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1 **Title: The pathophysiology of anaphylaxis**

2

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31

32 ***Abbreviations used:***

33 ASA: Active systemic anaphylaxis
34 CysLT: Cysteinyl leukotriene
35 DT: Diphtheria toxin
36 DTR: Diphtheria toxin receptor
37 HDC: Histidine decarboxylase
38 Ig: Immunoglobulin
39 LT: Leukotriene
40 mAb: Monoclonal antibody
41 MCPT: Mast cell protease
42 MPO: Myeloperoxidase
43 OVA: Ovalbumin
44 PAF: Platelet-activating factor
45 PAF-AH: Platelet-activating factor acetylhydrolase
46 PAFR: Platelet-activating factor receptor
47 PCA: Passive cutaneous anaphylaxis
48 PGD₂: Prostaglandin D₂
49 PSA: Passive systemic anaphylaxis

50 **Abstract**

51 Anaphylaxis is a severe, systemic hypersensitivity reaction that is rapid in onset and
52 characterized by life-threatening airway, breathing, and/or circulatory problems, and that is
53 usually associated with skin and mucosal changes. Because it can be triggered in some people
54 by minute amounts of antigen (e.g. certain foods or single insect stings), anaphylaxis can be
55 considered the most aberrant example of an imbalance between the cost and benefit of an
56 immune response. This review will describe current understanding of the
57 immunopathogenesis and pathophysiology of anaphylaxis, focusing on the roles of IgE and
58 IgG antibodies, immune effector cells, and mediators thought to contribute to examples of the
59 disorder. Evidence from studies of anaphylaxis in humans will be discussed, as well as
60 insights gained from analyses of animal models, including mice genetically deficient in the
61 antibodies, antibody receptors, effector cells, or mediators implicated in anaphylaxis, and
62 mice which have been “humanized” for some of these elements. We also will review possible
63 host factors which may influence the occurrence or severity of anaphylaxis. Finally, we will
64 speculate about anaphylaxis from an evolutionary perspective, and argue that, in the context
65 of severe envenomation by arthropods or reptiles, anaphylaxis may even provide a survival
66 advantage.

67

68 **Introduction**

69 The recent “International Consensus on (ICON) Anaphylaxis” described anaphylaxis as “a serious,
70 generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal”.¹
71 This definition is intentionally “generic”, in that it doesn’t mention any of the specific
72 immune elements that might be involved in particular instances of the disorder, as these may
73 vary depending on individual circumstances. In this review, we will describe the key immune
74 elements, such as antibody isotypes, effector cells, and biological mediators, which can
75 contribute to development and pathophysiological manifestations of anaphylaxis. We in
76 particular will note the extent of evidence implicating these immune components in
77 anaphylaxis in humans versus that induced in mouse models of the disorder, focusing
78 especially on forms of anaphylaxis induced by the reactions of allergens with antigen-specific
79 antibodies. We will not extensively review forms of anaphylaxis induced by the antibody-
80 independent activation of effector cells such as mast cells and basophils, topics which have
81 been reviewed elsewhere.^{2,3}

82

83

84 Clinical Anaphylaxis

85 The clinical definition, classification, nomenclature, and treatment of anaphylaxis have been
86 points of controversy, varying among different medical subspecialties and in different
87 countries, and it became clear that an important goal for the field would be to achieve a true
88 international consensus on these important points.⁴ Subsequently, multinational,
89 multidisciplinary symposia were convened to agree on the definition of anaphylaxis, the
90 clinical criteria for its diagnosis, and its management⁵. Participants agreed on a description of
91 anaphylaxis as “a serious allergic reaction that is rapid in onset and may cause death”, as well
92 as on three sets of clinical criteria to diagnose anaphylaxis.⁵ These criteria were re-affirmed in
93 the recent “International Consensus on (ICON) Anaphylaxis”¹ and are more extensively
94 reviewed elsewhere in this issue (Castells *et al.*⁶). A minority of patients exhibit biphasic
95 allergic reactions, in which signs and symptoms of anaphylaxis recur hours after the early
96 phase of the reaction has waned, and in some patients late phase reactions occur without
97 initial hypotension or airway obstruction.^{7,8} In addition to the biphasic reactions observed in
98 some patients with anaphylaxis induced by a variety of causes, patients who have IgE reactive
99 with the oligosaccharide galactose-alpha-1,3-galactose (“alpha-gal”), which is present in
100 mammalian meat and in some therapeutic antibodies, can exhibit anaphylaxis after a delay of
101 several hours during which no signs or symptoms are apparent.⁹

102 Although there is broad consensus on many aspects of the treatment of anaphylaxis¹⁰⁻
103 ¹² (see also Castells *et al.*⁶), such recommendations are based largely on observational studies,
104 extrapolation from retrospective case reviews, and a few clinical trials.^{10, 11} Injectable
105 epinephrine is universally agreed upon as the first line therapy for anaphylaxis,¹⁰⁻¹² and may
106 counteract many pathophysiological changes in anaphylaxis by acting through: alpha-1
107 adrenergic receptors to induce vasoconstriction, which prevents or diminishes tissue/airway
108 edema, hypotension and distributive shock; beta-1 adrenergic receptors to increase heart rate

109 and cardiac contractility; and beta-2 adrenergic receptors to dilate airways.¹¹ In addition,
110 epinephrine's action on beta-2 adrenergic receptors may potentially block further release of
111 mediators (histamine and eicosanoids) by mast cells and perhaps other effector cells.^{13, 14}

112 Other therapies should be considered second line – and not a substitute for
113 epinephrine. Guidelines generally agree that patients should be placed in a supine position and
114 given crystalloid to maintain perfusion, and oxygen.^{10, 12} H1 and H2 antihistamines may be
115 helpful in treating cutaneous and upper respiratory signs and symptoms, and corticosteroids
116 may help to prevent biphasic reactions, but neither prevent nor treat airway obstruction or
117 circulatory collapse and therefore can't be considered as alternatives to epinephrine.¹⁰⁻¹²
118 Development of novel therapies for anaphylaxis is likely to be guided mainly by limited data
119 from humans and by observations made using animal models.

120

121 **Immunological mechanisms of anaphylaxis**

122 Only limited data on immunological mechanisms of anaphylaxis from human subjects
123 are available due to the life-threatening nature of anaphylaxis and obvious ethical concerns.
124 Human studies of anaphylaxis have included inducing anaphylaxis in volunteers (most often
125 through hymenoptera sting challenge) and collecting samples from patients presenting for
126 emergency management of anaphylaxis. Data obtained in such studies, as well as key findings
127 obtained using mouse models of anaphylaxis, are summarized below, in **Figure 1** and in
128 **Table 1**. The major pathophysiological changes observed during anaphylaxis, and some of
129 the mediators that are thought to contribute to them, are shown in **Figure 2**.

130

131 **Effector molecules and receptors**

132

133 **IgE-dependent anaphylaxis**

134 IgE antibodies undeniably can play an important role in conferring immunological
135 specificity to effector cell activation in anaphylaxis and other allergic diseases.¹⁵⁻¹⁸ IgE is by
136 far the isotype found at the lowest concentrations in the circulation (50-200 ng/ml total
137 circulating IgE in healthy individuals *vs.* ~10 mg/ml for IgG);¹⁵ however, IgE can be found at
138 much higher levels in individuals with allergic diseases.^{16, 19} IgE binds to the high affinity
139 receptor, FcεRI, on the surface of blood basophils and tissue resident mast cells,²⁰ and (in
140 humans to a greater extent than in mice) other cell types, including neutrophils, eosinophils,
141 monocytes and dendritic cells, and platelets.²⁰ Upon exposure to a bi- or multi-valent allergen,
142 crosslinking of FcεRI-bound IgE induces activation of mast cells and basophils, and the
143 immediate release of preformed mediators such as histamine and various proteases, as well as
144 *de novo* synthesis of many inflammatory mediators such as certain leukotrienes,
145 prostaglandins, and cytokines.^{16, 20} The importance of that reaction was demonstrated 50 years
146 ago, when different groups realized that purified IgE was capable of transferring skin
147 reactivity from a sensitized human subjects to naive hosts.^{17, 21-23} Similarly, transfer of
148 antigen-specific IgE into naïve mice sensitizes the animals to develop anaphylaxis upon
149 subsequent exposure to that allergen.^{24, 25} Such IgE-mediated anaphylaxis is abrogated in
150 mice lacking the high affinity IgE receptor FcεRI²⁵, as well as in mast cell-deficient mice,²⁶⁻²⁸
151 highlighting the importance of IgE-mediated mast cell activation in such models of
152 anaphylaxis.

153 Ever since the discovery that IgE can transfer allergen reactivity, the development of
154 antigen-specific IgE antibodies has been regarded as a key risk factor for the development of
155 allergy and/or anaphylaxis upon subsequent antigen exposure. Indeed, quantification of
156 specific IgE levels are used as part of the diagnostic evaluation of those thought to have
157 allergic diseases, and is used to identify potential triggers of anaphylaxis in patients with a

158 history of anaphylaxis.²⁹ Several trials have concluded that the use of the anti-IgE therapeutic
159 antibody omalizumab as adjunctive treatment during food or venom immunotherapies can
160 decrease the risks of severe allergic reactions, including anaphylaxis, and in some but not all
161 trials also has been reported to improve the rapidity and efficacy of immunotherapy in
162 achieving desensitization.³⁰⁻³⁴ In addition, limited clinical data also suggest that omalizumab
163 may prevent spontaneous episodes of anaphylaxis in patients with systemic mastocytosis, a
164 disease characterized by marked increases in mast cell numbers and activity³⁵ (also see the
165 review by Akin *et al.*³⁶ in this issue of JACI).

166 Clearly, however, IgE levels alone do not explain an individual's susceptibility to
167 anaphylaxis. Some patients can experience near fatal anaphylaxis despite having low or
168 undetectable levels of circulating allergen-specific IgE.³⁷ Conversely, allergen-specific IgE
169 can be detected in the plasma of many subjects who do not develop clinical symptoms when
170 exposed to that allergen.³⁸ This is particularly true for hymenoptera venom, where the vast
171 majority (~80%) of people with IgE antibodies specific for hymenoptera venoms have no
172 history of systemic reactions to such venoms.³⁹⁻⁴² Therefore, the presence of antigen-specific
173 IgE antibodies, taken in isolation, does not indicate that the person necessarily will exhibit
174 any, let alone severe, clinical reactivity to the recognized antigens.⁴³⁻⁴⁹

175

176 **IgE-independent anaphylaxis**

177 The fact that some patients experience anaphylaxis despite having undetectable levels of
178 circulating allergen-specific IgE³⁷ suggests the existence of IgE-independent pathways of
179 anaphylaxis. However, it should be noted that a lack of detection of free IgE does not mean
180 that such patients don't have enough FcεRI-bound IgE to experience IgE-mediated
181 anaphylaxis. More definitive evidence for IgE-independent anaphylaxis has been obtained
182 using mouse models (**Table 1**).

183

184 **Role of IgG and FcγRs**

185 Besides IgE, we now know that mouse IgG also can induce passive systemic
186 anaphylaxis (PSA) reactions, with physiological manifestations similar to those seen in IgE-
187 dependent PSA (mainly hypothermia, vasodilatation and cardiopulmonary changes).⁵⁰⁻⁶⁰
188 Whether IgG antibodies also mediate anaphylaxis in humans still remains to be proven, and is
189 the topic of a recent review.² As demonstrated in mice, IgG-mediated anaphylaxis typically
190 requires a much larger dose of antigen than does IgE-mediated anaphylaxis,⁶¹ and systemic
191 anaphylaxis also requires systemic absorption of ingested antigen.⁶² Such conditions could be
192 encountered in the case of anaphylaxis occurring in response to infusion of large quantities of
193 a drug or a therapeutic monoclonal antibody (mAb)² (**Table 1**).

194

195 **Role of complement**

196 Activation of the complement cascade occurs in response to many stimuli, and leads to
197 generation of small polypeptides: C3a, C4a and C5a, also named anaphylatoxins, which are
198 potent inflammatory mediators.⁶³ Multiple lines of evidence suggest that anaphylatoxins
199 might be involved in anaphylaxis. Depletion of complement levels and production of C3a and
200 C5a is observed in human anaphylaxis.^{64, 65} Anaphylatoxins can activate various myeloid
201 cells, including mast cells and basophils.⁶³ Injection of low doses of C3a, C4a or C5a into the
202 skin of healthy volunteers induces immediate wheal and flare reactions.⁶⁶⁻⁶⁹ In addition, one
203 study showed that blood levels of C3a, C4a and C5a correlated with the severity of
204 anaphylaxis in humans.⁶⁵ Several transgenic mouse models have been used to study the
205 importance of the complement pathway in anaphylaxis. Data obtained using these transgenic
206 models are reviewed in **Table 1**, and suggest that, in mice, the effect of complement

207 components on anaphylaxis may be in most cases largely redundant with that of other
208 mediators and may depend on the specific model used.

209

210 **Potential effector cells of anaphylaxis**

211

212 **Mast cells**

213 Mast cells are viewed as key players in IgE-dependent allergies and anaphylaxis.^{16, 70}

214 Mast cells ordinarily express large numbers of the high affinity IgE receptor, FcεRI. During

215 IgE-dependent immune responses, the antigen-dependent cross-linking of antigen-specific

216 IgE bound to FcεRI induces the aggregation of FcεRI, promoting the activation of

217 downstream signaling events that lead to the secretion of several biologically active products

218 thought to be implicated in allergic reactions, such as histamine and various cysteinyl

219 leukotrienes (Cys-LTs).^{16, 71-73} The molecular mechanisms of such IgE-dependent stimulation

220 of mast cells have been extensively reviewed.^{16, 71, 73-75} There is compelling evidence of

221 activation of mast cells during acute anaphylaxis. Although histamine detection can be used

222 to diagnose anaphylaxis (see **Histamine**, below), detection of histamine in clinical blood

223 specimens is difficult due to its extremely short half-life, and histamine isn't a mast cell-

224 specific product, since it can also be released by other cells, including basophils⁷⁶ and

225 neutrophils.^{77, 78} Tryptase is much more stable than histamine, and is considered to be a

226 largely mast cell-derived product.⁷⁹ Mature β-tryptase is stored in mast cell granules and

227 released upon activation, such as in anaphylaxis, whereas α- and β- protryptases are secreted

228 constitutively by mast cells and therefore increased blood levels may indicate increased mast

229 cell burden rather than anaphylaxis.⁷⁹ Elevated levels of tryptase have been detected during

230 acute anaphylaxis in humans.^{65, 79-82} However, the roles of tryptase or other mast cell-derived

231 proteases in anaphylaxis remain unknown. Moreover, in some patients with anaphylaxis, such
232 as children with food allergen-induced anaphylaxis, elevated blood levels of tryptase have not
233 been detected.⁸³ Additional evidence for a role of mast cells in anaphylaxis comes from the
234 observation that patients suffering from mastocytosis, a disease characterized by the presence
235 of high numbers of mast cells in various organs,⁸⁴ have a high occurrence of anaphylaxis.⁸⁵ In
236 children with mastocytosis, increased serum tryptase levels, used as an indicator of mast cell
237 burden, is a risk factor for anaphylaxis and for the severity of anaphylaxis episodes.^{86, 87}

238 Studies using various strains of mast cell-deficient mice also confirmed the key role of
239 mast cells in IgE-mediated anaphylaxis.^{26-28, 58, 88} Several reports now demonstrate that mast
240 cell-deficient mice also have reduced peanut-induced anaphylaxis in active systemic
241 anaphylaxis (ASA) models.⁸⁹⁻⁹³ However, the role of mast cells in ASA models using other
242 antigens/allergens is more controversial (summarized in **Table 1**). Therefore, it is likely that
243 mast cells play either dominant or largely redundant roles in anaphylaxis, and that the mast
244 cells' role can be enhanced - or masked - depending on the exact model, adjuvant and allergen
245 used.

246

247 **Basophils**

248 Human basophils also express high levels of the high affinity IgE receptor FcεRI,⁹⁴ and
249 express the activating IgG receptor FcγRIIA and the inhibitory IgG receptor FcγRIIB.⁹⁵
250 Several lines of evidence suggest that basophils participate in anaphylaxis.⁷⁶ For example,
251 IgE-dependent activation of human basophils is associated with elevations in the levels of
252 certain basophil cell surface markers, such as CD203c or CD63, and this forms the basis of
253 “basophil activation tests” which can be used to diagnose or confirm allergen sensitization,
254 and to monitor the effects of efforts to treat these conditions with immunotherapy.⁹⁶⁻⁹⁹
255 However, it is difficult to ascertain how important a contribution basophils make to the

256 pathology of anaphylaxis in humans, given the concomitant mast cell activation that occurs in
257 this setting. Even in mice, the role of basophils in anaphylaxis is unsettled (**Table 1**).

258

259 **Monocytes/macrophages**

260 Monocytes and macrophages express high levels of activating FcγRs,¹⁰⁰ and can also
261 respond to anaphylatoxins.¹⁰¹ Studies in mice have shown that depletion of
262 monocytes/macrophages using clodronate liposomes can reduce anaphylaxis in both IgG-
263 mediated passive models and active models^{52, 89, 92, 102, 103} (**Table 1**). These data suggest that
264 monocytes/macrophages might play an important role in anaphylaxis. However, to the best of
265 our knowledge, the extent to which monocytes/macrophages can contribute to anaphylaxis in
266 humans has not yet been determined.

267

268 **Neutrophils**

269 The potential functions of neutrophils in anaphylaxis have been recently reviewed in
270 detail.¹⁰⁴ Human and mouse neutrophils express several activating FcγRs,¹⁰⁴ can produce
271 histamine,^{77, 78} and can release platelet-activating factor (PAF; please see below for details on
272 the role of PAF in anaphylaxis) in response to stimulation with immune complexes *in vitro*.⁵³
273 Moreover, human neutrophils reportedly can express FcεRI, particularly in some patients with
274 asthma.¹⁰⁵ The major enzyme stored in neutrophils is myeloperoxidase (MPO). A recent
275 report shows that circulating MPO levels are increased in patients with anaphylaxis as
276 compared to healthy donors.¹⁰⁶ Consistent with this, elevated MPO activity can also be
277 detected as soon as two minutes after antigen challenge in an active mouse model of
278 anaphylaxis.⁵³ However, it should be noted that these results do not provide definitive proof
279 of neutrophil activation in anaphylaxis, since MPO could also be potentially released by other

280 cell populations, including macrophages.¹⁰⁷ Reduced expression of the activating IgG
281 receptors FcγRIII and FcγRIV on mouse neutrophils occurs after IgG-mediated PSA, which
282 suggest more definitely that neutrophils could be directly activated by IgG immune
283 complexes during anaphylaxis.^{52, 55} Antibody-mediated neutrophil depletion can reduce
284 anaphylaxis in IgG-mediated PSA^{52, 53, 56} and mast cell-independent ASA models.^{53, 103}
285 However, neutrophil-depleting antibodies had no effect in a mast cell-dependent ASA model
286 induced without artificial adjuvants.¹⁰³ This suggests that neutrophils may be particularly
287 prominent in ASA models induced with adjuvants and that such models may not require any
288 non-redundant contributions of mast cells (**Table 1**).

289

290 **Platelets**

291 Anaphylaxis in humans is associated with platelet activation,¹⁰⁸ presumably in response
292 to PAF and/or other mechanisms, and activated platelets can release mediators, such as
293 platelet factor 4 (PF4) and serotonin,¹⁰⁸ which might contribute to the pathophysiology of
294 anaphylaxis. Moreover, human (but not mouse) platelets can express FcεRI, FcεRII and
295 FcγRIIA,^{95, 109, 110} and platelets can be activated *ex vivo* following incubation with serum from
296 allergic patients and subsequent exposure to the relevant allergen.¹¹¹ Two recent reports have
297 shown that, during basophil activation tests performed in blood specimens *ex vivo*, basophils
298 (a potential source of PAF) can form associations with platelets,^{112, 113} identifying this
299 interaction as one which should be investigated further in the context of anaphylaxis.

300

301 **Potential mediators of anaphylaxis**

302

303 **Histamine**

304 Histamine has long been considered to be an important mediator of anaphylaxis.
305 Woodrow and colleagues showed that aerosol administration of histamine induces
306 bronchoconstriction in healthy volunteers, although the effect of histamine was much less
307 potent than that of leukotrienes (see **Leukotrienes**, below).^{114, 115} Intravenous administration
308 of histamine in volunteers can reproduce many of the signs and symptoms of anaphylaxis,
309 including cutaneous flushing, headache, airway obstruction and transient hemodynamic
310 changes, mainly represented by systemic hypotension, tachycardia, and increased left
311 ventricular performance.^{116, 117} There are four known histamine receptors, named H1-4.¹¹⁸
312 Studies using receptor antagonists suggest that some of the systemic effects of histamine,
313 including airway obstruction and tachycardia, are mainly mediated through H1R, while some
314 others, including cutaneous flushing and headaches, seem to be mediated through both H1
315 and H2 receptors.¹¹⁶ H1 antihistamines are commonly used as adjunctive treatment for acute
316 anaphylaxis and anaphylactoid reactions.¹¹⁹ The contribution of histamine to anaphylaxis has
317 also been confirmed using mouse models (summarized in **Table 1**). Mast cells and basophils
318 likely represent the main sources of histamine in anaphylaxis. In agreement with that,
319 histamine release is abrogated in mast cell-deficient mice in a model of IgE-mediated PSA,²⁷
320 and increases in plasma histamine levels are also abrogated, in two models of ASA, in mice
321 deficient for both mast cells and basophils.^{91, 103}

322

323 **Platelet-Activating Factor (PAF)**

324 PAF is a potent phospholipid-derived mediator implicated in platelet aggregation and
325 thought to play important roles in a variety of immune and inflammatory responses. The
326 biology of PAF and its potential role in anaphylaxis have been recently reviewed in detail.¹²⁰
327 PAF can be released by a variety of human cells, including purified lung mast cells and blood
328 basophils after *ex vivo* stimulation with anti-IgE antibodies,¹²¹ and by purified neutrophils

329 after incubation *in vitro* with heat-aggregated human IgG.¹²² Many of the cell populations
330 which produce PAF can also respond to PAF, including platelets, mast cells, neutrophils and
331 macrophages (reviewed in¹²⁰). Injection of PAF in the skin of healthy volunteers induces
332 wheal and flare reactions.¹²³⁻¹²⁵ Since these reactions could be blocked by H1-antihistamines,
333 it was first proposed that PAF induced wheals via secondary histamine release by dermal
334 mast cells.^{124, 125} However, unlike human lung mast cells and peripheral blood-derived mast
335 cells, skin mast cells do not degranulate in response to PAF stimulation *ex vivo*.¹²⁶ In addition,
336 Krause and collaborators showed that intradermal injection of PAF, unlike that of histamine
337 and codeine, did not cause a statistically significant rise in dermal histamine levels in healthy
338 volunteers.¹²⁷ A limited number of reports have assessed concentrations of PAF or PAF-
339 acetylhydrolase (PAF-AH) - an enzyme responsible for the rapid degradation of PAF - after
340 anaphylaxis in humans. In these reports, circulating PAF levels were increased and circulating
341 PAF-AH activity was inversely correlated with the severity of anaphylaxis.^{65, 82, 128}

342 The contribution of PAF to anaphylaxis has been studied in more detail using
343 pharmacologic and genetic approaches in mouse models (reviewed in **Table 1**). In most
344 models, combined inhibition of histamine and PAF almost entirely blocked anaphylaxis,
345 suggesting additive or synergistic effects of histamine and PAF. The main cellular source of
346 PAF in these reports likely depends on the exact anaphylaxis model used. Using an adjuvant-
347 free active anaphylaxis model, we recently reported that the PAFR antagonist CV-6209 can
348 reduce anaphylaxis in wild-type mice, but has no effect on the residual anaphylaxis observed
349 in monocyte/macrophage-depleted mice, suggesting that monocytes/macrophages represent
350 the major source of PAF in this model.¹⁰³

351

352 **Cysteinyl leukotrienes (CysLTs)**

353 A third class of potential mediators of anaphylaxis was originally termed ‘slow-reacting
354 substance of anaphylaxis’ (SRS-A), and consists of three bioactive cysteinyl leukotrienes
355 (CysLTs): leukotriene B₄ (LTB₄), LTC₄ and LTD₄ (reviewed in¹²⁹). CysLTs are synthesized
356 from arachidonic acid by a variety of cells, including mast cells, basophils and
357 macrophages.¹³⁰ CysLTs and their metabolites can be measured by mass spectrometry, and
358 several reports show that levels of some of these products, namely LTE₄, 2,3-dinor-9 α ,11 β -
359 PGF₂, and 9 α ,11 β -PGF₂, are increased during the onset of anaphylaxis.¹³¹⁻¹³³ While these
360 reports indicate that CysLTs and their metabolites might be good biomarkers of anaphylaxis,
361 they do not prove that these compounds make an important contribution to the clinical
362 manifestations of anaphylaxis. However, multiple observations suggest that CysLTs can
363 promote acute allergic reactions. When injected intradermally in healthy volunteers, each of
364 the three CysLTs elicited a wheal and flare reaction.¹³⁴ In addition, aerosol administration of
365 LTC₄ and LTD₄ in healthy subjects induced bronchoconstriction with 1,000-fold more
366 potency than histamine^{114, 115, 129} (**Table 1**).

367 More definitive evidence for a role of CysLTs in anaphylaxis comes from studies in
368 mice. Mice deficient for LTC₄S (a protein responsible for biosynthesis of LTC₄) or for the
369 Cys-LT receptor CysLT₁R have markedly reduced IgE-mediated passive cutaneous
370 anaphylaxis (PCA).^{135, 136}

371

372 **Other potential mediators**

373 Anaphylaxis induces changes in levels of many other mediators which could potentially
374 contribute (positively or negatively) to the clinical signs and symptoms (**Table 1**). This
375 includes tryptase,^{64, 80, 137-139} prostaglandins^{132, 137} and cytokines/chemokines.^{65, 138} Depletion
376 of the bradykinin precursor, high molecular weight kininogen, has been observed in
377 anaphylaxis, likely through activation of the plasma contact system and kallakrein.^{64, 140, 141}

378 Anaphylaxis patients may also experience depletion of clotting factors, including Factors V
379 and VIII, and in extreme cases develop diffuse intravascular coagulation.^{64, 142} While most
380 patients promptly treated for anaphylaxis recover without obvious sequelae, some develop
381 recurrent signs and symptoms which require continued treatment with epinephrine and for
382 which corticosteroids are administered.^{10, 143} Such sequelae are thought to reflect the “late”
383 consequences of some of the mediators released by effectors of anaphylaxis, such as cysteinyl
384 leukotrienes, cytokines and chemokines, or by structural cells activated in this setting.¹⁴³
385 Finally, mast cells can release adenosine upon IgE-dependent activation, and adenosine can
386 have complex effects, mediated via various adenosine receptors with distinct functions, which
387 have the potential to influence the pathophysiology of anaphylaxis.¹⁴⁴ However, more work is
388 needed to define the importance of most of these mediators in anaphylaxis, particularly in
389 humans.

390

391 **Insights from humanized models of anaphylaxis**

392 Several ‘humanized’ mouse models of anaphylaxis have been developed to investigate
393 the functions of human antibodies, Fc receptors and effector cells in anaphylaxis. Transgenic
394 mice expressing human FcεRI instead of the mouse protein (*hFcεRI^{Tg}* mice) were generated,
395 and the expression profile of the hFcεRI transgene is very similar to that found in humans.¹⁴⁵⁻
396 ¹⁴⁸ *hFcεRI^{Tg}* mice can develop systemic anaphylaxis in response to intravenous sensitization
397 with mouse or human IgE (mouse IgE can bind to human FcεRI, while human IgE can’t bind
398 to the mouse receptor) followed by systemic antigen challenge,^{145, 148} cutaneous anaphylaxis
399 when they are sensitized intra-dermally with serum from peanut-allergic patients and then
400 intravenously challenged with peanut extract.¹⁴⁹ *hFcγRI^{Tg}* and *hFcγRIIA^{Tg}* mice have also
401 been generated, and the expression of hFcγRI or hFcγRIIA in such transgenic mice

402 recapitulates that found in humans.^{150, 151} Each of these transgenic models can develop IgG-
403 mediated anaphylaxis through a mechanism involving monocytes/macrophages and
404 neutrophils.^{122, 152} More recently, Gillis and collaborators developed a novel mouse strain in
405 which the human low-affinity IgG receptor locus, comprising both activating (hFcγRIIA,
406 hFcγRIIIA, and hFcγRIIIB) and inhibitory (hFcγRIIB) hFcγR genes, has been *knocked-in* into
407 the equivalent mouse locus.¹⁵³ These *knock-in* mice are susceptible to PSA induced by
408 injection of heat-aggregated human intravenous immunoglobulin (IVIg). The contribution of
409 hFcγRIIA to anaphylaxis is predominant in these mice, as revealed in experiments using an
410 anti-FcγRIIA blocking antibody.¹⁵³ Antibody-mediated depletion of neutrophils, and to a
411 lesser extent basophils, also ameliorated signs of anaphylaxis. Finally, such anaphylaxis also
412 could be partially inhibited using either a PAF receptor antagonist or a histamine receptor 1
413 antagonist.¹⁵³

414 Recently, three groups independently attempted to generate ‘humanized’ models of
415 anaphylaxis using different strains of highly immunodeficient NOD-scid gamma (NSG) mice
416 engrafted with human stem cells.¹⁵⁴⁻¹⁵⁶ Bryce and colleagues used NSG mice expressing
417 human SCF, IL3 and GM-CSF transgenes (NSG-SGM3 mice), and engrafted them with
418 human thymus, liver, and hematopoietic stem cells. Such engraftment resulted in the
419 development of large numbers of ‘human’ mast cells in NSG-SGM3 mice in the peritoneal
420 cavity and peripheral tissues.¹⁵⁶ The authors could induce both PCA and PSA reactions upon
421 sensitization with a chimeric IgE containing the human constant region, and challenge with
422 the relevant antigen.¹⁵⁶ Burton and colleagues used NSG mice carrying a human SCF
423 transgene and engrafted with human hematopoietic stem cells.¹⁵⁴ The authors demonstrated
424 that such engrafted mice also develop large numbers of ‘human’ mast cells, produce human
425 IgE (hIgE) in response to gavage with peanut extract, and develop anaphylaxis upon
426 subsequent oral challenge with peanut.¹⁵⁴ Importantly, anaphylaxis in this model could be

427 blocked in mice treated with the anti-hIgE antibody omalizumab (which does not recognize
428 mouse IgE).¹⁵⁴ Pagovich et al. also developed a ‘humanized’ model of peanut anaphylaxis in
429 NSG mice engrafted with blood mononuclear cells from patients with peanut allergy with a
430 clinical history of anaphylaxis.¹⁵⁵ These mice produced human IgE and IgG antibodies in
431 response to intraperitoneal sensitizations with peanut, and developed anaphylaxis upon
432 subsequent oral challenges with peanut.¹⁵⁵ Again, anaphylaxis was reduced in mice treated
433 with omalizumab, as well as in mice which had received an adeno-associated virus (AAV)
434 coding for omalizumab.¹⁵⁵

435 Altogether, results from such humanized models of anaphylaxis suggest that both hIgE
436 and hIgG have the potential to induce anaphylaxis through their respective Fc receptors, and
437 also suggest that peanut anaphylaxis is highly dependent on IgE.

438

439 **Genetic diversity/host factors influencing anaphylaxis**

440 Genetic modifiers may influence mast cell activation and the development of
441 anaphylaxis, as demonstrated in differences observed between the 129/Sv and C57BL/6
442 strains of mice.¹⁵⁷ 129/Sv mice demonstrated higher levels of plasma histamine than did
443 C57BL/6 mice following anaphylaxis induced by anti-IgE. Although higher numbers of mast
444 cells and serum IgE levels in the 129/Sv mice could potentially explain these differences, the
445 authors also demonstrated that bone marrow-derived cultured mast cells from 129/Sv mice
446 degranulated more robustly than those from C57BL/6 while synthesizing similar quantities of
447 cytokines.¹⁵⁷ However, the specific genetic modifiers responsible for these observed
448 differences between the two strains of mice remain unknown.

449 Ethnic differences in rates of food allergy and anaphylaxis suggest that genetic
450 modifiers also may exist in human populations.^{158, 159} Reasons for these ethnic disparities
451 remain unclear, but may reflect true genetic differences, environmental factors, including

452 socioeconomic status, or a combination of factors. Nevertheless, a handful of genetic
453 polymorphisms have been described that may influence development of anaphylaxis. Genetic
454 polymorphisms in IL-4R α , IL-10, and IL-13 have been linked to the development of
455 anaphylaxis to drugs and latex¹⁶⁰⁻¹⁶² but theoretically may influence allergen sensitization
456 more than (or in addition to) effector mechanisms during anaphylaxis.

457 Polymorphisms affecting metabolism of mediators of anaphylaxis also may influence
458 anaphylaxis severity. As mentioned above, PAF-AH activity levels inversely correlated with
459 severity of anaphylaxis.^{65, 82, 128} A loss of function mutation in PAF-AH, V279F has been
460 linked with asthma, but not yet with anaphylaxis.¹⁶³ Individuals with variants in
461 angiotensinogen, i.e. the MM genotype associated with decreased levels of angiotensinogen,
462 were reported to have increased rates of hymenoptera venom allergy and more severe
463 reactions during venom immunotherapy.¹⁶⁴ Similarly, amongst patients with tree nut and
464 peanut allergies, lower serum ACE levels were associated with more severe pharyngeal
465 edema, presumably through decreased bradykinin metabolism.¹⁶⁵

466 A few mutations have been described that may influence development and severity of
467 anaphylaxis. An activating mutation in *c-KIT*, D816V, promotes mast cell proliferation in
468 clonal mast cell disorders including mastocytosis^{166, 167} (also see Akins *et al*³⁶ in this issue of
469 JACI). D816V mutations are also found in some patients with recurrent anaphylaxis who do
470 not have increased mast cell numbers on pathology and therefore do not meet criteria for
471 mastocytosis;¹⁶⁸ while this suggests that that their mast cells are hyperresponsive, this has not
472 yet been substantiated. In autosomal dominant hyper-IgE syndrome caused by loss-of-
473 function mutations in *STAT3*, patients have increased levels of total and allergen specific
474 IgEs, but clinically lower rates of anaphylaxis.¹⁶⁹ This clinical observation may be explained,
475 at least in part, by decreased mast cell degranulation¹⁶⁹ and/or by inhibition of enhanced

476 vascular permeability through increased resilience of adherens junctions in patients and cells
477 with STAT3 loss of function mutations.¹⁷⁰

478 The role of sex hormones in anaphylaxis is unclear. Anaphylaxis occurs more
479 commonly in women than men.^{171, 172} Moreover, in a model of PSA, female mice exhibited a
480 greater drop in body temperature than did male mice, and this sex difference could be
481 abrogated by ovariectomy or administration of estrogen antagonist to female mice.¹⁷³
482 However, analysis of patients in an anaphylaxis registry revealed an increased severity of
483 anaphylaxis in male versus female patients of 13-56 years of age, but no sex differences in
484 anaphylaxis severity for prepubescent individuals or those older than 56 years old.¹⁷⁴

485

486 **Recovery from anaphylaxis**

487 Many of those who have experienced anaphylaxis and were not treated have survived the
488 episode, particularly those with less severe presentations. What is the basis of such recovery?
489 Variations in metabolism of mediators, including PAF and bradykinin, may influence
490 manifestations of anaphylaxis^{65, 82, 128, 165} and theoretically the ability to recover from these
491 manifestations. In animal models of anaphylaxis and in humans undergoing insect sting
492 challenge, levels of substances with endogenous vasopressor activity, including epinephrine,
493 norepinephrine and angiotensin II, are increased within minutes following development of
494 anaphylaxis,^{175, 176} likely to compensate for the vasodilation and fluid extravasation occurring
495 during anaphylaxis. Observations that beta-adrenergic blockade can exacerbate systemic
496 anaphylaxis in mouse and rat models^{177, 178} and in people with severe anaphylaxis due to
497 multiple causes,¹⁷⁹⁻¹⁸² particularly when combined with angiotensin converting enzyme
498 (ACE) inhibitors,¹⁸³ support a role for endogenous vasopressors in limiting the severity of
499 pathophysiological changes in anaphylaxis. Mast cell degranulation releases chymase, which
500 can convert angiotensin I to angiotensin II,¹⁸⁴ and may thereby directly contribute to increased

501 angiotensin II levels observed following anaphylaxis. In a recent paper, Nakamura and
502 colleagues showed that mice in which mast cells cannot produce prostaglandin D₂ (PGD₂)
503 have enhanced manifestations of IgE-mediated anaphylaxis. Therefore, it appears that mast
504 cells also can secrete anti-anaphylactic mediators which might help to limit anaphylactic
505 responses.¹⁸⁵ Finally, it is possible that genetically-determined or other differences in mast
506 cell activation or mediator release profiles also might contribute to differences in the
507 manifestations of, or recovery from, anaphylaxis.

508

509 **Can anaphylaxis be beneficial?**

510 Using mouse models, we recently reported that the development of a type 2 immune
511 response to honeybee venom (BV) could increase the survival of mice challenged with whole
512 BV¹⁸⁶. Also, others have shown in mice that a type 2 immune response to BV phospholipase
513 A₂ (bvPLA₂, which is considered to be the major BV allergen in humans) could diminish the
514 drop in body temperature induced by challenge with a “near-lethal” dose of bvPLA₂.¹⁸⁷
515 Importantly, these effects were dependent on IgE,¹⁸⁶ and on the high affinity IgE receptor,
516 FcεRI.^{186, 187} In a follow-up study, we also provided evidence that IgE, FcεRI and mast cells
517 can enhance the survival of mice injected with Russell's viper venom.¹⁸⁸ One of the
518 mechanisms by which innate activation of mouse mast cells can enhance the survival of naïve
519 mice upon their first exposure to various arthropod¹⁸⁹ or reptile¹⁸⁸⁻¹⁹⁰ venoms is the
520 proteolytic reduction of the toxicity of venom components by mast cell-derived
521 carboxypeptidase 3A^{190, 191} or mouse mast cell protease 4 (chymase).¹⁸⁹ Given that snake (or
522 arthropod) envenomation in the field can result in systemic distribution of the venom, one
523 could argue that systemic IgE-dependent mast cell activation in this setting could both
524 produce the clinical picture of anaphylaxis and also result in the systemic release of mediators
525 (i.e. mast cell proteases) that can degrade toxic components of the venom. In such settings,

526 anaphylaxis could be beneficial, if it prevents death by envenomation -- and the unfortunate
527 individual also survives the anaphylaxis. Although we don't know whether human IgE also
528 can enhance resistance to venoms (and we imagine that we would have some trouble enlisting
529 volunteers for such a study), it is tempting to speculate that anaphylaxis induced by small
530 amounts of venom (e.g. a single or wasp bee sting) represents only the most extreme and
531 maladaptive end of a spectrum of acquired IgE-mediated immune responses to venom that
532 includes, at the other end of the spectrum, appropriately regulated immune responses that can
533 enhance resistance to such venoms.

534

535 **Concluding remarks**

536 Anaphylaxis represents one of the most urgent of medical emergencies, where rapid
537 diagnosis and prompt and appropriate treatment can mean the difference between life and
538 death. While there has been steady progress in our understanding of the antibodies, effector
539 cells and mediators that can contribute to the development and manifestations of anaphylaxis,
540 especially in the context of mouse models of the disorder, the basic clinical management of
541 anaphylaxis has changed little in decades (see Castells *et al.*⁶ in this issue of JACI) and **Table**
542 **2**. In a report published in 2005, Sampson *et al.*⁵ identified as major research needs both the
543 development of "universally accepted diagnostic criteria" and the importance of identifying
544 "reliable laboratory biomarkers to confirm the clinical impression". As noted in our
545 Introduction, the first need largely has been addressed by international, interdisciplinary
546 efforts to forge consensus. But the second need remains essentially unfulfilled. It is our hope
547 that further progress in understanding the immunopathogenesis and pathophysiology of
548 anaphylaxis in all of its various forms will help to guide efforts to devise more effective
549 strategies for preventing this disorder and also to provide more effective options for rapidly
550 diagnosing and effectively treating anaphylaxis when it occurs.

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1123 **Figure legends**

1124

1125 **Figure 1. Multiple potential pathways in antibody-mediated anaphylaxis. A.** Antigen-
1126 specific IgE antibodies and FcεRI-bearing effector cells (e.g. mast cells, basophils) play a
1127 dominant role in anaphylaxis induced (sometimes by very small amounts of antigen) when
1128 concentrations of IgG antibodies are low. **B.** Mouse models of anaphylaxis suggest that IgG
1129 antibodies and FcγR-bearing effector cells (e.g. basophils, macrophages, neutrophils, as well
1130 as mast cells) can be important effectors of anaphylaxis induced by large amounts of antigen
1131 in the presence of high concentrations of IgG antibodies. Some examples of anaphylaxis
1132 likely involve both pathways (A and B). Note that co-engagement of ITAM-containing
1133 activating FcγRs or FcεRI with the ITIM-bearing FcγRIIB (on mast cells [in mice, but
1134 perhaps not in humans] or basophils [in humans and mice]) can act to diminish effector cell
1135 activation. In red: Strong evidence for the importance of these mediators in human
1136 anaphylaxis induced by antigen; in blue: These elements can participate in models of
1137 anaphylaxis in mice but their importance in human anaphylaxis is not yet clear; in grey:
1138 Elements with the potential to influence anaphylaxis, but their importance in human or mouse
1139 anaphylaxis not yet clear (e.g., human mast cells are thought to make little or no serotonin).

1140

1141 **Figure 2. Pathophysiological changes in anaphylaxis and mediators that have been**
1142 **implicated in these processes.** Note: As mentioned in the text, first line treatment of
1143 anaphylaxis consists of the rapid administration of epinephrine (see Castells *et al.*⁶). Although
1144 there is evidence that the mediators shown in the figure, particularly histamine and cysteinyl
1145 leukotrienes, contribute to some of the various signs and symptoms of anaphylaxis, and anti-
1146 histamines are routinely administered to patients with anaphylaxis, pharmacological targeting

1147 of such mediators represents second line treatment and should not be considered as an
1148 alternative to epinephrine. In red: Strong evidence for the importance of that mediator, in
1149 humans, in the development of some of the signs and symptoms listed in the adjacent box; in
1150 blue: these elements can be important in mouse models of anaphylaxis but their importance in
1151 human anaphylaxis is not yet clear (studies in human subjects suggest that cysteinyl
1152 leukotrienes may contribute importantly to the bronchoconstriction and enhanced vascular
1153 permeability associated with anaphylaxis [see text]); in grey: elements with the potential to
1154 influence anaphylaxis, but their importance in human or mouse anaphylaxis not yet clear.
1155 Note that some mediators (underlined) are likely to contribute to the development of late
1156 consequences of anaphylaxis.

Effector mechanisms		Humans	Mice
Antibody isotypes	IgE	<ul style="list-style-type: none"> - Elevated IgE levels in individuals with allergic diseases^{16, 19} - Purified IgE can transfer skin reactivity from a sensitized human subject to a naive host^{17, 21-23} - The anti-IgE Ab omalizumab can decrease the risks of anaphylaxis³⁰⁻³⁵ 	<ul style="list-style-type: none"> - PCA and PSA induced by transfer of antigen-specific IgE into naïve mice and challenge with the antigen^{24, 25} - IgE-mediated PCA and PSA is abrogated in mice lacking the high affinity IgE receptor FcεRI²⁵ - ASA partially reduced in IgE-deficient or <i>FcεRI</i>^{-/-} mice in some models, but not in others^{53, 89, 93, 103, 192, 193}
	IgG	<ul style="list-style-type: none"> - No definitive evidence to date - Cases of anaphylaxis reported following treatment with therapeutic mAbs without detectable levels of anti-drug IgE^{58, 194-196} 	<ul style="list-style-type: none"> - IgG1, IgG2a and IgG2b (but not IgG3) can induce PSA⁵⁰⁻⁶⁰ - IgG-PSA is reduced in <i>FcγRIII</i>^{-/-} mice^{51, 52} - IgG1- and IgG2b- (but not IgG2a-) PSA is enhanced in <i>FcγRIIB</i>^{-/-} mice⁵² - Mice deficient in FcεRIα exhibit enhanced systemic anaphylaxis upon challenge with 2.4G2 anti-FcγRII/III Abs²⁰ - Mice deficient for IgG1 or FcγRIII are largely protected in several ASA models^{89, 102, 103} - ‘Humanized’ mice expressing human FcγRI or FcγRIIA can develop IgG-mediated anaphylaxis^{150, 151, 153}
Complement	Anaphylatoxins	<ul style="list-style-type: none"> - Injection of low doses of C3a, C4a or C5a in the skin of healthy volunteers induces immediate wheal and flare reactions⁶⁶⁻⁶⁹ - Blood levels of C3a, C4a and C5a correlate with the severity of anaphylaxis in humans⁶⁵ 	<ul style="list-style-type: none"> - Reduced peanut-induced anaphylaxis in <i>C4</i>^{-/-} mice¹⁹⁷ - Reduced IgE-PCA in mice in which mast cells lack C3aR or C5aR¹⁹⁸ - Anaphylaxis induced by direct activation of complement by peanut extract in one model¹⁷⁷ - <i>C3</i>^{-/-} mice can fully develop IgG-PSA model¹⁹⁹ - ASA is not affected in C2-, C5- and C5aR-deficient mice, or after depletion of complement using cobra venom factor^{192, 200}
Effector cells	Mast cells	<ul style="list-style-type: none"> - Elevated levels of tryptase have been detected during acute anaphylaxis in humans^{65, 79-82} - High occurrence of anaphylaxis in patients with mastocytosis⁸⁵⁻⁸⁷ 	<ul style="list-style-type: none"> - IgE-PCA and PSA markedly reduced in various strains of mast cell-deficient mice^{26-28, 58, 88} - ASA reduced in mast cell-deficient mice in some studies, but not in others^{51, 54, 89-93, 103, 192, 201}
	Basophils	<ul style="list-style-type: none"> - No definitive evidence to date - ‘basophil activation tests’ used to diagnose or confirm allergen sensitization⁹⁶⁻⁹⁹ 	<ul style="list-style-type: none"> - Controversial: some reports indicate a contribution of basophils to IgG-PSA^{52, 54, 56} or ASA^{53, 89, 91}, while others found no significant role for basophils^{52, 92, 103, 199, 202}
	Neutrophils	<ul style="list-style-type: none"> - MPO levels are increased in patients with anaphylaxis as compared to healthy donors¹⁰⁶ 	<ul style="list-style-type: none"> - Antibody-mediated neutrophil depletion reduces IgG-PSA and ASA in some^{52, 53, 56} but not all^{91, 103} models
	Monocytes/ macrophages	<ul style="list-style-type: none"> - Not yet determined 	<ul style="list-style-type: none"> - Depletion of monocytes/macrophages using clodronate liposomes can reduce IgG-PSA and ASA^{52, 89, 92, 102, 103}
	Platelets	<ul style="list-style-type: none"> - No definitive evidence to date - Anaphylaxis in humans is associated with platelet activation¹⁰⁸ 	<ul style="list-style-type: none"> - No definitive evidence to date - Depletion of platelets with anti-platelet antibodies (daily for 3 days) or neuraminidase does not reduce ASA¹⁰²
Mediators	Histamine	<ul style="list-style-type: none"> - Aerosol administration of histamine induces bronchoconstriction in healthy volunteers^{114, 115} - Intravenous administration of histamine in volunteers can reproduce many of the symptoms of anaphylaxis^{116, 117} - H1 antihistamines are commonly used as adjunctive therapy for acute anaphylaxis and anaphylactoid reactions¹¹⁹ 	<ul style="list-style-type: none"> - Histamine injection induces anaphylaxis^{203, 204} - H1 antihistamine reduces IgE-PSA²⁰³ - IgG-PSA and ASA are reduced in mice pre-treated with H1 antihistamine in some models^{52, 103, 205}, but not in others^{53, 102} - Mice deficient for the histidine decarboxylase (HDC) gene are protected from IgE-PSA²⁰³ - H1R- and H2R-deficient mice are partially protected from IgE-PSA²⁰⁴
	Cysteinyl leukotrienes (CysLTs)	<ul style="list-style-type: none"> - Levels of some CysLTs are increased during the onset of anaphylaxis¹³¹⁻¹³³ - Intradermal injection of leukotriene B₄ (LTB₄), LTC₄ and LTD₄ induces a wheal and flare reaction in healthy volunteers¹³⁴ - Aerosol administration of LTC₄ and LTD₄ in healthy subjects induces bronchoconstriction^{114, 115,} 	<ul style="list-style-type: none"> - Reduced IgE-PSA in mice deficient for LTC4S¹³⁵ - Mice deficient for CysLT1R also have significantly reduced IgE-PCA¹³⁶

	129	
PAF	- Injection of PAF in the skin of healthy volunteers induces wheal and flare reactions ¹²³⁻¹²⁵ - Circulating PAF levels increase and circulating PAF-AH activity decreases in proportion to the severity of anaphylaxis ^{65, 82, 128}	- PAF is released during IgG-PSA and ASA ^{53, 91} - Injection of PAF induces anaphylaxis ²⁰⁶ - Reduced ASA in mice deficient for the PAF receptor (PAFR) ²⁰⁷ - PAFR antagonists can partially reduce anaphylaxis in IgG-PSA and ASA models ^{52, 53, 57, 58, 91, 102, 103}
Others	- Anaphylaxis induces increases in levels of many mediators which could potentially contribute (positively or negatively) to the clinical signs and symptoms. This includes various cytokines and chemokines, prostaglandins, tryptase, bradykinin, serotonin, etc.	- Mast cell-derived prostaglandin D ₂ (PGD ₂) can limit IgE-PCA and IgE-PSA ¹⁸⁵

1157 **Table 1. Roles (or potential roles) of various antibodies, effector cells and mediators in**
 1158 **anaphylaxis in humans and mice**
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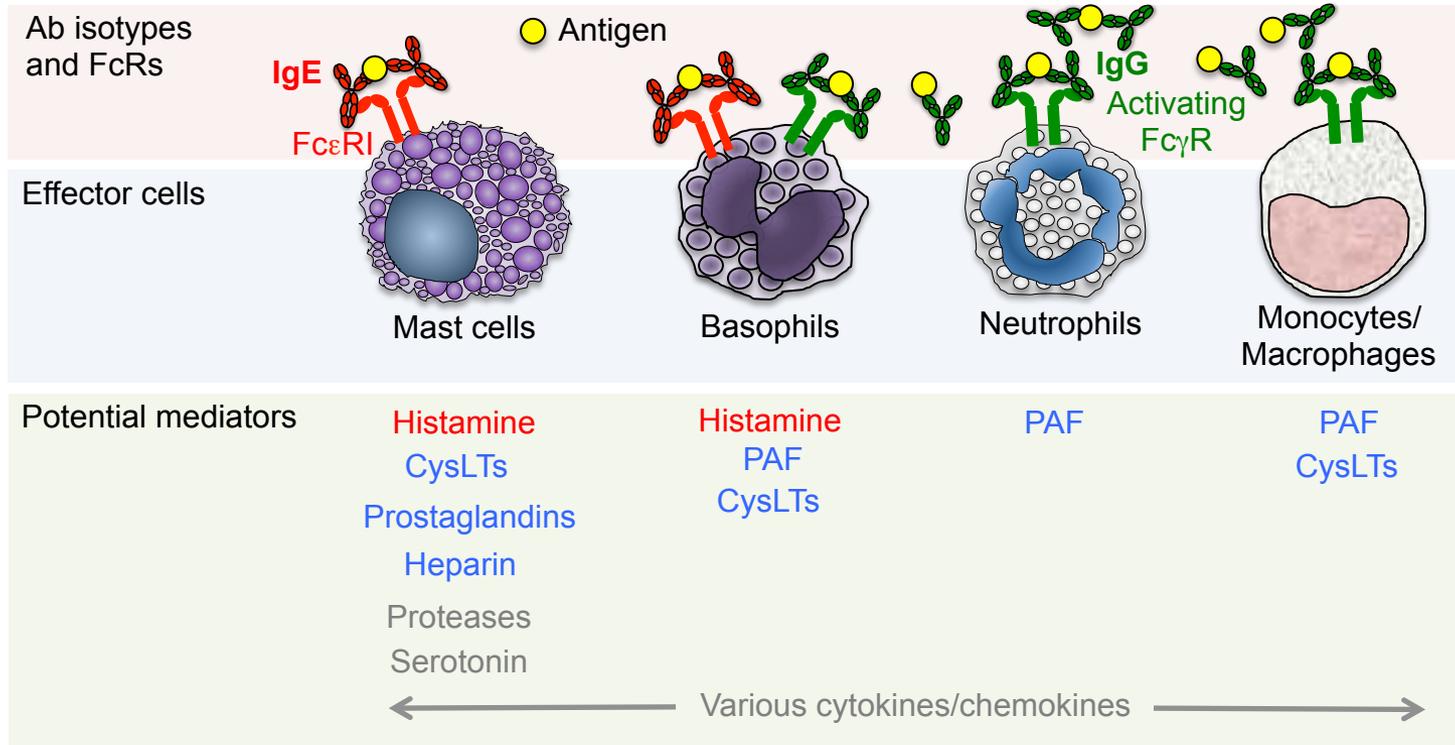
Table 2. Key concepts and therapeutic implications.

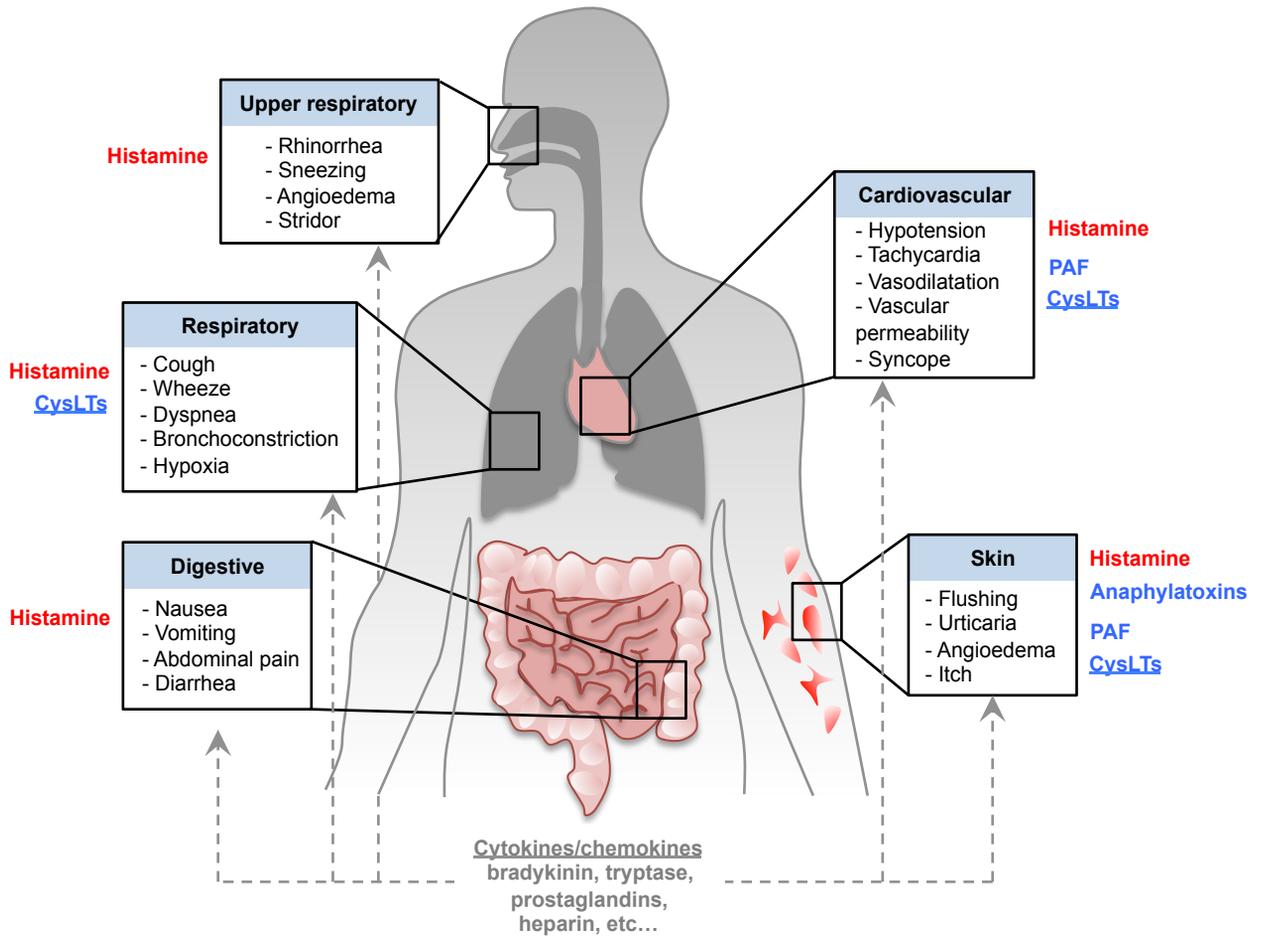
- Although mice clearly can develop both IgE- and IgG- dependent anaphylaxis, the existence of IgG-mediated anaphylaxis in humans has not been conclusively demonstrated.
 - In addition to mast cells and basophils, macrophages, neutrophils, and perhaps other leukocytes, and platelets, also may produce a diverse array of inflammatory mediators during anaphylaxis, and such products have the potential to contribute to reactions that may be difficult to treat, protracted in nature, or biphasic.
 - Genetic modifiers and other host factors, as well as gene-environment interactions, may influence the development of anaphylactic reactivity, as well as the presentation and/or severity of anaphylaxis.
 - Although the potential evolutionary benefit of anaphylaxis remains uncertain, recent evidence in mice suggests that anaphylaxis may have effects that can reduce the toxic effects of certain arthropod or reptile venoms.
-

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A. At low concentration of IgG Abs

B. At high concentration of antigen/IgG Abs





Histamine

Upper respiratory

- Rhinorrhea
- Sneezing
- Angioedema
- Stridor

Histamine
CysLTs

Respiratory

- Cough
- Wheeze
- Dyspnea
- Bronchoconstriction
- Hypoxia

Histamine

Digestive

- Nausea
- Vomiting
- Abdominal pain
- Diarrhea

Histamine
PAF
CysLTs

Cardiovascular

- Hypotension
- Tachycardia
- Vasodilatation
- Vascular permeability
- Syncope

Histamine
Anaphylatoxins
PAF
CysLTs

Skin

- Flushing
- Urticaria
- Angioedema
- Itch

Cytokines/chemokines
bradykinin, tryptase,
prostaglandins,
heparin, etc...