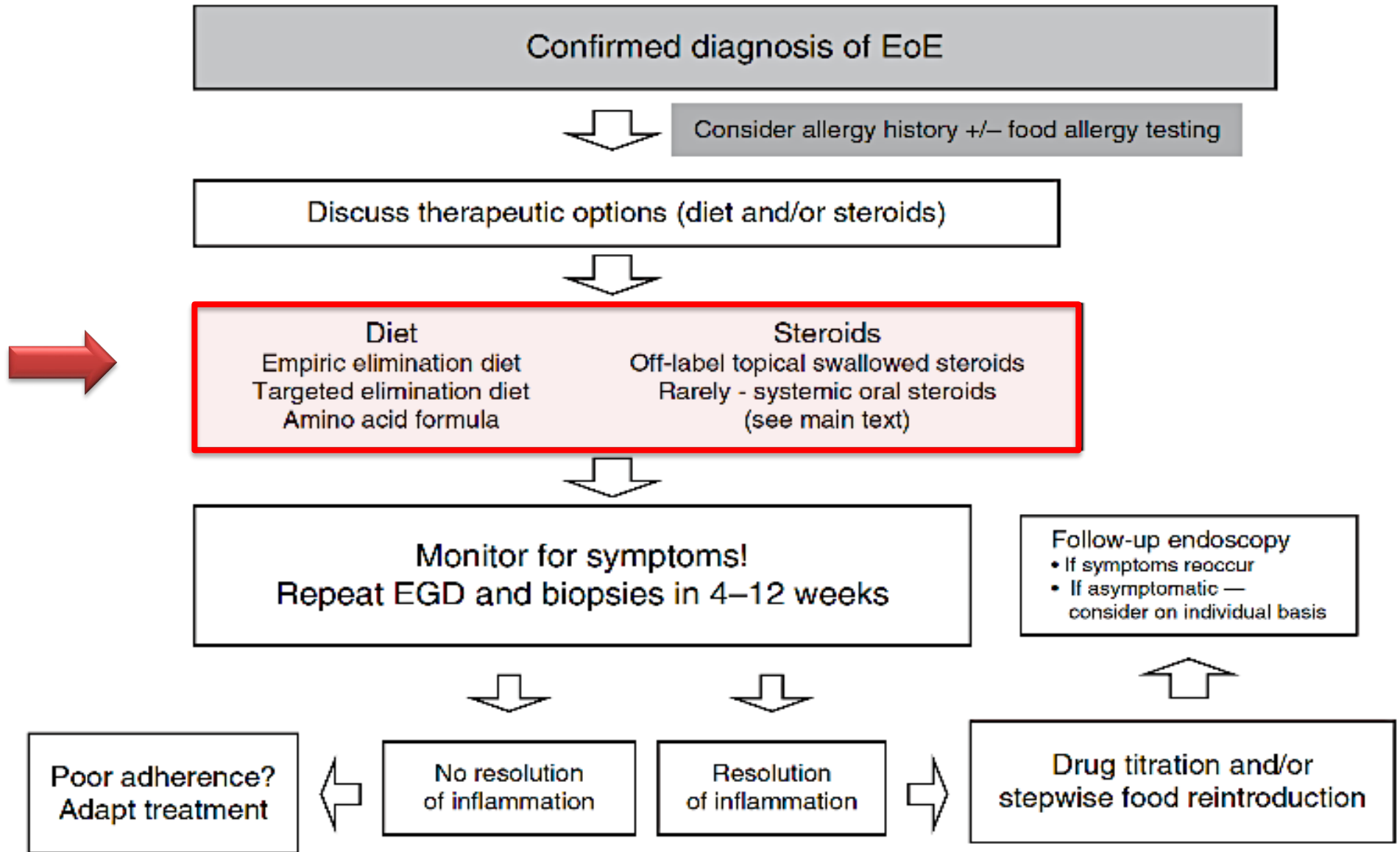
Choosing the appropriate substitute formula in different presentations (original source: DRACMA guidelines)

Clinical presentation	1st choice	2nd choice	3rd choice
Anaphylaxis	AAF ^a	eHF ^{e, d}	SF
Immediate gastrointestinal allergy	eHF ^{d, b}	AAF ^f /SF ^g	
Food protein-induced enterocolitis syndrome (FPIES)	AAF	eHF ^c	
Asthma and rhinitis	eHF ^{d, b}	AAF ^f /SF ^g	
Acute urticaria or angioedema	eHF ^{d, b}	AAF ^f /SF ^g	
Atopic dermatitis	eHF ^{d, b}	AAF ^f /SF ^g	
Gastroesophageal reflux disease (GERD)	eHF ^b	AAF	
Allergic eosinophilic oesophagitis	AAF		
Cow's milk protein-induced enteropathy	eHF ^{d, b}	AAF	
Constipation	eHF ^b	AAF	Donkey milk ⁱ
Severe irritability (colic)	eHF ^b	AAF	
CM protein-induced gastroenteritis and proctocolitis	eHF ^b	AAF	
Milk-induced chronic pulmonary disease (Heiner's syndrome)	AAF ^f	SF	eHF

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Therapeutic Algorithm of EoE



Terapia personalizzata EoE

	Dieta elementare	Dieta empirica dei 6 alimenti	Dieta guidata da SPT & APT	Steroidi topici
Guarigione mucosale	> 98%	70-80%	77% solo in bambini	50-87%
Effetti collaterali (medici)	Nessuno	Nessuno	Nessuno	Scarsi
Possibili deficit nutrizionali	Nessuno	Possibili	Possibili	Assenti
Effetti collaterali (psicosociali)	Non evidenti	Notevoli	Variabili	Bassi
Accettabilità	Scarsa	Scarsa	Moderata	Alta
Costi	Alti	Moderati	Moderati	Bassi

1. Forme severe
 2. Bambino piccolo
 (steroidi nebulizzato ?? Esigenze nutrizionali specifiche)
 1. Malnutrizione
 (svantaggiose le diete di eliminazione)

1. Tutte le forme
 2. Bambino grande (steroidi nebulizzato)
 3. Tutte le età nella forma viscosa
 4. Indipendentemente dallo stato di nutrizione

1. Forme moderate
 2. Bambino piccolo
 (difficile uso steroidi spray)
 1. Buono stato nutrizionale
 (coinvolgendo un nutrizionista)

EXTENSIVE HYDROLYZED FORMULAE (eHF)

DEPENDING ON THE MANUFACTURER, THE SIZE OF THE PEPTIDES VARIES.

According to ESPHGAN, to meet the definition of eHF a product has not only to prove DBPCFC-negative in a proportion of CMA children greater than 90 % but it is also required that:

- 1) ALL PEPTIDES HAVE A MW LOWER THAN 5000 DA
- 2) A HIGH PROPORTION OF THEM MUST HAVE A MW EVEN LOWER
- 3) FORMULA UNCONTAMINATED WITH NATIVE WHOLE PROTEINS

EXTENSIVE HYDROLYZED FORMULAE

CRITICAL REMARKS:

IS A MW <5000 DA A SUFFICIENT WARRANTY OF NON-EXPOSURE TO COW'S MILK PROTEINS?

Peptides with 25 AAs can contain ***two sequential epitopes***, and peptides with only 10 AAs can include ***one sequential epitope*** - A 1500 Da peptide may contain 11 amino acids, a 3000 Da peptide 22 and a 5000 Da peptide may contain 36 amino acids.

Peptides with a MW between 3000 and 5000 Da could possibly carry two sequential epitopes, whereas peptides with a MW of 1500 Da could contain one sequential epitope.

➤ ***A molecule carrying two epitopes could well determine an allergic reaction***, while smaller fragments, containing only one sequential epitope, are not able to establish a bridge between two IgE molecules, and consequently the allergic reaction would not take place.

EXTENSIVE HYDROLYZED FORMULAE

CRITICAL REMARKS:

- *Palatability*
- *Cost*
- *Higher solute renal load*
- *Possible effects of a predigested formula in inducing delay in the intestinal enzymatic maturation.*

Similar problems may arise with elemental, amino-acid based formulae.



Could a completely different protein source (soy or rice) be used ?

RICE HYDROLISED FORMULAE: a plausible alternative

- ✓ *RICE IS ONE OF THE LESS ALLERGENIC STAPLE FOODS, REACTING IN <1 % OF ALLERGIC CHILDREN.*
- ✓ *IT HAS NO LACTOSE*
- ✓ *IT HAS NO PHYTOESTROGENS.*

REMARKS:

The biological value of rice proteins naturally different from bovine proteins

3 limiting essential amino-acids do not reach the respective value contained in breastmilk (*Lysine, Threonine, Tryptophan*)

RICE HYDROLISED FORMULAE: a plausible alternative

*There is an **FDA warning** against the use of rice in infants and young children regarding rice feed thickeners and rice cereals.*

*Therefore the **ARSENIC CONTENT** in rice based infant formula should be determined and declared on the label.*

*The **ARSENIC CONTENT** in available rHF is reported to be within the safety limits.*

SOY FORMULA

- ✓ *SOY FORMULAS frequently used for economic reasons in countries with limited access to hypoallergenic formulas*
- ✓ *Current SOY FORMULAS supplemented with appropriate quantities of limiting amino acids such as **Methionine, Taurine, and Carnitine***
- ✓ *SOY FORMULAS in the treatment of infants with CMA controversial. Generally, SOY FORMULAS not recommended as a first-line treatment in infants with CMA under 6 months of age*

SOY FORMULA

- ✓ *No mental or developmental disorders have been detected among children fed with soy formulas as compared to cow's milk formulas*
- ✓ *Since the late eighties, phytates are almost totally removed from the soy formulae, resulting in substantially enhanced absorption of important micronutrients (a systematic review proved no significant differences in several biochemical parameters)*
- ✓ *Raffinose and stachyose, responsible for bacterial fermentation and secondary flatulence, are nowadays removed from soybean products.*

SOY FORMULA: potential drawbacks

- ✓ possible hormonal effects on the reproductive system presumed due to phytoestrogens in the form of isoflavones
- ✓ use of transgenic soy in formulae (*data from the US Department of Agriculture, up to 93 % of soybean crops are transgenic*): available evidence suggests no deleterious effects on the human genome



- ❖ *isoflavones have also been associated with a suppression of immune sensitization by suppressing Dendritic Cell (DC) maturation and its subsequent DC-mediated effector cell functions*

Soy protein infant formulae and follow-on formulae:
a commentary by the ESPGHAN Committee on Nutrition.

ESPGHAN Committee on Nutrition

J Pediatr Gastroenterol Nutr. 2006;42:352-61

- **Before 6 months**

- **Soy not recommended**
- Extensive protein hydrolysates recommended
- if eHF not tolerated: amino-acid based formula

- **After 6 months**

- **Soy can be used if tolerance first established**
- benefit : acceptability, cost...



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SPECIAL FORMULAE FOR CHILDREN WITH COW'S MILK ALLERGY: NUTRITIONAL ISSUES - I

- ✓ **Are the apparently reassuring effects on growth pattern of extensively hydrolyzed formulae (eHF), rice hydrolyzed formulae (RHF), or amino acid formulae (AAF) maintained over time?**
- ✓ **Have babies fed eHF, RHF, soy formulae (SF) or AAF long-term effects on neurodevelopment similar to those breastfed?**
- ✓ **If not, which are the effects associated to eHF, RHF, SF or AAF feeding on neurodevelopment, in relation to the different protein in the infant formula composition respect to standard cow's milk infant formula?**

SPECIAL FORMULAE FOR CHILDREN WITH COW'S MILK ALLERGY: NUTRITIONAL ISSUES - II

- ✓ **How does the use eHF, RHF, SF or AAF influence the epigenetic process in the brain?**
- ✓ **How does the “brain-body loop” work in children fed with eHF, RHF, SF or AAF?**
- ✓ **Are eHF, RHF, SF or AAF modifying the development of senses?**
- ✓ **Is the gut of the baby with CMA fed with eHF, RHF, SF or AAF functioning the same?**



DESPITE THE FACT THAT FORMULAE ARE MODELED AFTER BREASTMILK, THE HUMAN MILK CONTAINS INIMITABLE MOLECULES WITH POTENTIAL IMMUNE MODULATING ACTIVITIES

- **maternal antibodies, including anti-idiotypic antibodies, able to sustain and regulate immune cell populations through a priming of fetal and neonatal cells;**
- **cytokines (TGF- β 2, IL-10, thymic stromal lymphopoietin) and chemokines, influencing the development of allergy and atopic diseases;**
- **hormones and growth factors, influencing the maturation of the infant gut and of the associated lymphoid tissues;**
- **PUFAs, nucleotides, glycoproteins, oligosaccharides and microRNA, able in turn to exert immune functions.**