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Intervenção precoce na aquisição de tolerância

Márcia Quaresma
18º Congresso SPP – 2017

Intervenção precoce na aquisição de tolerância

-  prevalência alergia alimentar (população pediátrica): 30 anos

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- Fatores: genéticos / **ambientais**

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- Fatores ambientais que atuam numa fase precoce da vida. Maior suscetibilidade imunológica

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- Alimentação – Nutrientes - Alergénios

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação

- A restrição dietética de alimentos alergénicos a mulheres de risco:
 - Contra-indicada durante a gestação: não reduz de modo significativo o risco de doença atópica e essas dietas podem alterar o estado nutricional fetal e materno
 - Durante amamentação: 1º) pensava-se que reduzia a incidência de doença atópica no lactente.
2º) a redução deve-se a menor exposição do alérgeno por via ambiental – menos alérgeno veiculado pela via transcutânea. VIA DE SENSIBILIZAÇÃO CUTÂNEA!

Flohr C *et al.* J Invest Dermatol 2014;134:345-50

Fox AT *et al.* JACI 2009;123:417-23

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação
- 2. Aleitamento materno**

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação

2. **Aleitamento materno**

- Os estudos não têm revelado de uma forma consistente um efeito protetor do aleitamento materno no desenvolvimento de atopia ou de alergia alimentar

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação
2. Aleitamento materno
3. **Fórmulas hidrolisadas**

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação

2. Aleitamento materno

3. Fórmulas hidrolisadas

- Osborn DA, Sinn J. Cochrane Database Syst Rev 2006;4:CD003664
 - Evidência limitada: lactentes de alto risco de atopia, incapazes de serem alimentados com LM exclusivo, a alimentação com fórmula hidrolisada poderia proteger contra dermatite atópica e APLV

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação

2. Aleitamento materno

3. Fórmulas hidrolisadas

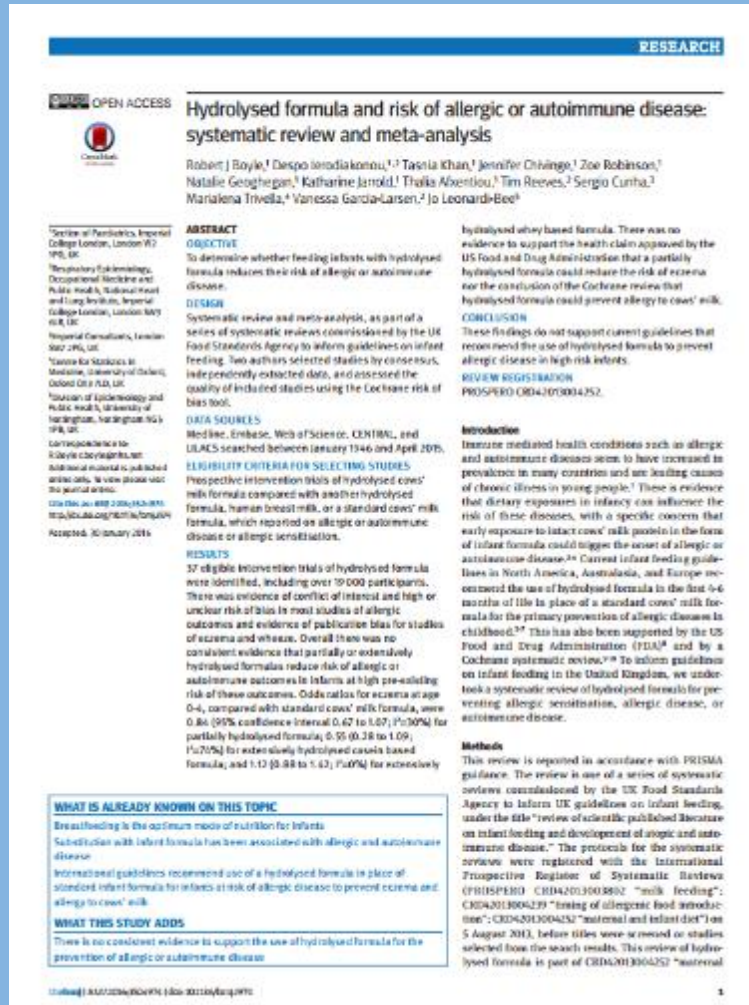
- Osborn DA, Sinn J. Cochrane Database Syst Rev 2006;4:CD003664
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- Boyle RJ *et al.* BMJ 2016; 352 doi: <https://doi.org/10.1136/bmj.i974>

Intervenção precoce na aquisição de tolerância

1. C

2. A

3. I



“(...) There was no consistente evidence that partially or extensively hydrolysed formulas reduce risk of allergic or autoimmune outcomes in infants at high pre-existing risk (...)”

“(...) There was evidence of conflict of interest and high or nuclear risk of bias in most studies of allergic outcomes and evidence of publication bias (...)”

LM exclusivo, a

These findings do not support current guidelines that recommend the use of hydrolysed formula to prevent allergic disease in high risk infants.

Intervenção precoce na aquisição de tolerância

1. Dieta materna durante gestação/amamentação
2. Aleitamento materno
3. Fórmulas hidrolisadas
4. **Diversificação alimentar**

Intervenção precoce na aquisição de tolerância

- Anos 90 do século passado: guidelines sobre diversificação alimentar de Sociedades Pediátricas, Alergológicas, Gastroenterológicas, OMS:
PROTELAR!

Intervenção precoce na aquisição de tolerância

- Anos 90 do século passado: guidelines sobre diversificação alimentar de Sociedades Pediátricas, Alergológicas, Gastroenterológicas, OMS:
PROTELAR!
- 2005: estudos observacionais

Intervenção precoce na aquisição de tolerância

- Anos 90 do século passado: guidelines sobre diversificação alimentar de Sociedades Pediátricas, Alergológicas, Gastroenterológicas, OMS:
PROTELAR!
- 2005: estudos observacionais
- 2015: estudos prospetivos e randomizados: ANTECIPAR!

LEAP	<i>Learning Early About Peanut Allergy</i>	2015	Reino Unido	Prospetivo, randomizado, aberto	Eczema moderado-grave e/ou alergia ao ovo	Amendoim, 4M-11M
EAT	<i>Enquiring About Tolerance</i>	2016	Reino Unido	Prospetivo, randomizado, aberto	população geral	logurte, amendoim, sésamo, ovo cozido, peixe, trigo, 3M
PETIT	<i>Prevention of Egg Allergy</i>	2016	Japão	Prospetivo, randomizado, duplo-cego, placebo-controlado	Eczema moderado-grave	Ovo cozido, 6M
HEAP	<i>Hens Egg Early Prevention</i>	2015	Alemanha	Prospetivo, randomizado, placebo-controlado	População geral	Ovo cru, 4M-6M
STAR	<i>Solids Timing for Allergy Research</i>	2013	Austrália	Prospetivo, randomizado, duplo-cego, placebo-controlado	Eczema moderado-grave	Ovo cru, 4M
STEP	<i>Starting Time for Egg Protein</i>	2017	Austrália	Prospetivo, randomizado, duplo-cego, placebo-controlado	Filhos de mães atópicas	Ovo cru, 4M-6M
BEAT	<i>Beating Egg Allergy</i>	2017	Austrália	Prospetivo, randomizado, duplo-cego, placebo-controlado	AF de doença atópica	Ovo cru, 4M-6M

LEAP Study (*Learning about Peanut Allergy*)

Du Toit, *et al.* N Engl J Med 2015;372:803-13

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Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H.,
Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D.,
Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D.,
Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

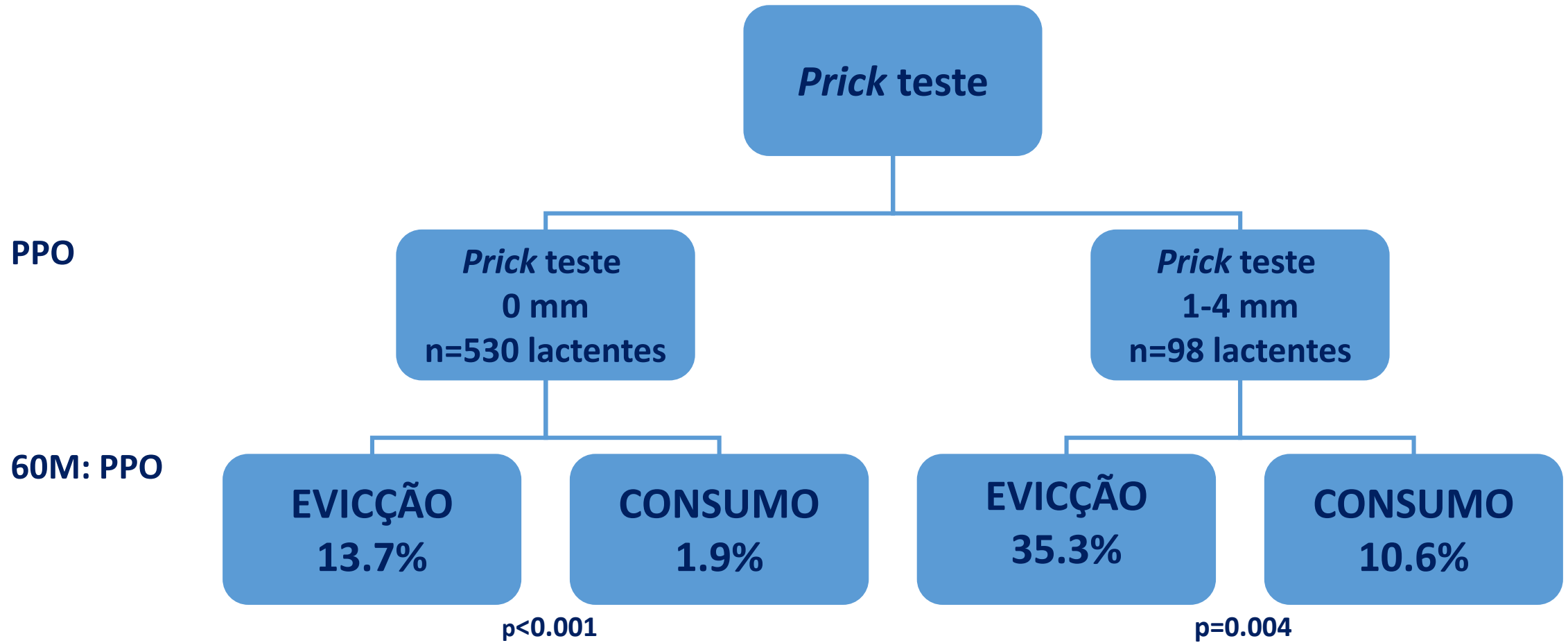
LEAP *Study*

- Prevalência alergia amendoim: duplicou países ocidentais (últimos 10 anos)
- Estudo observacional prévio sobre prevalência de alergia ao amendoim
Du Toit G. JACI 2008;122:984-91
 - Crianças judaicas residentes no Reino Unido 10x+ do que nas residentes em Israel
 - Ancestrais similares
 - Reino Unido após 12M. Israel aos 7M

LEAP *Study*

- Lactentes 4-11M com eczema grave e/ou alergia ao ovo
- 2 grupos: evicção / consumo amendoins (60M de idade)
- 6g proteína de amendoim/semana
- Objetivo: avaliar a prevalência de alergia ao amendoim aos 60M idade

LEAP Study



- Grupo evicção: ↑ IgE
- Grupo consumo: ↑ IgG4
- Sem diferenças significativas: efeitos adversos

Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants

Primary contributors: David M. Fleischer, MD,¹ Scott Sicherer, MD,² Matthew Greenhawt, MD,³ Dianne Campbell, MB BS, FRACP, PhD,⁴ Edmond Chan, MD,⁵ Antonella Muraro, MD, PhD,⁶ Susanne Halken, MD,⁶ Yitzhak Katz, MD,⁷ Motohiro Ebisawa, MD, PhD,⁸ Lawrence Eichenfield, MD,⁹ and Hugh Sampson, MD,¹⁰

For the LEAP Study Team: Gideon Lack, MB, BCh,¹⁰ George Du Toit, MB, BCh,⁶ Graham Roberts, DM,⁶ Henry Bahnson, MPH,¹¹ and Mary Feeney, MSc, RD¹⁰

Secondary contributors: Jonathan Hourihane, MD,¹ Jonathan Spergel, MD, PhD,¹ Michael Young, MD,¹ Amal As'aad, MD,³ Katrina Allen, BMedSc, MB BS, FRACP, PhD,⁴ Susan Prescott, BMedSc, MB BS, FRACP, PhD,⁴ Sandeep Kapur, MD,⁵ Hirohisa Saito, MD, PhD,⁵ Ioana Agache, MD,⁶ Cezmi A. Akdis, MD, PhD,⁶ Hasan Arshad, MD,⁶ Kirsten Beyer, MD,⁶ Anthony Dubois, MD,⁶ Philippe Eigenmann, MD,⁶ Monserrat Fernandez-Rivas, MD,⁶ Kate Grimshaw, PhD, RD, RNutr,⁶ Karin Hoffman-Sommergruber, PhD,⁶ Arne Host, MD,⁶ Susanne Lau, MD,⁶ Liam O'Mahony, MD,⁶ Clare Mills, PhD,⁶ Nikolaus Papadopoulos, MD,⁶ Carina Venter, BSc, PhD,⁶ Nancy Agmon-Levin, MD,⁷ Aaron Kessel, MD,⁷ Richard Antaya, MD,⁹ Beth Drolet, MD,⁹ and Lanny Rosenwasser, MD¹⁰

The purpose of this brief communication is to highlight emerging evidence to existing guidelines regarding potential benefits of supporting early, rather than delayed, peanut introduction during the period of complementary food introduction in infants. This document should be considered as interim guidance based on consensus among the following organizations: American Academy of Allergy, Asthma & Immunology, American Academy of Pediatrics, American

College of Allergy, Asthma & Immunology, Australasian Society of Clinical Immunology and Allergy, Canadian Society of Allergy and Clinical Immunology, European Academy of Allergy and Clinical Immunology, Israel Association of Allergy and Clinical Immunology, Japanese Society for Allergology, Society for Pediatric Dermatology, and World Allergy Organization. More formal guidelines regarding early-life, complementary feeding practices and the risk of allergy development will follow in the next year from the National Institute of Allergy and Infectious Diseases-sponsored Working Group and the European Academy of Allergy and Clinical Immunology. (J Allergy Clin Immunol 2015;136:258-61.)

Key words: Allergy prevention, complementary feeding, peanut allergy

Discuss this article on the JACI Journal Club blog: www.jaci-online.blogspot.com.

INTRODUCTION AND RATIONALE

Peanut allergy is an increasingly troubling global health problem affecting between 1% and 3% of children in many westernized countries. Although multiple methods of measurement have been used and specific estimates differ, there appears to have been a sudden increase in the number of cases in the past 10- to 15-year period, suggesting that the prevalence might have tripled in some countries, such as the United States. Extrapolating the currently estimated prevalence, this translates to nearly 100,000 new cases annually (in the United States and United Kingdom), affecting some 1 in 50 primary school-aged children in the United States, Canada, the United Kingdom, and Australia. A similar increase in incidence is now being noted in developing countries, such as Ghana.¹⁻⁶

¹American Academy of Allergy, Asthma & Immunology (AAAAI)

²American Academy of Pediatrics (AAP)

³American College of Allergy, Asthma & Immunology (ACAAI)

⁴Australasian Society of Clinical Immunology and Allergy (ASCLA)

⁵Canadian Society of Allergy and Clinical Immunology (CSACI)

⁶European Academy of Allergy and Clinical Immunology (EAACI)

⁷Israel Association of Allergy and Clinical Immunology (ISACI)

⁸Japanese Society for Allergology (JSA)

⁹Society for Pediatric Dermatology (SPD)

¹⁰World Allergy Organization (WAO)

¹¹Rho Federal Systems Division, Inc

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Corresponding author: David M. Fleischer, MD, Children's Hospital Colorado, 13123 E 16th Ave, B518, Aurora, CO 80045. E-mail: david.fleischer@childrenscolorado.org. 0091-6749/\$36.00

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LEAP Study

- Não incluiu crianças da população em geral
- Não incluiu crianças com *prick* teste >4 mm
- Qual a dose ideal?
- Qual o mínimo de tempo necessário de consumo para induzir tolerância?
- Potenciais riscos de uma descontinuação precoce ou esporádica?
- Não estuda outros alimentos

EAT Study (*Enquiring About Tolerance*)

Perkin MR, *et al.* N Engl J Med 2016;374:1733-43

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

Michael R. Perkin, Ph.D., Kirsty Logan, Ph.D., Anna Tseng, R.D.,
Bunmi Raji, R.D., Salma Ayis, Ph.D., Janet Peacock, Ph.D., Helen Brough, Ph.D.,
Tom Marrs, B.M., B.S., Suzana Radulovic, M.D., Joanna Craven, M.P.H.,
Carsten Flohr, Ph.D., and Gideon Lack, M.B., B.Ch., for the EAT Study Team*

EAT Study

- Lactentes 3M, sob LM exclusivo, recrutados da população geral
- 2 grupos:
 - *Standard-Introduction Group* (n=595)
 - *Early-Introduction Group* (n=567): iogurte, amendoim, sésamo, ovo cozido, peixe, trigo
- Objetivo: prevalência de alergia alimentar 1-3 anos de idade

YOUR BABY'S EARLY INTRODUCTION FOODS SCHEDULE
(After 5-7 days on just baby rice cereal, puréed fruits or vegetables)

WEEK 1

MON	TUES	WED	THURS	FRI	SAT	SUN
Baby Rice	Cow's Milk Yoghurt	Baby Rice	Cow's Milk Yoghurt	Baby Rice		

WEEK 2

MON	TUES	WED	THURS	FRI	SAT	SUN
★ 1	Cow's Milk Yoghurt	★ 1	Cow's Milk Yoghurt	★ 2		★ 2

WEEK 3

MON	TUES	WED	THURS	FRI	SAT	SUN
★ 1	Cow's Milk Yoghurt ★ 3	★ 1	Cow's Milk Yoghurt ★ 3	★ 2	★ 4	★ 2

WEEK 4

MON	TUES	WED	THURS	FRI	SAT	SUN
★ 1 ★ 4	Cow's Milk Yoghurt ★ 3	★ 1 Wheat*	Cow's Milk Yoghurt ★ 3	★ 2 Wheat*	★ 4	★ 2

WEEK 5 and Onwards

MON	TUES	WED	THURS	FRI	SAT	SUN
★ 1 ★ 4	Cow's Milk Yoghurt ★ 3	★ 1 Wheat	Cow's Milk Yoghurt ★ 3	★ 2 Wheat	★ 4	★ 2

*Wait till your baby is at least 4 months of age before you introduce wheat!

Food 1: **PEANUT**

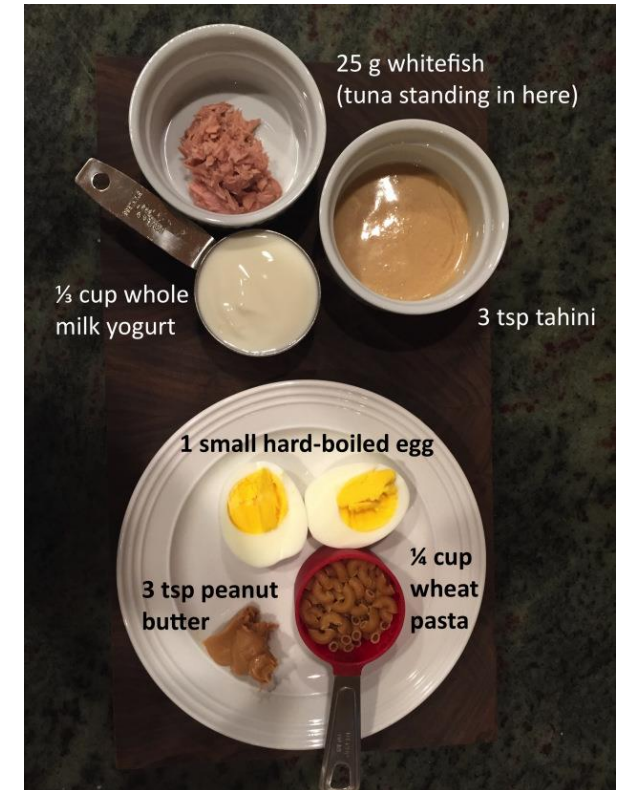
Food 2: **SESAME**

Food 3: **EGG**

Food 4: **FISH**

Guideline Amounts Per Week (or equivalents)

- ☐ 2 fish fingers or $\frac{1}{4}$ fish fillet (25 grams)
- ☐ 2 small pots cow's milk yoghurt (40-60 grams per pot)
- ☐ 2 wheat based biscuit cereal (e.g. Weetabix)
- ☐ 1 small hard-boiled egg
- ☐ 3 rounded teaspoons peanut butter
- ☐ 3 teaspoons tahini (sesame paste)



4 g proteína/semana

EAT Study

	<i>Standard-Introduction Group</i>	<i>Early-Introduction Group</i>	
Amendoim	2.5%	0%	p=0.003
Ovo	5.5%	1.4%	p=0.009

- Sem resultados com significado estatístico em relação aos outros alimentos. MAS! Estudo com problemas de adesão. E a eficácia do estudo tinha a ver com a quantidade e duração do consumo entre os 3-6M
- Intervenção segura
- Não interferiu com LM

PETIT Study (Prevention of Egg Allergy)

Natsume O, *et al.* Lancet 2016;389:276-86

Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial



Osamu Natsume*, Shigenori Kabashima*, Junko Nakazato, Kiwako Yamamoto-Hanada, Masami Narita, Mai Kondo, Mayako Saito, Ai Kishino, Tetsuya Takimoto, Eisuke Inoue, Julian Tang, Hiroshi Kido, Gary W K Wong, Kenji Matsumoto, Hirohisa Saito, Yukihiro Ohya, for the PETIT Study Team†

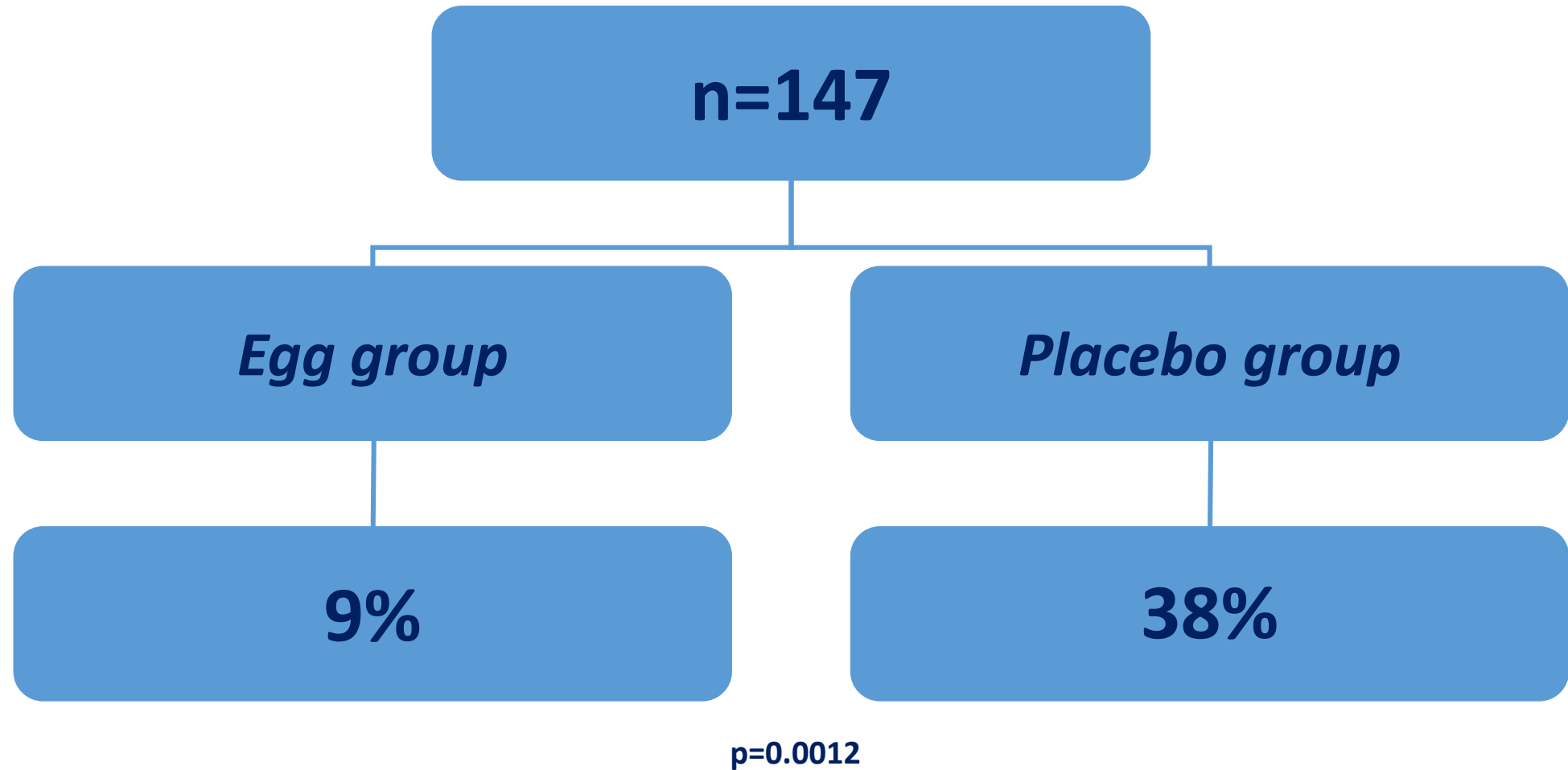
PETIT *Study*

- Sensibilização ao ovo 1A: fortemente associada a sensibilização a aeroalergénios 3A
- Eczema do lactente: associado a um aumento do risco de sensibilização percutânea a alergénios alimentares

PETIT *Study*

- Prospectivo, randomizado, duplo-cego, placebo-controlado
- Objetivo: avaliar se a introdução precoce (6M) de ovo cozido na dieta de lactentes com eczema, associado ao tratamento tópico do eczema, previne a alergia ao ovo ao ano de idade
- 6-9M: 50 mg ovo cozido (25 mg); 9-12M: 250 mg ovo cozido (125 mg)

PETIT *Study*



- Intervenção segura

LEAP	<i>Learning Early About Peanut Allergy</i>	2015	Reino Unido	Prospetivo, randomizado, aberto	Eczema moderado-grave e/ou alergia ao ovo	Amendoim, 4M-11M
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PETIT	<i>Prevention of Egg Allergy</i>	2016	Japão	Prospetivo, randomizado, duplo-cego, placebo-controlado	Eczema moderado-grave	Ovo cozido, 6M
HEAP	<i>Hens Egg Early Prevention</i>	2015	Alemanha	Prospetivo, randomizado, placebo-controlado	População geral	Ovo cru, 4M-6M Não ↓ alergia ovo ↑ anafilaxia
STAR	<i>Solids Timing for Allergy Research</i>	2013	Austrália	Prospetivo, randomizado, duplo-cego, placebo-controlado	Eczema moderado-grave	Ovo cru, 4M ↓ não sign alergia ovo ↑ efeitos 2 ^{os}
STEP	<i>Starting Time for Egg Protein</i>	2017	Austrália	Prospetivo, randomizado, duplo-cego, placebo-controlado	Filhos de mães atópicas	Ovo cru, 4M-6M ↓ não sign alergia ovo ↑ sign IgG4. Seguro
BEAT	<i>Beating Egg Allergy</i>	2017	Austrália	Prospetivo, randomizado, duplo-cego, placebo-controlado	AF de doença atópica	Ovo cru, 4M-6M ↓ sign alergia ovo ↑ sign IgG4. Seguro

- Mudança de paradigma

Estratégias de protelar/evitar alimentos alergénicos



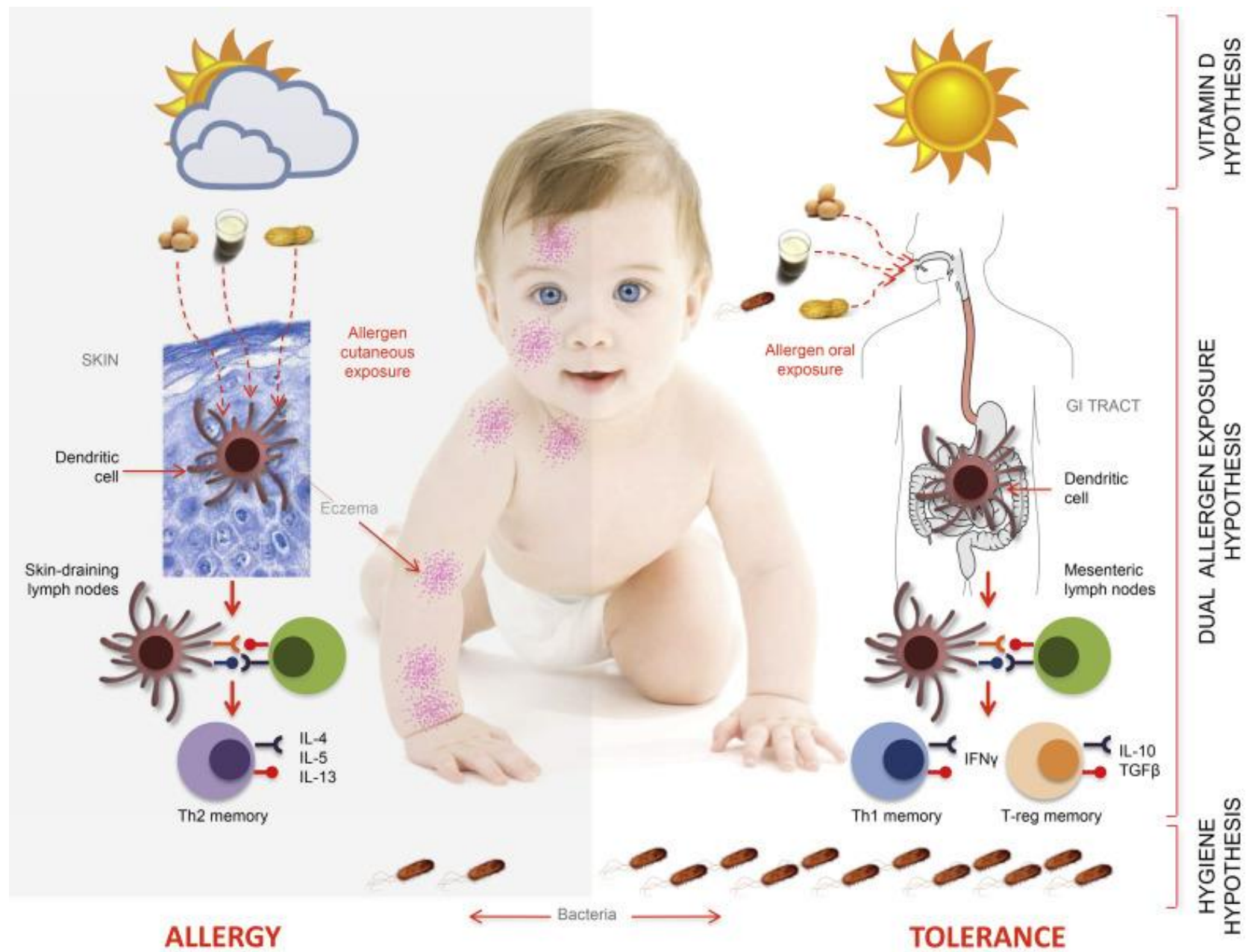
Estratégias de consumo precoce de alimentos alergénicos

- Mantém-se em aberto muitas questões

Que lactentes beneficiam com esta medida

Forma adequada de efetuar a diversificação alimentar precoce (Quando? Como?

Com que alimentos? Em que quantidade?)





Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel

Alkis Togias, MD,^a Susan F. Cooper, MSc,^a Maria L. Acebal, JD,^b Amal Assa'ad, MD,^c James R. Baker, Jr, MD,^d Lisa A. Beck, MD,^e Julie Block,^f Carol Byrd-Bredbenner, PhD, RD, FAND,^g Edmond S. Chan, MD, FRCPC,^h Lawrence F. Eichenfield, MD,ⁱ David M. Fleischer, MD,^j George J. Fuchs III, MD,^k Glenn T. Furuta, MD,^l Matthew J. Greenhawt, MD, MBA, MSc,^m Ruchi S. Gupta, MD, MPH,ⁿ Michele Habich, DNP, APN/CNS, CPN,^o Stacie M. Jones, MD,^p Kari Keaton,^q Antonella Muraro, MD, PhD,^r Marshall Plaut, MD,^s Lanny J. Rosenwasser, MD,^t Daniel Rotrosen, MD,^u Hugh A. Sampson, MD,^v Lynda C. Schneider, MD,^w Scott H. Sicherer, MD,^x Robert Sidbury, MD, MPH,^y Jonathan Spergel, MD, PhD,^z David R. Stukus, MD,^{aa} Carina Venter, PhD, RD,^{ab} and Joshua A. Boyce, MD^{ac}

Bethesda, Md; McLean, Va; Cincinnati and Columbus, Ohio; Ann Arbor, Mich; San Rafael and San Diego, Calif; New Brunswick, NJ; Vancouver, British Columbia, Canada; Aurora, Colo; Lexington, Ky; Chicago and Winfield, Ill; Little Rock, Ark; Rockville, Md; Padua, Italy; Kansas City, Mo; New York, NY; Boston, Mass; Seattle, Wash; and Philadelphia, Pa

Background: Food allergy is an important public health problem because it affects children and adults, can be severe and even life-threatening, and may be increasing in prevalence. Beginning in 2008, the National Institute of Allergy and Infectious Diseases, working with other organizations and advocacy groups, led the development of the first clinical guidelines for the diagnosis and management of food allergy. A recent landmark clinical trial and other emerging data suggest that peanut allergy can be prevented through introduction of peanut-containing foods beginning in infancy. **Objectives:** Prompted by these findings, along with 25 professional organizations, federal agencies, and patient advocacy groups, the National Institute of Allergy and Infectious Diseases facilitated development of addendum guidelines to specifically address the prevention of peanut allergy. **Results:** The addendum provides 3 separate guidelines for infants at various risk levels for the development of peanut allergy and is intended for use by a wide variety of health care providers. Topics addressed include the definition of risk

categories, appropriate use of testing (specific IgE measurement, skin prick tests, and oral food challenges), and the timing and approaches for introduction of peanut-containing foods in the health care provider's office or at home. The addendum guidelines provide the background, rationale, and strength of evidence for each recommendation.

Conclusions: Guidelines have been developed for early introduction of peanut-containing foods into the diets of infants at various risk levels for peanut allergy. (*J Allergy Clin Immunol* 2017;139:29-44.)

Key words: Food, peanut, allergy, prevention, guidelines

Discuss this article on the JACI Journal Club blog: www.jaci-online.blogspot.com.

Peanut allergy is a growing public health problem. In 1999, peanut allergy was estimated to affect 0.4% of children and 0.7% of adults in the United States,¹ and by 2010, peanut allergy prevalence had increased to approximately 2% among children

From ^athe National Institute of Allergy and Infectious Diseases, Bethesda, Md; ^bthe Board of Directors, Food Allergy Research & Education, McLean; ^cthe Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, University of Cincinnati; ^dFood Allergy Research & Education, McLean, and the Division of Allergy and Clinical Immunology, University of Michigan Health System, Ann Arbor; ^ethe Department of Dermatology, University of Rochester Medical Center; ^fthe National Eczema Association, San Rafael; ^gthe Department of Nutritional Sciences, Rutgers University, New Brunswick; ^hthe Division of Allergy and Immunology, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver; ⁱthe Departments of Dermatology and Pediatrics, University of California, San Diego School of Medicine, Rady Children's Hospital, San Diego; ^jthe Section of Allergy and Immunology, Department of Pediatrics, Children's Hospital Colorado, University of Colorado Denver School of Medicine, Aurora; ^kthe Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Kentucky College of Medicine, Kentucky Children's Hospital, Lexington; ^lthe Digestive Health Institute, Children's Hospital Colorado, Aurora, and the Section of Pediatric Gastroenterology, University of Colorado Denver School of Medicine, Aurora, Colo; ^mthe Division of Academic General Pediatrics and Primary Care, Department

of Pediatrics, and the Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago; ⁿNorthwestern Medicine, Central DuPage Hospital, Winfield; ^othe Division of Allergy and Immunology, Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock; ^pMetro DC Food Allergy Support Group, Rockville; ^qthe Food Allergy Referral Centre, Department of Women and Child Health, Padua University Hospital; ^rUniversity of Missouri-Kansas City School of Medicine, Kansas City; ^sthe Division of Allergy and Immunology, Department of Pediatrics, and ^tthe Division of Pediatric Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York; ^uthe Division of Allergy and Immunology, Boston Children's Hospital; ^vthe Department of Pediatrics, Division of Dermatology, Seattle Children's Hospital, University of Washington School of Medicine, Seattle; ^wthe Division of Allergy and Immunology, Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, Philadelphia; ^xthe Department of Pediatrics, Section of Allergy and Immunology, Nationwide Children's Hospital, Ohio State University College of Medicine, Columbus; ^ythe Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center; and ^zthe Departments of Medicine and Pediatrics, Harvard Medical School, Boston.

Alikis Togias, MD,^a Susan F. Cooper, MSc,^a Maria L. Acebal, JD,^b Amal Assa'ad, MD,^c James R. Baker, Jr, MD,^d Lisa A. Beck, MD,^e Julie Block,^f Carol Byrd-Bredbenner, PhD, RD, FAND,^g Edmond S. Chan, MD, FRCPc,^h Lawrence F. Eichenfield, MD,ⁱ David M. Fleischer, MD,^j George J. Fuchs III, MD,^k Glenn T. Furuta, MD,^l Matthew J. Greenhawt, MD, MBA, MSc,^m Ruchi S. Gupta, MD, MPH,ⁿ Michele Habib, DNP, APN/CNS, CPN,^o Stacie M. Jones, MD,^p Kari Keaton,^q Antonella Muraro, MD, PhD,^r Marshall Plaut, MD,^s Lanny J. Rosenwasser, MD,^t Daniel Rotrosen, MD,^u Hugh A. Sampson, MD,^v Lynda C. Schneider, MD,¹ Scott H. Sicherer, MD,^w Robert Sidbury, MD, MPH,^x Jonathan Spergel, MD, PhD,^y David R. Stukus, MD,^z Carina Venter, PhD, RD,^y and Joshua A. Boyce, MD^z

Bethesda, Md; McLean, Va; Cincinnati and Columbus, Ohio; Ann Arbor, Mich; San Rafael and San

Joshua A. Boyce, MD² *Bethesda, Md; McLean, Va; Cincinnati and Columbus, Ohio; Ann Arbor, Mich; San Rafael and San Diego, Calif; New Brunswick, NJ; Vancouver, British Columbia, Canada; Aurora, Colo; Lexington, Ky; Chicago and Winfield, Ill; Little Rock,*

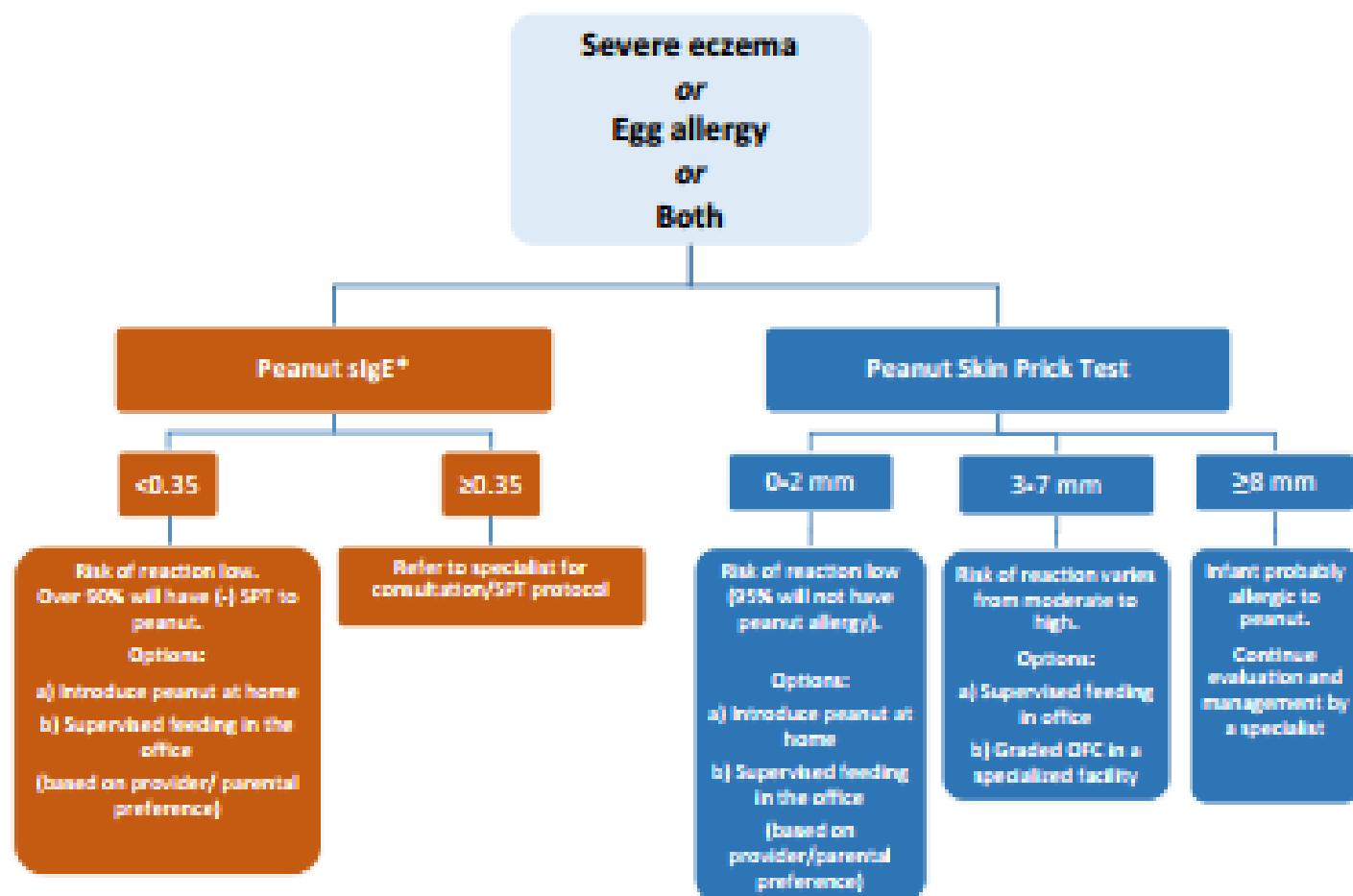
infants at various risk levels for the development of peanut allergy and is intended for use by a wide variety of health care providers. Topics addressed include the definition of risk

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TABLE I. Summary of addendum guidelines 1, 2, and 3

Addendum guideline	Infant criteria	Recommendations	Earliest age of peanut introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods.	4-6 months
2	Mild-to-moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices



Original Article

An Australian Consensus on Infant Feeding Guidelines to Prevent Food Allergy: Outcomes From the Australian Infant Feeding Summit

Merryn J. Netting, BSc, BND, PhD^{a,b}, Dianne E. Campbell, MBBS, FRACP, PhD^{c,d}, Jennifer J. Koplin, PhD^e, Kathy M. Beck, BSc, Grad Dip Nut Diet, MHSc^f, Vicki McWilliam, BSc, MND^{g,h}, Shyamali C. Dharmage, MBBS, MSc, MD, PhDⁱ, Mimi L.K. Tang, FRACP, PhD^{g,i}, Anne-Louise Ponsonby, MD, PhD^h, Susan L. Prescott, MBBS, PhD, FRACP^k, Sandra Vale, BSc(Nut)^l, Richard K.S. Loh, FRACP^m, Maria Makrides, BSc, BND, PhD, FNSA, FAHMS^{a,b}, and Katrina J. Allen, MBBS, BMed Sci, FRACP, PhD, FAAAAI, FAHMS^{e,g,h,n}; on behalf of the Centre for Food and Allergy Research, the Australasian Society of Clinical Immunology and Allergy, the National Allergy Strategy, and the Australian Infant Feeding Summit Consensus Group *Adelaide, South Australia, Australia; Sydney, New South Wales, Australia; Parkville, Victoria, Australia; South Brisbane, Queensland, Australia; Perth, Western Australia, Australia; Balgowlah, New South Wales, Australia; and Manchester, United Kingdom*

Original

**An Australian
Guideline
From**

Merryn J.
Kathy M.
Shyamali C.
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Research,
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Victoria, Au
Australia; a

1. When your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron-rich foods, while continuing breast-feeding.
2. All infants should be given allergenic solid foods including peanut butter, cooked egg, dairy, and wheat products in the first year of life. This includes infants at high risk of allergy.
3. Hydrolyzed (partially or extensively) infant formula is not recommended for the prevention of allergic disease.

PhD^h,

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Australian
Parkville,
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CONCLUSIONS: Consensus was achieved in a context in which there is a high prevalence of food allergy. Guidelines for other countries are being updated. Provision of consistent wording related to infant feeding to reduce food allergy risk will ensure clear consumer advice. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

PhD^h,

Allergy
Australian
Parkville,
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