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EAACI guidelines: Anaphylaxis (2021 update)

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1

2 PROF. MARGITTA WORM (Orcid ID : 0000-0002-3449-1245)

3 DR. CHERRY ALVIANI (Orcid ID : 0000-0003-1527-0495)

4 DR. VICTORIA CARDONA (Orcid ID : 0000-0003-2197-9767)

5 DR. AUDREY DUNNGALVIN (Orcid ID : 0000-0002-1540-3959)

6 DR. LENE HEISE GARVEY (Orcid ID : 0000-0002-7777-4501)

7 DR. CARMEN RIGGIONI (Orcid ID : 0000-0002-8745-0228)

8 DR. DEBRA DE SILVA (Orcid ID : 0000-0001-8413-5487)

9 DR. STEFANIA ARASI (Orcid ID : 0000-0002-8135-0568)

10 PROF. ABDELOUAHAB BELLOU (Orcid ID : 0000-0003-3457-5585)

11 DR. MARIA BEATRICE BILÒ (Orcid ID : 0000-0002-9324-6039)

12 PROF. KNUT BROCKOW (Orcid ID : 0000-0002-2775-3681)

13 DR. MONTSERRAT FERNANDEZ-RIVAS (Orcid ID : 0000-0003-1748-2328)

14 DR. EKATERINA KHALEVA (Orcid ID : 0000-0002-2220-7745)

15 DR. BERBER J Vlieg - BOERSTRA (Orcid ID : 0000-0001-7962-5406)

16 PROF. GRAHAM C ROBERTS (Orcid ID : 0000-0003-2252-1248)

17

18

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24 Antonella Muraro*, Margitta Worm*, Cherry Alviani, Victoria Cardona, Audrey
25 DunnGalvin, Lene H. Garvey, Carmen Riggioni, Debra de Silva, Elizabeth Angier,
26 Stefania Arasi, Abdelouahab Bellou, Kirsten Beyer, Diola Bijlhout, M Beatrice Bilò,
27 Carsten Bindslev-Jensen, Knut Brockow, Montserrat Fernandez-Rivas, Susanne
28 Halken, Britt Jensen, Ekaterina Khaleva, Louise J Michaelis, Hanneke N.G. Oude
29 Elberink, Lynne Regent, Angel Sanchez, Berber J. Vlieg-Boerstra, Graham Roberts*
30 on behalf of European Academy of Allergy and Clinical Immunology Food Allergy
31 and Anaphylaxis Guidelines Group.

32 *Equal contribution as guideline chairs

33 **AFFILIATIONS**

34 Antonella Muraro: Food Allergy Referral Centre Veneto Region, Department of
35 Women and Child Health, Padua General University Hospital, Padua, Italy.

36 Margitta Worm: Division of Allergy and Immunology, Department of Dermatology,
37 Venerology and Allergy, Charité Universitätsmedizin Berlin, Germany.

38 Cherry Alviani: Clinical and Experimental Sciences and Human Development in
39 Health, Faculty of Medicine, University of Southampton, UK.

40 Victoria Cardona: Allergy Section, Department of Internal Medicine, Hospital Vall
41 d'Hebron, Barcelona, Spain & ARADyAL Research Network. (Orchid: 0000-0003-
42 2197-9767)

43 Audrey DunnGalvin: University College Cork, Ireland. Sechnov University Moscow,
44 Ireland.

45 Lene Heise Garvey: Allergy Clinic, Department of Dermatology and allergy,
46 Copenhagen University Hospital Gentofte, Copenhagen, Denmark and Department
47 of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (Orchid:
48 0000-0002-7777-4501)

49 Carmen Riggioni: Allergy, Immunology and Rheumatology Division, Department of
50 Pediatrics, Yong Loo Lin School of Medicine, National University of Singapore,
51 Singapore. (Orchid:0000-0002-8745-0228)

52 Debra de Silva: The Evidence Centre Ltd, London, UK.

53 Elizabeth Angier: Primary Care, Population Science and Medical Education, Faculty
54 of Medicine, University of Southampton, Southampton, UK (Orchid: 0000-0002-
55 8565-7655)

56 Stefania Arasi, Allergy Unit - Area of Translational Research in Pediatric Specialities,
57 Bambino Gesù Children's Hospital, IRCCS, Rome, Italy. (Orchid: 0000-0002-8135-
58 0568)

59 Abdelouahab Bellou: European Society for Emergency Medicine, Brussels, Belgium;
60 Wayne State University School of Medicine, Department of Emergency Medicine,
61 Detroit, USA; University of Rennes 1, Rennes, France.

62 Kirsten Beyer: Department of Pediatric Respiratory Medicine, Immunology and
63 Critical Care Medicine; Charité Universitätsmedizin Berlin; Berlin, Germany.

64 Diola Bijlhout: Association for Teacher Education in Europe (ATEE), Brussels,
65 Belgium. (Orchid: 0000-0003-1746-4752)

66 M Beatrice Bilò: Allergy Unit, Department of Clinical and Molecular Sciences,
67 Polytechnic University of Marche, Ancona, Department of Internal Medicine,
68 University Hospital of Ancona - Italy. (Orchid: 0002-9324-6039)

69 Carsten Bindslev-Jensen: Department of Dermatology and Allergy Centre, Odense
70 Research Centre for Anaphylaxis (ORCA), Odense University Hospital, Odense,
71 Denmark. (Orchid: 0000-0002-8940-038X)

72 Knut Brockow: Department of Dermatology and Allergy Biederstein, Technical
73 University of Munich, Munich, Germany. (Orchid: 0000-0002-2775-3681)

74 Montserrat Fernandez-Rivas: Allergy Department, Hospital Clinico San Carlos,
75 Facultad Medicina Universidad Complutense, IdISSC, ARADyAL, Madrid, Spain.
76 (Orchid: 0000-0003-1748-2328)

77 Susanne Halcken: Hans Christian Andersen Children's Hospital, Odense University
78 Hospital, Odense, Denmark. (Orchid: 0000-0003-0161-8278)

79 Britt Jensen: Department of Dermatology and Allergy Centre, Odense Research
80 Centre for Anaphylaxis (ORCA), Odense University Hospital, Odense, Denmark.
81 (Orchid: 0000 - 0001 – 7924 – 9244)

82 Ekaterina Khaleva: Clinical and Experimental Sciences and Human Development in
83 Health, Faculty of Medicine, University of Southampton, Southampton, UK. (Orchid:
84 0000-0002-2220-7745)

85 Louise J Michaelis: Department of Paediatric Immunology, Allergy, and Infectious
86 Diseases, Great North Children's Hospital Newcastle upon Tyne, UK; Faculty of
87 Medical Sciences, Population Health Sciences Institute, Newcastle University,
88 Newcastle upon Tyne, UK. (Orchid: 0000 0001 8229 154X)

89 Hanneke N.G. Oude Elberink: Department of Allergology, University Medical Center
90 Groningen, University of Groningen, and Groningen Research Institute for Asthma
91 and COPD, Groningen, The Netherlands.

92 Lynne Regent: Anaphylaxis Campaign, Farnborough, UK.

93 Angel Sanchez: AEPNAA Spanish Association for People with Food and Latex
94 Allergy, Spain.

95 Berber J. Vlieg-Boerstra: OLVG Hospital, Department of Paediatrics, Amsterdam
96 (Orchid: 0000-0001-7962-5406)

97 Graham Roberts: NIHR Southampton Biomedical Research Centre, University
98 Hospital Southampton NHS Foundation Trust, Southampton; Clinical and
99 Experimental Sciences and Human Development in Health, Faculty of Medicine,
100 University of Southampton, Southampton; and The David Hide Asthma and Allergy
101 Research Centre, St Mary's Hospital, Isle of Wight, UK. (Orchid: 0000-0003-2252-
102 1248)

103 **CORRESPONDING AUTHOR**

104 Antonella Muraro, Food Allergy Referral Centre Veneto Region, Department of
105 Women and Child Health, Padua General University Hospital, Padua, Italy. Email:
106 muraro@centroallergiealimentari.eu

107

108 **SHORT TITLE**

109 EAACI anaphylaxis guideline

110

111 **FUNDING**

112 European Academy of Allergy and Clinical Immunology

113

114 **ABSTRACT**

115 Anaphylaxis is a clinical emergency which all healthcare professionals need to be
116 able to recognise and manage. The European Academy of Allergy and Clinical
117 Immunology Anaphylaxis multidisciplinary Task Force has updated the 2014
118 guideline. The guideline was developed using the AGREE II framework and the
119 GRADE approach. The evidence was systematically reviewed and recommendations
120 were created by weighing up benefits and harms. The guideline was peer-reviewed
121 by external experts and reviewed in a public consultation. The use of clinical criteria
122 to identify anaphylaxis is suggested with blood sampling for the later measurement
123 of tryptase. The prompt use of intramuscular adrenaline as first line management is
124 recommended with the availability of adrenaline autoinjectors to patients in the
125 community. Pharmacokinetic data should be provided for adrenaline autoinjector
126 devices. Structured, comprehensive training for people at risk of anaphylaxis is
127 recommended. Simulation training and visual prompts for healthcare professionals
128 are suggested to improve the management of anaphylaxis. It is suggested that
129 school policies reflect anaphylaxis guidelines. The evidence for the management of
130 anaphylaxis remains mostly at a very low level. There is an urgent need to prioritise
131 clinical trials with the potential to improve the management of patients at risk of
132 anaphylaxis.

133

134 **KEY WORDS**

135 Anaphylaxis; children; adults; guidelines

136

137 **INTRODUCTION**

138 This paper sets out the updated European Academy of Allergy and Clinical
139 Immunology's (EAACI) guideline regarding the diagnosis, acute management and
140 prevention of anaphylaxis. Anaphylaxis is a clinical emergency and all health care
141 professionals need to be familiar with its recognition and management. Anaphylaxis
142 is a life-threatening reaction characterised by acute onset of symptoms involving
143 different organ systems and requiring immediate medical intervention.¹ Although the
144 fatality rate due to anaphylaxis remains low,² the frequency of hospitalisation from
145 food and drug-induced anaphylaxis has been increasing in recent years.³

146 The symptoms of anaphylaxis are highly variable.^{4,5} Data from patients experiencing
147 anaphylaxis revealed that skin and mucosal symptoms occur most frequently (>90%
148 of cases) followed by symptoms involving the respiratory and cardiovascular
149 systems (>50%). Food, drug and Hymenoptera venom are the most common
150 elicitors of anaphylactic reactions.^{5,6} The prevalence of the various causes of
151 anaphylaxis are age-dependent and vary in different geographical regions. In
152 Europe, typical causes of food-induced anaphylaxis in children are peanut, hazelnut,
153 milk and egg and in adults, wheat, celery and shellfish; fruits such as peach are also
154 typical causes of food-induced anaphylaxis in adults in some European countries
155 such as Spain and Italy.^{7,8} Venom-induced anaphylaxis is typically caused by wasp
156 and bee venom⁹. Drug-induced anaphylaxis is typically caused by antibiotics and
157 non-steroidal anti-inflammatory drugs.^{10,11} Among antibiotics, beta-lactam antibiotics
158 are the leading eliciting allergens.¹² At times there is an occupational cause^{11,2}. Co-
159 factors may be aggravating factors in anaphylaxis, examples are exercise, stress,
160 infection, non-steroidal anti-inflammatory drugs and alcohol.¹³⁻¹⁵ In some cases the
161 cause is not obvious (idiopathic anaphylaxis) and investigations for rarer allergens or
162 differential diagnoses should be considered.¹⁶⁻¹⁸

163 This guideline, updated from 2014,¹⁹ provides evidence-based guidance to help
164 manage anaphylaxis. The primary audience is clinical allergists (specialists and
165 subspecialists), primary care, paediatricians, emergency physicians, anaesthetists

166 and intensivists, nurses, dieticians and other healthcare professionals. The guideline
167 was developed by EAACI's Anaphylaxis Guideline Update task force (TF) and
168 informed by a systematic review (SR).²⁰ Where published evidence was lacking, the
169 findings of the review were supplemented with expert consensus opinion.

170 **METHODOLOGY**

171 This guideline was generated using the Appraisal of Guidelines for Research and
172 Evaluation (AGREE II) approach^{21,22} to ensure appropriate representation of the full
173 range of stakeholders, a systematic search for and critical appraisal of, the relevant
174 literature, and a systematic approach to formulating and presenting
175 recommendations, with steps to minimise the risk of bias at each step. The Grading
176 of Recommendations Assessment, Development and Evaluation (GRADE) approach
177 provided a structured way to evaluate evidence and potential recommendations.²³
178 The process commenced in September 2019 with a face-to-face discussion to agree
179 the protocol and the key clinical areas. Regular webconferences took place through
180 to November 2020 with additional email discussion to complete the guideline.

181 **Clarifying the scope and purpose of the guidelines**

182 This guideline provides evidence-based recommendations for the diagnosis,
183 management and prevention of anaphylaxis in children and adults. It also highlights
184 gaps where future research is required. Reactions to allergen immunotherapy are
185 outside the scope of this guideline.²⁴

186 **Ensuring appropriate stakeholder involvement**

187 The EAACI TF was drawn from 9 countries and included allergists (specialist and
188 subspecialists), pediatricians, primary care, immunologists, emergency physicians,
189 anaesthetists, dieticians, nurses, psychologist, education and patient organisation
190 representatives. Methodologists took the lead in undertaking the SR, while clinical
191 academics took the lead in formulating recommendations for clinical care.

192 **Systematic review of the evidence**

193 The SR aimed to assess the effectiveness of any approach for the immediate
194 diagnosis, emergency management and prevention or long-term management of

195 anaphylaxis in children and adults.^{20,25} It was undertaken by independent
196 methodologists using GRADE Pro GDT (www.grade.pro). Comparative studies
197 were eligible for inclusion plus, in the case of diagnosis and adrenaline only,
198 prospective case series with at least 20 participants were eligible. We continued to
199 track evidence published after our SR cut-off date of 20th April 2020, and studies
200 were considered by the TF chairs where relevant.

201 Evidence summaries for each question were prepared by methodologists, including
202 assessments of the risk of bias and certainty of evidence.²⁶ TF members reviewed
203 the summaries and provided feedback. The certainty of the evidence was assessed
204 as high, moderate, low, or very low based on consideration of risk of bias, directness
205 of evidence, consistency and precision of the estimates, and other considerations.²⁷

206 **Formulating recommendations**

207 The TF used the GRADE approach to grade the strength and consistency of key
208 findings from the SR,²⁰ which in turn contributed to formulating evidence-based
209 recommendations for clinical care.²³ In generating recommendations, the TF
210 evaluated the importance of the problem, desirable and undesirable effects, certainty
211 of evidence, values, balance of effects, resources required, cost-effectiveness,
212 equity, acceptability, and feasibility. All recommendations were agreed by consensus
213 with a threshold of agreement set at 80%. Table 1 describes the conventions used in
214 this guideline to describe the strength of recommendations and how this relates to
215 policy and practice. Recommendations apply to all ages unless otherwise indicated.

216 TF members identified the resource implications of implementing the
217 recommendations, barriers, and facilitators to the implementation of each
218 recommendation, advised on approaches to implementing the recommendations,
219 and suggested audit criteria that can help with assessing organizational compliance
220 with each recommendation.

221

222

223

Table 1. Conventions used in Guideline wording			
Strength and direction	Guideline wording	Implications for practice	Policy implications
Strong recommendation for an intervention	“The EAACI Task Force recommends ...”	Most people in this situation should be offered the intervention	The recommendation can be adopted as a policy in most situations
Conditional recommendation for an intervention	“The EAACI Task Force suggests ...”	Different choices will be appropriate for different people. Clinicians could help each patient make decisions consistent with the patient’s preferences	Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders
Strong recommendation against an intervention	“The EAACI Task Force recommends against ...”	Most people in this situation should not use this intervention	The recommendation can be adopted as a policy in most situations
Conditional recommendation against an intervention	“The EAACI Task Force suggests against ...”	Different choices will be appropriate for different people. Clinicians could help each patient make decisions consistent with the patient’s preferences	Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders
No recommendation	“There is no recommendation for or against using ...”	Different choices will be appropriate for different people. Clinicians could help each patient make decisions consistent with the patient’s preferences	Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders

224

225 **Peer review and public comment**

226 A draft of these guidelines was externally peer-reviewed by invited experts from a
 227 range of organizations, countries, and professional backgrounds. Additionally, the
 228 draft guideline was made publicly available on the EAACI website for a 3-week
 229 period in February 2021 to allow a broader array of stakeholders to comment. All
 230 feedback was considered by the TF members and, where appropriate, final revisions
 231 were made in light of the feedback received. We will be pleased to continue to
 232 receive feedback on this guideline, addressed to the corresponding author.

233 **Identification of evidence gaps**

234 During the development of the guideline, areas where evidence is lacking were
235 identified and gaps to fill prioritized.

236 **Editorial independence and managing conflict of interests**

237 The guideline development process was funded by EAACI. The funder did not have
238 any influence on the guideline contents or on the decision to publish. TF members'
239 conflicts of interest were declared at the start of the process and taken into account
240 by the TF chairs, as recommendations were formulated. Specifically, anyone who
241 had a potential financial conflict of interest was not able to be involved in final
242 decisions about that recommendation (this did not apply to any task force members).
243 Evidence about effectiveness was compiled independently by methodologists who
244 had no conflict of interests. Additionally, final decisions about strength of evidence
245 for recommendations were checked by the methodologists who had no conflict of
246 interests.

247 **Updating the guidelines**

248 European Academy of Allergy and Clinical Immunology plans to update this
249 guideline in 2026 unless there are important advances before then.

250

251

252 **GUIDELINE RECOMENDATIONS**

253 Table 2 summarises the guideline recommendations. The following sections explore
254 these recommendations in more detail. The evidence is summarised narratively, with
255 individual studies not described as these details can be found in our published SR.²⁰
256 The online supplement provides a detailed rationale with the relevant evidence for
257 each recommendation (Online Supplement Tables S1-4).

258 **Table 2. EAACI anaphylaxis guideline recommendations**

Recommendation	Certainty of
----------------	--------------

	evidence
Diagnosing anaphylaxis in an emergency setting	
The EAACI task force suggests using clinical criteria, including rapid onset of multiple symptoms and signs, for identifying anaphylaxis in an acute context.	Very low
The EAACI task force suggests measuring serum tryptase half to two hours after the start of the reaction, and baseline tryptase at least 24 hours after complete resolution of symptoms, to support diagnosing anaphylaxis retrospectively.	Very low
Emergency management of anaphylaxis	
The EAACI task force recommends promptly using intramuscular adrenaline in the mid-thigh area as first-line management of anaphylaxis.	Very low
The EAACI task force suggests using adrenaline autoinjectors for the first-line management of anaphylaxis in the community.	Very low
The EAACI task force recommends that pharmacokinetic data should be provided for each adrenaline autoinjector product as they cannot be regarded as interchangeable.	Very low
The EAACI task force suggests prescribing 0.15mg adrenaline autoinjectors for children from 7.5kg to 25-30kg and 0.3mg adrenaline autoinjectors for children from 25-30kg, and at least 0.3mg adrenaline autoinjectors for adolescents and adults at risk of anaphylaxis.	Very low
Long-term management of anaphylaxis	
The EAACI task force recommends providing structured, comprehensive training to improve recognition of anaphylaxis and use of adrenaline autoinjectors in people at risk of anaphylaxis. This is in addition to basic instructions about autoinjector use.	Low
The EAACI task force makes no recommendation for or against using premedication with antihistamine to prevent anaphylaxis.	Very low
The EAACI task force suggests using premedication with subcutaneous adrenaline to prevent anaphylaxis when snake bite anti-venom is given to a patient.	Very low
The EAACI task force suggests that school policies reflect anaphylaxis guidelines but more research is needed to understand how guidelines and legislation in schools is best implemented.	Very low
Education and training for healthcare professionals	
The EAACI task force suggests using simulation training and visual prompts to improve healthcare professionals' recognition and management of anaphylaxis in emergency situations.	Very low

259

260 **DIAGNOSIS OF ANAPHYLAXIS IN AN ACUTE CONTEXT**

261 This section deals with making a diagnosis of anaphylaxis in a situation where
262 someone has symptoms and signs of an acute allergic reaction. Further justification
263 about each of the recommendations about diagnosing anaphylaxis is included in
264 online supplement Table S1.

265 Making a diagnosis of anaphylaxis

266 *The EAACI task force suggests using clinical criteria, including rapid onset of*
267 *multiple symptoms and signs, for identifying anaphylaxis in an acute context.*

268 *Reason for recommendation:* Anaphylaxis is a clinical emergency so the diagnosis
269 needs to be made rapidly. Research suggests that National Institute of Allergy and
270 Infectious Disease and Food Allergy and Anaphylaxis Network clinical criteria has
271 high sensitivity.^{28,29} (Box 1)

272 *Strength of recommendation:* This is a conditional recommendation as the evidence
273 is of very low certainty and derives from case series or retrospective case-control
274 studies.

275 *Practical implications:* Anaphylaxis has variable presentations, occasionally with no
276 cutaneous involvement, and relatively low prevalence so it may not be easy to
277 diagnose. Health care professionals require training in how to recognise
278 anaphylaxis³⁰ (Box 1) and differentiate it from other diagnoses^{31,32} (Box 2).

279

Box 1. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips–tongue–uvula AND AT LEAST ONE OF THE FOLLOWING
 - a. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin–mucosal tissue (e.g., generalized hives, itch-flush, swollen lips–tongue–uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*
 - b. Adults: systolic BP of <90 mmHg or >30% decrease from that person’s baseline

PEF, peak expiratory flow; BP, blood pressure. *Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.

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280

281 Serum tryptase level may help to support the diagnosis later in the allergy
282 consultation

283 *The EAACI task force suggests measuring serum tryptase half to two hours after the*
284 *start of the reaction, and baseline tryptase at least 24 hours after complete resolution*
285 *of symptoms, to support diagnosing anaphylaxis respectively.*

286 *Reason for recommendation:* Although measuring serum tryptase will not help to
287 make a diagnosis of anaphylaxis in a clinical emergency, an elevated level within two
288 hours of the reaction compared to a baseline value (measured before or after the
289 reaction) can be helpful in confirming the diagnosis of anaphylaxis during
290 subsequent allergy consultation.

291 *Strength of recommendation:* This is a conditional recommendation. Several studies
292 have assessed the diagnostic accuracy of serum tryptase measurements for

293 anaphylaxis, but the evidence is of very low certainty, deriving from consecutive case
294 series or case control studies.³³⁻³⁵

295 *Practical implications:* Taking the sample should not delay treating a patient with
296 adrenaline where necessary. A sample taken later than two hours after the reaction
297 may still demonstrate a raised tryptase level. A level of serum tryptase half to two
298 hours after the start of the reaction (1.2 x baseline tryptase) + 2 µg/L supports a
299 diagnosis of anaphylaxis.^{36,37} A raised serum tryptase level can be associated with a
300 mast cell disorder or hereditary alpha tryptasaemia³⁸⁻⁴⁰, so it is important to compare
301 with a baseline level at least 24 hours after complete resolution of a reaction. Also,
302 serum tryptase is not always elevated in anaphylaxis, especially in children and with
303 food triggers in all ages.³⁷ So failing to find an elevated tryptase level does not rule
304 out anaphylaxis.

305

306

307

Box 2. Differential diagnosis of anaphylaxis

Skin or mucosal

- chronic remittent or physical urticaria and angioedema
- pollen food allergy syndrome (just oral symptoms)

Respiratory diseases

- acute laryngotracheitis
- laryngeal, tracheal or bronchial obstruction (e.g., foreign substances, intermittent laryngeal obstruction or vocal cord dysfunction)
- status asthmaticus (without involvement of other organs)

Cardiovascular diseases

- vasovagal syncope
- pulmonary embolism
- myocardial infarction
- cardiac arrhythmias
- cardiogenic shock

Pharmacological or toxic reactions

- ethanol
- histamine, e.g. scombroid fish poisoning
- opiates

Neuropsychiatric diseases

- hyperventilation syndrome
- anxiety and panic disorder
- somatoform disorder (e.g., psychogenic dyspnea)
- dissociative disorder and conversion (e.g., globus hystericus)
- epilepsy
- cerebrovascular event
- psychoses
- factitious disorder

Endocrinological diseases

- hypoglycemia
- thyrotoxic crisis
- carcinoid syndrome
- vasointestinal polypeptide tumors
- pheochromocytoma

308

309

310 **EMERGENCY MANAGEMENT OF ANAPHYLAXIS**

311 In addition to the early use of adrenaline, the trigger should be removed where
312 possible, posture should be optimised and assistance should be sought from
313 emergency medical services in the community or the emergency team in hospital. To
314 ensure adequate venous return patients experiencing anaphylaxis should lie flat with
315 their legs raised. Where respiratory distress is the predominant presentation,
316 patients may prefer to sit up with elevated legs. If pregnant, they can be placed on

317 their left side with the bed in a head-down position.⁴¹ Where unconscious, patients
318 can be placed in the recovery position. Avoid any abrupt change to a more upright
319 posture.⁴²

320 Further justification about each of the recommendations about managing
321 anaphylaxis is included in online supplement Table S2. A checklist for managing
322 anaphylaxis is presented in Box 3 and an algorithm approach to managing this
323 clinical emergency is presented in Figure 1.

324 **First line intervention: adrenaline**

325 Route of administration

326 *The EAACI task force recommends promptly using intramuscular adrenaline in the*
327 *mid-thigh area as first-line management of anaphylaxis.*

328 *Reason for recommendation:* Adrenaline has historically been used as first-line
329 treatment for anaphylaxis, without evidence of serious harm. Early use of adrenaline
330 appears to reduce the risk of biphasic reactions.⁴³⁻⁴⁶ There is evidence that
331 intramuscular adrenaline gives higher plasma levels than adrenaline via a metered
332 dose inhaler.⁴⁷⁻⁵⁰ The evidence comparing intramuscular with subcutaneous
333 adrenaline is confounded by injection site but suggests that the former is associated
334 with higher plasma adrenaline levels.^{51,52} Injection mid-thigh gives higher levels than
335 injection into deltoid.⁵² There is little evidence of harm when adrenaline is given
336 intramuscularly unlike with the intravenous dosing.²⁰

337 *Strength of recommendation:* This is a strong recommendation in favour of
338 adrenaline. The research evidence is of low certainty due to the challenges of
339 undertaking randomised controlled trials in anaphylaxis. Given the totality of the
340 evidence and clinical experience over many decades, the task force felt that a strong
341 recommendation for the use of intramuscular adrenaline was appropriate.

342 *Practical implications:* Professionals who may need to manage anaphylaxis should
343 be trained in how to promptly administer intramuscular adrenaline. The task force
344 consider that adrenaline is best used early especially in patients who have had
345 previous life-threatening reactions in similar circumstances (eg insect sting) although

346 our literature search did not focus on this and no relevant good quality evidence was
347 found. Assistance from colleagues should be sought early when managing a patient
348 with anaphylaxis. In severe reactions, especially involving the cardiovascular system,
349 intravenous fluids should also be given early with the second dose of intramuscular
350 adrenaline.⁵³ In some special circumstances, intramuscular adrenaline may not be
351 effective (eg refractory respiratory distress, hypotension) so intravenous adrenaline
352 should be used; this is likely to be more effective at reversing refractory
353 bronchospasm or hypotension. The use of intravenous adrenaline should be
354 restricted to healthcare professionals who are trained to use it and to monitored
355 settings such as the emergency room, operating theatres, or intensive care unit.
356 Patients on a beta-blocker may also respond poorly to adrenaline.

357 Adrenaline autoinjector or needle-syringe

358 *The EAACI task force suggests using adrenaline autoinjectors for the first-line*
359 *management of anaphylaxis in the community.*

360 *Reason for recommendation:* The benefits of using an autoinjector outweigh the risks
361 compared with using a (pre-filled) needle-syringe (online supplement Table S2).
362 Adrenaline autoinjectors are convenient, relatively safe, have a low risk of error and
363 are faster to administer compared to a needle-syringe approach. If autoinjectors are
364 also used to treat anaphylaxis in healthcare settings, the patient can practice using it
365 or at least observe how they are used and experience its effectiveness for managing
366 anaphylaxis.

367 *Strength of recommendation:* This is a conditional recommendation for using
368 autoinjectors because the certainty of evidence is very low due to the available trials
369 being at moderate or high risk of bias.^{54,55}

370 *Practical implications:* A number of different adrenaline autoinjectors are available,
 371 each of which have slightly different mechanisms. Device specific training is
 372 therefore essential for each autoinjector and with further training if device is
 373 changed. Adrenaline autoinjectors are designed to be kept at 20-25°C and have a
 374 limited shelf life due to degradation of the adrenaline. Autoinjectors occasionally fail
 375 to deploy and the European Medicines Agency has stated that patients should have
 376 access to two devices⁵⁶ (see Table 3 for arguments for prescribing one or two
 377 devices). In many countries adrenaline autoinjectors are not available or not
 378 affordable or there are supply issues with adrenaline autoinjectors. In these
 379 circumstances a prefilled syringe is an alternative. Indications for the prescription of

Box 3. Checklist for managing an acute allergic reaction

1. Stay with patient
2. Remove the trigger (e.g. food, drug, venom)
3. Look for signs of anaphylaxis
4. Administer adrenaline if signs of anaphylaxis (eg breathing or circulatory problems)
5. Call for help
6. Lie flat with their legs raised unless in respiratory distress where patient may prefer to sit sit up with elevated legs
7. Repeat adrenaline if no improvement or worsening of symptoms 5-10 minutes after first administration
8. Do not forget oxygen, beta-2 agonist or i.v. fluids as indicated

Adrenaline is effective for all symptoms

380 self-injectable adrenaline are described in Box 4.

381

382 **Box 4. Indications for the prescription of self-injectable adrenaline**

Table 3. Reasons for prescribing one or two adrenaline autoinjectors

Arguments for two autoinjectors	Arguments for one autoinjector
<ul style="list-style-type: none"> • European Medicines Agency recommends that two autoinjectors are prescribed⁵⁶ • About 10% patients require a second dose of adrenaline due to insufficient response to the first dose⁵⁸ • Rarely, an autoinjector will misfire or be injected in the wrong place⁵⁶ • Where there is a likelihood of delayed medical assistance, eg remote location or travel 	<ul style="list-style-type: none"> • Only needing to carry one device may improve adherence to carriage which is low • Most autoinjectors are not used and have to be replaced after 12-18 months when they expire • Most patients respond to one dose and second doses are usually administered by emergency services^{57,58}

Recommendation	Key references	Rationale
Absolute indications for adrenaline auto-injectors		
Previous anaphylaxis triggered by food, latex, or aeroallergens	59,60	High risk of recurrent anaphylaxis
Previous exercise-induced anaphylaxis	61	High risk of recurrent anaphylaxis
Previous idiopathic anaphylaxis	57	High risk of recurrent anaphylaxis
Co-existing unstable or moderate to severe, persistent asthma and a food allergy*	62,63	Asthma is a risk factor for experiencing anaphylaxis in the context of food allergy
<p>Hymenoptera venom allergy in untreated patients with more than cutaneous/mucosal systemic reactions or high risk of re-exposure</p> <p>During and after VIT, in patients with more than cutaneous/mucosal systemic reactions if risk factors for relapse are present</p>	24,64	High risk of recurrent anaphylaxis
<p>Underlying systemic mastocytosis in adults with any previous systemic reaction.</p> <p>Children with very severe skin involvement (>50% body surface) and increased basal serum tryptase levels (>20ng/ml) and with blistering in the first three years of life.</p>	65-68	Systemic mastocytosis is associated with a high risk of recurrent anaphylaxis and it is not possible to identify individual at risk patients
Consider prescribing adrenaline auto-injectors with any of the following additional factors (especially if more than one is present)		
<p>Previous mild-to-moderate allergic reaction* to foods known to be associated with anaphylaxis in patient's region (eg peanut and/or tree nut, cow's milk, sea food depending on triggers for anaphylactic reactions at that location)</p>	69,70, 113-116	<p>Relatively high risk of experiencing anaphylaxis in the future with any peanut or tree nut allergy in many countries. Increasing number of fatal anaphylaxis with cow's milk in school age children and young adults. Seafood is an important hidden allergen in some countries.</p>
<p>Teenager or young adult with a food allergy with previous mild-to-moderate reactions*</p>	71,72	<p>This age group is at higher risk of experiencing anaphylaxis due to their life style or risk behaviours</p>
<p>Remote from medical help or prolonged travel abroad in the context of previous mild-to-moderate allergic reaction to a food, Hymenoptera venom, latex, or</p>	73	<p>Medical help may not be easily available during travel. Risks are more difficult to control due to language barriers and new foods.</p>

aeroallergens		
Previous mild-to-moderate allergic reaction to traces of food*	42,73,74	Contact with a large amount of the food in the future may result in a more severe reaction
Hymenoptera venom or drug allergy in patients with more than cutaneous/mucosal systemic reactions and cardiovascular disease	5,75	Cardiovascular diseases appear to be associated with a greater risk of severe or fatal anaphylaxis (venom and drug anaphylaxis)
Oral immunotherapy for food allergy	76	Anaphylaxis is a known adverse effect of oral immunotherapy for food allergy

383 *Excluding pollen food allergy syndrome unless patient has previously experienced systemic
384 symptoms. VIT: Hymenoptera venom immunotherapy. Supporting references taken from the
385 anaphylaxis systematic review with additional ones taken from a specific review of the literature
386 focused on indications.

387 Pharmacokinetic data for adrenaline autoinjectors and needle-syringe

388 *The EAACI task force recommends that pharmacokinetic data should be provided for*
389 *each adrenaline autoinjector product as they cannot be regarded as*
390 *interchangeable. Reason for recommendation:* Pharmacokinetic data are now
391 available for many of the adrenaline autoinjector products. These data demonstrate
392 that each type delivers very different plasma adrenaline levels. It had been thought
393 that the length of the needle was critical to optimising the delivery of adrenaline.
394 However, the pharmacokinetic data indicate that needle length does not dictate
395 adrenaline plasma levels.⁷⁷ For example, when the same autoinjectors were used for
396 adults with different skin to muscle depths (associated with body mass index), some
397 devices have a similar plasma adrenaline profile in all⁷⁸ whereas there is marked
398 blunting of the height of the early peak in overweight individuals in others.⁷⁹ (see
399 online supplement Table S2). Plasma adrenaline levels may be more closely related
400 to the force at which adrenaline is deployed from the device.⁷⁸

401 *Strength of recommendation:* This is a strong recommendation for making
402 pharmacokinetic data available. Only some pharmacokinetic data have been
403 published in peer review journals and other data are available via information
404 submitted to European medicine regulators. Given the marked differences in
405 adrenaline profiles between different products and different patients they cannot be
406 seen as interchangeable. The task force considered that these data should be made

407 available by companies for all adrenaline devices to help predict their likely clinical
408 effectiveness.

409 *Practical considerations:* As we do not know what level of plasma adrenaline is
410 needed to successfully treat anaphylaxis, the results of these pharmacokinetic
411 studies need to be interpreted with some caution. A product that does not achieve
412 similar plasma levels to other autoinjectors is of concern.

413

414 Dose of adrenaline

415 *The EAACI task force suggests prescribing 0.15mg adrenaline autoinjectors for*
416 *children from 7.5kg to 25-30kg and 0.3mg adrenaline autoinjectors for children from*
417 *25-30kg, and at least 0.3mg adrenaline autoinjectors for adolescents and adults at*
418 *risk of anaphylaxis.*

419 *Reason for recommendation:* There are no published data for children weighing
420 under 15kg although the routinely advised intramuscular adrenaline dose is 0.01
421 mg/kg in healthcare settings. In the 2014 guideline we recommended using a
422 0.15mg adrenaline autoinjector for children from 7.5kg bodyweight on the basis that
423 a mild overdose does not represent a major risk in otherwise healthy children.³²
424 There have been no reports of any adverse consequences of this approach and
425 regulators have now licensed some autoinjectors down to 7.5kg in some European
426 countries (eg Germany).⁸⁰ However, there is a danger that the needle will hit the
427 underlying bone in small children.⁸¹ We are aware of a 0.1mg adrenaline autoinjector
428 product but this only appears to be available in the United States.¹¹⁷ We identified
429 only one study looking at plasma adrenaline levels with 0.15 and 0.3mg devices in
430 children.⁸² Similar plasma levels were seen but the 0.3mg dose was associated with
431 more side-effects in children under 30kg. Alternatively, children may rapidly outgrow
432 their dose and adverse effects need to be balanced against effectiveness. Countries
433 within Europe vary as to whether a switch happens at 25 or 30kg for different
434 devices. We therefore suggest using the 0.3mg dose only in children more than 25-
435 30kg in weight. A 0.5mg dose gives a substantially higher plasma level than a 0.3mg
436 dose with one device.⁸³ The optimal dose of adrenaline in anaphylaxis is not known

437 and 0.3mg devices have been found to be effective for treating anaphylaxis in most
438 patients,⁵⁷ so the 0.3mg adrenaline dose is preferred.

439 *Strength of recommendation:* This is a conditional positive recommendation because
440 it is based on small studies enrolling volunteers who were randomised to different
441 adrenaline autoinjectors. It is uncertain what plasma adrenaline level is therapeutic in
442 anaphylaxis, so it is difficult to make definitive recommendations.

443 *Practical considerations:* In the relatively rare case of an infant less than 7.5kg in
444 bodyweight at risk of anaphylaxis, a prefilled syringe and adrenaline dose of 0.01
445 mg/kg can be used instead of an autoinjector. For adolescents and adult patients, a
446 0.3mg device is recommended although a higher 0.5mg device can be considered
447 where a patient is overweight or has experienced a previous episode of life-
448 threatening anaphylaxis. In a clinical setting, where a patient presents with severe
449 anaphylaxis, a higher dose (eg 0.5mg or 0.3mg repeated for an older adolescent or
450 adult) may be considered.

451 **Other interventions**

452 Our systematic review found no eligible randomised controlled trials assessing the
453 effectiveness of other interventions for the acute management of anaphylaxis. It is
454 recognised that some may be useful as concomitant therapy with adrenaline. These
455 interventions are briefly described although no robust evidence is available.

456 Oxygen

457 Give high flow oxygen to a patient experiencing anaphylaxis.

458 Fluid support

459 Administer intravenous fluids early with first adrenaline dose to patients with
460 cardiovascular involvement as adrenaline may not be effective without restoring the
461 circulatory volume. Crystalloids are preferred given in boluses of 10 ml/kg (maximum
462 500ml per bolus) for children and 500ml in adults, repeated as needed. This should
463 be repeated if lack of response. Fluid support could also be given in severe
464 anaphylaxis with a respiratory presentation if a second dose of intramuscular
465 adrenaline is required.

466 H1 and H2 antihistamines

467 Systemic antihistamines have only been demonstrated to relieve cutaneous
468 symptoms⁸⁴ and a possible effect on non-cutaneous symptoms remains
469 unconfirmed.⁸⁵

470 Glucocorticoids

471 Glucocorticoids are commonly used in anaphylaxis as they are thought to prevent
472 protracted symptoms and possibly biphasic reactions but there is limited evidence of
473 their effectiveness and they may be deleterious in children.^{85,86}

474 Inhaled Beta2-Agonists

475 In the case of predominant bronchial obstruction, inhaled β -adrenoreceptor agonists,
476 (e.g. salbutamol) can be additionally administered (best using an oxygen driven
477 nebulizer or via metered dose inhaler using a “spacer”).

478 Inhaled adrenaline

479 In cases with suspected laryngeal/pharyngeal oedema inhaled administration of
480 adrenaline via a nebulizer together with oxygen is recommended. The systemic
481 absorption of inhaled adrenaline is negligible⁴⁸ and it should only be used as a
482 supplement to i.m. administration.

483

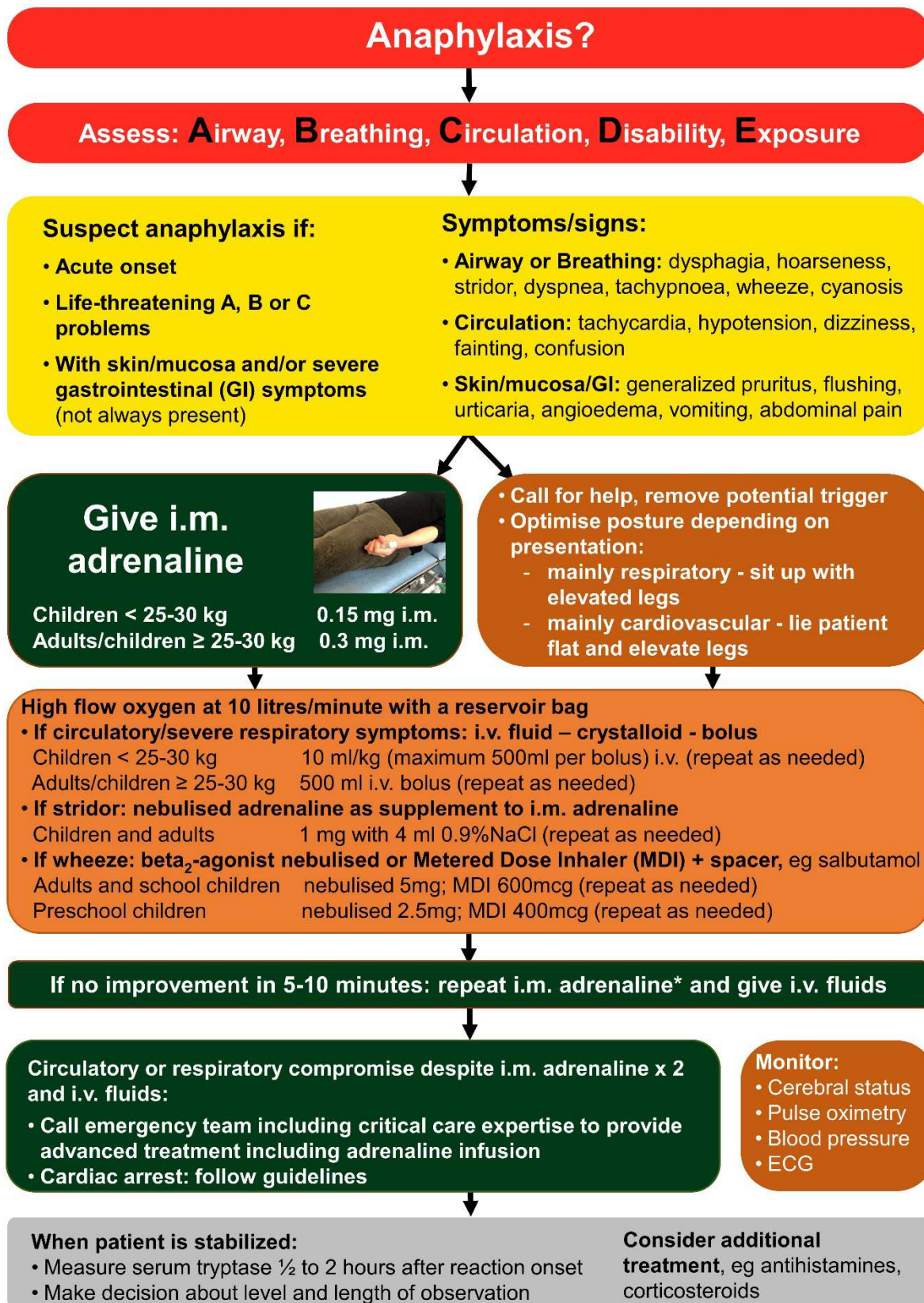
484 **Monitoring and discharge arrangements**

485 Patients with anaphylaxis are at risk of protracted reactions and of developing
486 biphasic reactions although the likelihood is low^{85,87} (Table 4). The Task Force
487 suggest that they are monitored for 6-8 hours with respiratory compromise and at
488 least 12–24 hours with hypotension. Before discharge, assess the risk of future
489 reactions and prescribe adrenaline auto-injectors to those at risk of recurrence (Box
490 4). Provide patients with written advice covering allergen avoidance measures and
491 instructions for when and how to use the adrenaline autoinjector. Refer patients to an
492 allergy specialist to investigate possible triggers. This is particularly important for
493 idiopathic anaphylaxis where reactions to hidden allergens, such as alpha-gal or

494 drug excipients, can be examined. The allergist will also assess the risk of further
495 reactions, and ensure that patients and caregivers are optimally equipped and
496 trained to manage any further reactions. A specialist dietitian can provide helpful
497 advice where the trigger is a food. Also signpost patients to local patient advocacy
498 groups as sources of further information and ongoing support.

499

500 **Figure 1. Schematic illustration of the initial management of anaphylaxis**



*Consider (i) giving second dose by needle and syringe in case of autoinjector failure and (ii) using 0.5mg dose for adolescents or adults.

Modified from the 2020 Danish National Anaphylaxis guideline (12.06.21)

501

502 **Table 4. Factors leading to need for prolonged observation following anaphylaxis**

Prolonged observation following anaphylaxis: factors to consider

Factors relating to the patient:

- Reactions in individuals with severe asthma⁸⁸
- Patients presenting in the evening or at night, or those who may not be able to respond to any deterioration⁸⁸
- Patients in areas where access to emergency care is difficult⁸⁸
- Patients with a previous history of biphasic reactions⁸⁸

Factors related to the reaction, potentially increasing the risk of a biphasic reaction:

- With multi-organ involvement⁸⁷
- With a severe respiratory component⁸⁸
- Needing administration of >1 dose of epinephrine for the treatment of the initial anaphylaxis⁸⁵
- Caused by allergen with continued absorption of the allergen, eg food⁸⁸
- With unknown elicitor⁸⁵

503 Supporting references taken from the anaphylaxis systematic review with additional ones from a
504 specific review of the literature focused on prolonged or biphasic reactions.

505

506

507 LONG-TERM MANAGEMENT OF ANAPHYLAXIS

508 The following sections detail the long-term management of patients at risk of
509 anaphylaxis. Further justification about each of the recommendations about
510 managing anaphylaxis is included in online supplement Table S3. A summary of
511 long-term management in the community is presented in Box 5. Boxes 6 and 7
512 provides examples of individualised paediatric emergency action plans.

Box 5. Summary of the long-term management in the community of patients at risk of anaphylaxis

Individualized management plan and emergency kit

- Provision of individualized management plan written clearly in simple, non-medical language; it must include:
 - personal identification data: name, address, contact number; also consider adding a photograph
 - details of the parents, guardian, or next of kin, allergist
 - family doctor and the local ambulance service
 - clear identification of the source of the allergens to be avoided and allergen avoidance advice
 - clear identification of any non-allergen triggers or cofactors (e.g. exercise) and avoidance advice
 - anaphylaxis emergency action plan
- Copy of plan must be kept by the patient, any caregivers, school staff, and family doctor
- Provision of emergency kit with copy of anaphylaxis emergency action plan and medications for self-treatment, e.g.
 - adrenaline auto-injector for treating anaphylaxis, where appropriate (EMA recommends that patients have access to two devices)
 - fast-acting, non-sedating, antihistamine for treating cutaneous allergic reactions, where appropriate
- Implementation of the patient's management plan in the community (e.g. nursery, school university work)
- Advice to carry mobile phone (if appropriate)
- Discuss a form of medic alert notification
- Review of plan including doses with age and weight

Education and training

- Training of patients and caregivers, this must include:
 - instructions on appropriate allergen avoidance measures,
 - including consultation with an allergy dietitian, where appropriate if food is the trigger
 - instructions on prompt recognition of symptoms of anaphylaxis
 - training on when and how to use an adrenaline auto-injector, where appropriate and to carry them at all times
 - explanation of expiry of devices, reminders and process for renewal and storage
- Reinforcement with revision at regular intervals, possibly with asthma reviews
- Retraining on device if device switched
- Sign post patient support groups

Specific therapy

- Venom immunotherapy as appropriate
- Desensitization for drug allergy as appropriate

Other considerations

- Psychological support as required to patient and family/carers
- Ensure optimal management of co-morbidities such as rhinitis and asthma
- Support during transition to adulthood with good communication specialist units advice on at risk behaviour
- Log allergies in hospital and community medical records
- Re-referral or advice and guidance to allergy unit if new symptoms with foods or repeat admissions

EMA: European Medicines Agency.

513

514

Box 6. Example of an individualised emergency action plan for a child

Action to take:

- Stay with the child, call or help if necessary
- Locate adrenaline autoinjectors
- Give long-acting, non-sedating antihistamine if required: medication _____, dose _____
- Phone parent/emergency contact: _____

Watch for signs of ANAPHYLAXIS (life-threatening allergic reaction)

Anaphylaxis may occur without skin symptoms: ALWAYS consider anaphylaxis in someone with known food allergy who has **SUDDEN BREATHING DIFFICULTY**

A: AIRWAY

- Persistent cough
- Hoarse voice
- Difficulty swallowing
- Swollen tongue

B: BREATHING

- Difficult or noisy breathing
- Wheeze or persistent cough

C: CIRCULATION

- Persistent dizziness
- Pale or floppy
- Suddenly sleepy
- Collapse/unconscious

IF ANY ONE (OR MORE) OF THESE SIGNS ABOVE ARE PRESENT:

1. Lie child flat with legs raised (if breathing is difficult, sit up with elevated legs)
2. Use Adrenaline autoinjector without delay (Device: _____, dose _____)
3. Dial _____ for ambulance and say ANAPHYLAXIS (“ANA-FIL-AX-IS”)

***** IF IN DOUBT, GIVE ADRENALINE *****

AFTER GIVING ADRENALINE:

1. Stay with child until ambulance arrives, **do NOT** stand child up
2. Commence CPR if there are no signs of life
3. Phone parent/emergency contact
4. If no improvement after 5-10 minutes, give a further adrenaline dose using a second autoinjectable device, if available.

You can dial emergency number from any phone, even if there is no credit left on a mobile. Medical observation in hospital is recommended after anaphylaxis.

Adapted from British Society of Allergy and Clinical Immunology paediatric allergy action plans (<https://www.bsaci.org/professional-resources/resources/paediatric-allergy-action-plans/>, last accessed 26th September 2020).

How to give an adrenaline autoinjector:

- Instructions for how to give an adrenaline autoinjector differ between devices.
- Patients should receive training in how to use the auto-injector they are prescribed.

515

516 Instructions as to how to administer a particular autoinjector can be added to the “How to give an
517 adrenaline autoinjector” box.

Box 7. Example of an individualised emergency action plan for a young person or adult

Mild/moderate reaction:

- Swollen lips, face or eyes
- Itchy/tingling mouth
- Hives or itchy skin rash
- Abdominal pain or vomiting

Action to take:

- Let others know, call for help if necessary
- Locate adrenaline autoinjectors
- Take long-acting, non-sedating antihistamine if required: medication _____, dose _____mg
- Watch for development of more severe symptoms

Watch for signs of ANAPHYLAXIS (life-threatening allergic reaction)

Anaphylaxis may occur without skin symptoms. If you have food allergy, ALWAYS consider anaphylaxis if you develop **SUDDEN BREATHING DIFFICULTY**

A: AIRWAY

- Persistent cough
- Hoarse voice
- Difficulty swallowing
- Swollen tongue

B: BREATHING

- Difficult or noisy breathing
- Wheeze or persistent cough

C: CIRCULATION

- Persistent dizziness
- Suddenly sleepy
- Collapse/unconsciousness

IF ANY ONE (OR MORE) OF THESE SIGNS ABOVE ARE PRESENT:

1. Lie flat with legs raised (if breathing is difficult, sit up with legs raised/bent)
2. Use Adrenaline autoinjector without delay (Device: _____, dose _____mg)
3. Dial _____ for ambulance and say ANAPHYLAXIS (“ANA-FIL-AX-IS”)

***** IF IN DOUBT, GIVE ADRENALINE *****

AFTER GIVING ADRENALINE:

1. Do **NOT** stand up
2. CPR should be started if there are no signs of life
3. Phone emergency contact (_____)
4. If no improvement after 5-10 minutes, give a further adrenaline dose using a second autoinjectable device, if available.

You can dial emergency number from any phone, even if there is no credit left on a mobile. Medical observation in hospital is recommended after anaphylaxis.

Adapted from British Society of Allergy and Clinical Immunology paediatric allergy action plans (<https://www.bsaci.org/professional-resources/resources/paediatric-allergy-action-plans/>, last accessed 26th September 2020).

How to give an adrenaline autoinjector:

- Instructions for how to give an adrenaline autoinjector differ between devices.
- Patients should receive training in how to use the auto-injector they are prescribed.

518

519 Instructions as to how to administer a particular autoinjector can be added to the “How to give an
520 adrenaline autoinjector” box.

521 **Education to improve acute management**

522 Education and training for patients at risk of anaphylaxis

523 *The EAACI Task Force recommends providing structured, comprehensive training to*
524 *improve knowledge and use of adrenaline autoinjectors in people at risk of*
525 *anaphylaxis. This is in addition to basic instructions about autoinjector use.*

526 *Reason for recommendation:* There is some evidence from research and clinical
527 experience that repeated information and support helps patients feel more
528 knowledgeable and confident about managing triggers and responding in an
529 emergency.^{89,90} (Box 5) (more details in Table S3).

530 *Strength for recommendation:* This is a conditional positive recommendation.
531 Although there are randomised controlled trials about educating patients, the
532 certainty of evidence was low. It is unclear what types of training and support are
533 most effective.

534 *Practical implications:* Education is essential if patients at risk of anaphylaxis are to
535 successfully recognise and manage future episodes. Many patient training
536 approaches are available, including the use of adrenaline autoinjector training
537 devices and online approaches.⁷¹

538 Other potential educational interventions

539 Some studies have also found that supporting patients to practise using an
540 adrenaline autoinjector or needle and syringe containing 0.9% saline can reduce
541 anxiety or improve quality of life.^{91,92} This approach may be helpful in anxious
542 patients but requires adequate resources and preparation. More research focused
543 on supervised self-injection with an adrenaline autoinjector with outcomes evaluated
544 using disease-specific quality-of-life and self-efficacy measures is needed. In the
545 case of anaphylaxis during an in-hospital based food/ drug challenge, patients and
546 carers may be encouraged to administer their own adrenaline autoinjector to improve
547 their confidence in this procedure.⁹³ It is also important for allergists to follow a
548 patient's anaphylaxis management plan during a provocation challenge (eg giving im
549 adrenaline with the first sign of anaphylaxis) to re-inforce this self-management
550 approach.

551

552 **Pharmacological approaches to prevent anaphylaxis**

553 Premedication with antihistamine

554 *The EAACI task force makes no recommendation for or against using premedication*
555 *with antihistamine to prevent anaphylaxis.*

556 *Reason for no recommendation:* We found insufficient evidence about the
557 effectiveness of antihistamines in preventing anaphylaxis.^{94,95} A recent meta-analysis
558 that included observational studies and studies where the outcome was
559 hypersensitivity not anaphylaxis concluded that antihistamines and or glucocorticoids
560 may prevent index reactions to chemotherapy but not radio-contrast media (very low
561 certainty evidence).⁸⁵

562 *Practical implications:* Antihistamines are helpful at reducing reactions to allergen
563 immunotherapy but this is outside the scope of the current guidelines.⁹⁶

564 Premedication with adrenaline for snake bite anti-venom

565 *The EAACI task force suggests using premedication with subcutaneous adrenaline*
566 *to prevent anaphylaxis when snake bite anti-venom is given to a patient.*

567 *Reason for recommendation:* There is some evidence that low dose, subcutaneous
568 adrenaline can prevent anaphylaxis caused when snake anti-venom is given to a
569 patient ^{97,98}(more details in Table S3).

570 *Practical implications:* For this very specific scenario, pre-medication with low dose,
571 subcutaneous adrenaline may be useful when a patient who has suffered a snake
572 bite is treated with snake anti-venom. The task force found no evidence that
573 antihistamines or hydrocortisone could prevent anaphylaxis associated with snake
574 bite anti-venom (online supplement Table S3).

575

576

577 **Approaches to prevent anaphylaxis in schools**

578 Use of policy to improve management in schools

579 *The EAACI task force suggests that school policies should reflect anaphylaxis*
580 *guidelines but more research is needed to understand how guidelines and legislation*
581 *in schools is best implemented.*

582 *Reason for recommendation:* There is emerging evidence to support the value of
583 school policies in improving the management of anaphylaxis in an education
584 setting.⁹⁹ Anaphylaxis due to food allergy, occurs in schools more than in any other
585 community location.^{100,101} It may therefore be helpful to target secondary schools and
586 community settings with educational support to help raise general awareness,
587 empower adolescents to confidently self-manage food allergy and enable schools to
588 develop protocols to minimise any adverse events if they occur (more details in
589 Table S3).

590 *Strength recommendation:* This is a conditional positive recommendation because
591 the certainty of the evidence is very low. Although there was only one study and it
592 was at high risk of bias, we believe that schools need more support to prioritise
593 systems to ensure that children at risk of anaphylaxis are protected in schools.

594 *Practical implications:* While there is some evidence to support a policy approach to
595 improving the management of anaphylaxis in schools. For example, in a pilot study
596 in two UK schools¹⁰², full stakeholder involvement in toolkit development, based on
597 EAACI guidelines, was found to raise awareness and empower pupils with/without
598 allergies to self-manage effectively. However, there are barriers to the
599 implementation of legislation¹⁰³. Work needs to be done to understand how best to
600 implement legislation and guidelines in schools, including how best to train schools
601 staff.¹⁰⁴ Furthermore, standard allergy policies, such as those supplied by national or
602 local authorities, may lack the school-specific practical solutions necessary for
603 effective implementation. A similar approach may be helpful for pre-school care
604 settings.

605 Other approaches

606 Other approaches researched to improve the management of anaphylaxis included
607 nurses checking whether students were carrying autoinjectors¹⁰⁵ and availability of a

608 24-hour helpline.¹⁰⁶ None of these had sufficient evidence to warrant a
609 recommendation.

610

611 **EDUCATION AND TRAINING FOR HEALTHCARE PROFESSIONALS**

612 Simulation training and visual prompts for healthcare professionals

613 *The EAACI task force suggests using simulation training and visual prompts to*
614 *improve healthcare professionals' recognition and management of anaphylaxis in*
615 *emergency situations.*

616 *Reason for recommendation:* Healthcare professionals are not well prepared to
617 recognise and manage anaphylaxis.^{107,108} Simulation-based training is well
618 established across medicine and there is emerging evidence that it may help
619 professionals recognise and react to anaphylaxis. (more details in Table S4).
620 Similarly, there is some evidence that visual aids such as wallet sized prompt sheets
621 or flow diagrams can help healthcare professionals understand and better manage
622 anaphylaxis.¹⁰⁹⁻¹¹¹

623 *Strength of recommendation:* This is a conditional positive recommendation as the
624 quantity and quality of available evidence is low. It is based on a number of small
625 randomised controlled trials, the majority of which were at high risk of bias and
626 focused on different endpoints so there was very low overall certainty in the
627 evidence.

628 *Practical implications:* Simulation training is well established and accepted as a
629 teaching method. Scenarios based on anaphylaxis could be included in simulation
630 training programmes for healthcare professionals. With regards to visual aids, these
631 need to be readily accessible to healthcare professionals who may encounter
632 anaphylaxis in their practice. A number of modalities can be considered, for example
633 wallet size prompt sheets, posters in emergency rooms or electronic apps.

634

635

637 **SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES**

638 This guideline is intended to provide the best current evidence on the appropriate
639 diagnosis and management of anaphylaxis both at the acute episode and in the
640 long- term management. The diagnosis of anaphylaxis is still based on the clinical
641 evaluation. In suspected reactions, measuring serum tryptase within the first 2 hours
642 of reaction can help the allergist to subsequently make a diagnosis. Adrenaline is
643 confirmed to be the first line treatment, to be administered intramuscularly and
644 timely. Likewise, the provision of the adrenaline auto-injector is the cornerstone for
645 the long term management. The task force recommends that pharmacokinetic data
646 should be made available, especially for any new devices. The European Medicines
647 Agency recommends “ *that two auto-injectors are prescribed to any patient at-risk*
648 *who should carry them all times.*”⁵⁶ Although this recommendation is valid in all the
649 EU countries, the task force is aware that there are differences in implementation,
650 availability of auto-injectors and reimbursement. Patients need an individualized plan
651 for managing anaphylaxis as well as education. Health professionals, nursery staff
652 and teachers also need training. We have considered the facilitators and barriers to
653 implementing these recommendations (Table 5).

654 **Strengths and limitations**

655 A strength of this guideline is that it is informed by a balance of evidence and expert
656 opinion. A comprehensive systematic review was undertaken evaluating the
657 evidence according to well-established GRADE methods. We focused on
658 randomised controlled trials to provide the highest quality available evidence. The
659 review was led by independent methodologists with no conflicts of interest. It is a
660 strength that the recommendations were also based on expert clinical and patient
661 opinion, balancing benefits and harms and considering values and preferences. This
662 included a range of countries, disciplines and clinical backgrounds, including primary
663 care and patient organisations. So where the evidence was not clear or sufficient, a
664 broad based consensus could be achieved.

665 A limitation of the guideline is that there is heterogeneity and gaps in existing
666 knowledge, making it difficult to draw firm conclusions. Much of the research does

667 not use robust diagnostic criteria for anaphylaxis and there are other methodological
668 weaknesses meaning that most recommendations are based on low or moderate
669 certainty evidence. The heterogeneity in the studies, including different study
670 populations, variations in interventions at different ages and duration, and varying
671 definitions of anaphylaxis made it challenging to interpret the evidence. It was not
672 appropriate to undertake meta-analysis to combine such heterogeneous studies.

673 **Research gaps**

674 There is much left to learn about diagnosing and managing anaphylaxis. Table 6
675 sets out key priorities. Where possible, evidence ought to be derived from double-
676 blind, placebo-controlled randomised trials. Future studies would ideally include a
677 harmonized definition and robust diagnostic criteria for anaphylaxis. High priority
678 gaps are the need of biomarkers which can predict the level of risk for a given
679 patient, the role of monoclonal antibodies in reducing the risk as well as getting
680 evidence on the most adequate educational intervention or combination of
681 interventions for prevention of the acute episode.

682 **Conclusions**

683 Implementing these recommendations would result in harmonization of the best
684 standards of practice for anaphylaxis. The ultimate goal would be the development of
685 an evidence- based, multifaceted and integrated patient-centric approach which
686 may help to alleviate the burden of anaphylaxis amongst individuals and families and
687 also reduce societal healthcare costs.

Topic	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
Using clinical criteria to identifying anaphylaxis in an emergency situation	Various definitions of anaphylaxis are still in place Lack of knowledge and experience	Training on validated list of rapid onset of signs and symptoms with accessible reminders (eg wallet, phone, internet)	Proportion of emergency settings in which the validated criteria is used	Cost of implementing standardized, validated, universal definition low
Measuring serum tryptase to support the diagnosis of anaphylaxis retrospectively	Lack of knowledge regarding tryptase in emergency department Tryptase sample should not delay acute diagnosis and treatment Lack of infrastructure for taking and analysing samples	Training about use of tryptase for emergency department staff Identification of laboratories with the relevant equipment	Proportion of anaphylaxis patients where tryptase is assessed	The cost of measuring tryptase, although low, needs to be taken into account
Healthcare professionals treating anaphylaxis with I.M. adrenaline and using the correct dosing	Differences in labelling of adrenaline (e.g. ratios 1:1000 or mass concentration 1mg/ml) Synonym epinephrine used in some countries Lack of training	Training healthcare professionals Standardization of labelling Add to mandatory annual training	Proportion of cases treated with I.M. adrenaline using the correct dosage	Resources needed for training and standardizing adrenaline
Use of adrenaline autoinjectors by patients	Lack of training Fear or embarrassment to use	Training patients and care givers with simulated scenarios Identify and treat needle phobia	Proportion of patients experiencing anaphylaxis who use an autoinjector	Autoinjectors are relatively expensive, most of not used and they have a relatively

	<p>Not carrying AAI all times</p> <p>Needle phobia</p>	<p>Use of trainer devices</p> <p>Reminders to carry devices</p> <p>Access to training materials including online videos</p>		<p>short shelf-life</p>
<p>Education and training for patients and carers in anaphylaxis recognition and management</p>	<p>Training packages need to be developed and harmonized across regions</p> <p>Unclear which elements and structure are most beneficial</p> <p>Repeated training is likely to be of greater benefit</p>	<p>Patients and patient groups place great value on patient training</p> <p>Multiple different modalities of training can be developed (face-to-face, virtual)</p> <p>Online training already provided by commercial companies and patient organizations</p>	<p>Proportion of patients/ carers who have been offered and accessed a comprehensive training package after diagnosis</p>	<p>Training packages are costly to develop and implement, both financially and in terms of the time taken</p>
<p>Use of simulation training and visual prompts for healthcare professionals</p>	<p>Anaphylaxis specific simulation training packages need to be developed and validated</p> <p>Visual prompts need to be of a suitable format and kept updated and accessible</p>	<p>Simulation training is a well-established training modality</p> <p>Visual prompts are used for other medical emergencies</p> <p>Standardisation of devices where possible</p>	<p>Proportion of healthcare professionals who have received simulation training</p> <p>Proportion of healthcare professionals with access to visual management prompts</p>	<p>For simulation training costs can be high; also time-consuming</p> <p>For visual prompts, costs are low as these are inexpensive to produce</p>
<p>Use of policy to improve management in schools</p>	<p>Inaccessible clinically focussed documents</p> <p>Impractical standard allergy policies</p>	<p>Identification of specific needs and concerns in order to develop practical applications for schools that can be</p>	<p>Implementation of policy in school</p> <p>Proportion of students</p>	<p>Initially relatively high, but subsequently low once protocols are in</p>

		implemented in real world context	who experience anaphylaxis	effect
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708 **Table 6. Gaps in the evidence for managing anaphylaxis**

Gaps	Suggestion to address	Priority
Data comparing the pharmacokinetics of different adrenaline auto-injector devices	Clinical randomised controlled trial	High (1 st)
Optimal dose and dosing intervals of intramuscular adrenaline in patients experiencing anaphylaxis	Clinical randomised controlled trial	High (2 nd)
Clinical definition and diagnostic criteria for anaphylaxis that are easy to use in emergency situations.	Large community based studies to develop, validate and assess ease of use of criteria	High (3 rd)
Identification of biomarkers to predict severity of anaphylaxis	Follow up of clinical cohorts at varying risks of anaphylaxis	Medium (4 th)
Biomarkers for bedside testing to support diagnosis	Clinical cohorts experiencing anaphylaxis and similar presentations	Medium (5 th)
Standardised severity grading for anaphylaxis	Clinical cohorts experiencing acute allergic reactions and consensus discussion	Medium (5 th)
Role antihistamines, corticosteroids or adrenaline to prevent anaphylactic reactions in high risk situations	Large randomised controlled trials in high risk situations (i.e. re-administration of contrast media after a previous reaction)	Medium (7 th)
Value of practising self-injection (using functioning adrenaline autoinjector devices) to a sub-group of patients that may be too anxious otherwise to use their auto-injector in real life.	Randomised controlled studies with outcomes focused on allergy specific quality of life, self-efficacy and anxiety	Medium (8 th)
Role of second-and third line drugs in the treatment of anaphylaxis	Clinical randomised controlled trial	Medium (9 th)
Identification of different endotypes of anaphylaxis which may benefit from different management	Analysis of large data sets considering different elicitors	Medium (10 th)
More convenient routes of administration of adrenaline eg intranasal, inhalational, sublingual	Clinical randomised controlled trial, initially pharmacokinetic studies in well individuals, then randomised controlled trials in high risk patients or situations	Low (11 th)

Effectiveness of smartphone based applications to improve recognition and management of anaphylaxis for patients	Community randomized controlled studies, with a focus on patient involvement in app development and patient engagement	Low (12 th)
Best approach to implementing guidelines and legislation in schools	Qualitative methods (e.g. Interviews/focus groups) with students and staff to identify specific needs and concerns in order to develop practical applications Then large school based randomised controlled trial to assess the effectiveness of implementation	Low (13 th)
Standardised questionnaires for quality of life for patients at risk of anaphylaxis from any elicitor	Analysis of large data sets from patients considering different elicitors	Low (14 th)

709 Prioritisation was agreed by consensus within the guideline task force.

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717

718 **AUTHOR CONTRIBUTIONS**

719 Antonella Muraro, Graham Robert and Margitta Worm chaired the EAACI
720 Anaphylaxis Guideline Task Force. Cherry Alviani, Victoria Cardona, Audrey
721 DunnGalvin, Lene H. Garvey, Carmen Riggioni, Graham Roberts and Margitta Worm
722 led the discussions for individual sections drafting the evidence table,
723 recommendations and gaps for specific sections based on the underpinning
724 systematic review and task force discussions which involved the authors. Graham
725 Roberts, Antonella Muraro and Margitta Worm wrote the initial draft of the guideline.
726 All authors participated in the discussion of the draft guideline, its revision and

727 approved the final version. Antonella Muraro chaired the EAACI Food Allergy and
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731

732 **CONFLICT OF INTERESTS**

733 Professor Muraro reports grants and personal fees from Aimmune and personal fees
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735 President of EAACI.

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742 Dr. Alviani has nothing to disclose.

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745 plus past WAO chair anaphylaxis committee.

746 Dr. DunnGalvin has nothing to disclose.

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749 Dr. Riggioni has nothing to disclose.

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