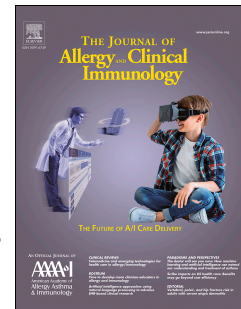


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Optimizing investigation of suspected allergy to polyethylene glycols

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32 **Conflicts of interest**

33 None of the authors report any conflicts of interest.

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Abstract

Background: Polyethylene glycols (PEGs) are polymers of varying molecular weight (MW) used widely as excipients in drugs and products, including the mRNA vaccines against COVID-19. Allergy to PEGs is very rare. Skin testing and graded challenge carries a high risk of inducing systemic reactions.

Objective: To evaluate skin prick test (SPT) and in-vitro reactivity over time to different MW PEGs and assess cross-sensitization patterns in PEG allergy.

Methods: Ten patients with previously diagnosed PEG allergy were skin prick tested twice with PEGs 26 months apart. Lower MW (PEG 300, 3000, 6000) were tested, followed by PEG 20,000 in stepwise, increasing concentrations. Cross-sensitization to polysorbate 80 and poloxamer 407 was assessed. SPT was performed in 16 healthy controls. In vitro Basophil Histamine Release (HR) test and passive sensitization HR test were performed in patients and controls.

Results: Patients previously testing positive on SPT to PEG 3000 and/or 6000 also tested positive to PEG 20,000. Patients with longer interval since diagnosis tested negative to lower MW PEGs and positive mainly to higher concentrations of PEG 20,000. Three patients developed systemic urticaria during SPT. Eight patients showed cross-sensitization to poloxamer 407 and three to polysorbate 80. All controls tested negative. In-vitro tests showed limited usefulness.

Conclusion: Skin test reactivity to PEG can decrease over time, but titrated SPT with increasing concentrations of PEG 20,000 can be diagnostic when lower MW PEGs test negative. To avoid systemic reactions stepwise SPT is mandatory.

76 **Clinical Implications:** An algorithm using a stepwise approach of skin prick testing to PEGs of
77 increasing molecular weights and concentrations can be used to diagnose allergy to PEGs.

78

79 **Capsule summary**

80 Patients with allergy to polyethylene glycols lose reactivity over time, impeding a correct diagnosis.
81 A stepwise approach with skin prick testing to PEG with increasing molecular weights in increasing
82 concentrations can be used diagnostically.

83

84 **Keywords**

85 Drug allergy, anaphylaxis, polyethylene glycol, PEG, macrogol, skin prick test, basophil histamine
86 release, COVID-19 vaccine

87

88 **Abbreviations**

89 PEGs polyethylene glycols

90 MW molecular weight

91 mRNA messenger RiboNucleic Acid

92 COVID corona virus disease

93 FDA U.S Food and Drug Administration

94 SPT skin prick test

95 HR histamine release

96 PS passive sensitization

97

98

99

100 Introduction

101 Polyethylene glycols (PEGs) or macrogols are hydrophilic polymers of varying molecular weight
102 (MW) used as excipients in many different products, including drugs and cosmetics.(1) Very
103 recently, PEGs have gained renewed interest as PEG 2000 is an excipient in the BioNTech/Pfizer
104 and Moderna mRNA vaccines against COVID-19. Two cases of anaphylaxis in the first days of
105 vaccination in the UK directed the suspicion against PEGs.(2) Allergy to PEGs is rare but an
106 increasing number of patients have been diagnosed over the past two decades.(1) In a review by
107 Wenande et al., 37 case reports of PEG allergy were identified between 1977 and 2016.(1) In the
108 USA, there are approximately four PEG-associated cases of anaphylaxis caused by laxatives per
109 year and the U.S Food and Drug Administration (FDA) has registered 133 reports associating PEG
110 with anaphylaxis since 1989.(3) The true prevalence of PEG allergy is unknown but suspected to be
111 significantly under-reported and a rise in the incidence of PEG allergy is expected due to the
112 continued extensive use and increased focus of this “hidden” allergen.(1,3,4)

113 PEGs are synthesized by polymerization of ethylene oxide and addition of water and they vary in
114 molecular weight and chain length. Low MW PEGs are viscous, clear liquids while high MW PEGs
115 are waxy, white solids.(1,5) There is potential for cross-sensitization to structurally related
116 derivatives sharing the same chemical groups as PEG.(3,5–8) Other excipients such as polysorbates
117 derived from pegylated sorbitan, and poloxamers comprising a trimer consisting of one moiety of
118 polypropylene glycol surrounded by two moieties of PEGs, have been reported to show cross-
119 sensitization (Figure 1).(1,9) Cross-sensitization is likely underestimated, rarely investigated and
120 the clinical significance is not clear.

121 Diagnosing patients with PEG allergy is challenging. They often present with repeated, severe
122 allergic reactions/anaphylaxis to structurally different drugs/products and PEGs are rarely
123 suspected. When suspected, skin prick testing (SPT) with a panel of different MW PEGs is the

recommended investigation although systemic reactions have been reported on skin prick testing.(1,10) Intradermal testing and graded challenge with PEG-containing products should only be performed with caution due to a relatively high risk of inducing anaphylaxis.(1,3,7,10–15) Skin test reactivity may decrease over time showing negative results on titrated SPT with recommended low MW (PEG 300, 3000, 6000) despite a strong clinical suspicion, putting patients at risk of inadvertent re-exposure if the diagnosis is not confirmed.

To date, there is very limited knowledge about skin test reactivity over time, cross-sensitization to structurally related polymers and supplemental diagnostic tests. In this study we evaluate skin test reactivity over time and cross-sensitization patterns in ten patients with confirmed allergy to PEG. We investigate whether titrated SPT with increasing concentrations of a PEG 20,000 MW can increase diagnostic sensitivity of SPT in PEG allergy. Further, as a reliable in-vitro test would minimize the risk to patients, we assess the basophil histamine release test with and without passive sensitization. Lastly, we present an investigation algorithm based on the study findings.

148 **Methods**

149

150 **Study design**

151 The study included SPT results and histamine release test results from the time of diagnosis and
152 initial allergy work-up. In addition, prospective testing was performed with a PEG SPT-series
153 developed for the study, as well as blood samples at two different time points 26 months apart.
154 Blood samples were analyzed with histamine release test with and without passive sensitization.
155 Written and oral informed consent was obtained from all patients and participants in the control
156 group.

157 The study was approved by the Ethics Committee, Capital Region (File H-17021145).

158

159 **Patients**

160 In total, 12 patients had been diagnosed with PEG allergy at the Allergy Clinic at Gentofte Hospital
161 from September 2010 to August 2019. The diagnosis was made at the initial work-up by a history
162 of one or more allergic reactions to PEG-containing products combined with a positive SPT to one
163 or more low MW PEGs.

164 In the current study, we included 10 patients diagnosed with PEG allergy aged ≥ 18 years at the
165 time of inclusion in the study. One patient had died, and one patient declined participation.

166 We included eight patients diagnosed until 2017, who consented to participate twice with a second
167 visit two years later in 2019. One patient later declined the second visit. We consecutively invited
168 patients newly diagnosed with PEG allergy between 2017 and 2019. Two patients were included
169 after 2017 and these only participated once in the study.

170

171 **Control group**

172 The control group comprised 16 healthy, non-allergic individuals matched for age and gender who
173 had a blood sample drawn and were tested once with the study PEG SPT-series.

174

175 **Skin prick testing**

176 PEGs and derivatives were prepared in sterile water at the Laboratory of Medical Allergology,
177 Gentofte Hospital, Hellerup, Denmark. (See table E1, appendix 1 in the Online Repository for
178 detailed procedure for preparing solutions for skin prick testing for PEG, poloxamer 407 and
179 Polysorbate 80). Skin prick testing was performed stepwise one concentration at a time with 20
180 minutes observation between each step. The PEG SPT-series developed for the study comprised:
181 Lower MW PEGs: PEG 300 (100%), PEG 3000 (50% w/v), PEG 6000 (50% w/v), Polysorbate 80
182 (20% w/v) and Poloxamer 407 (10% w/v) which were tested first in stepwise fashion. If only local
183 reactions occurred on testing, SPT was performed stepwise with PEG 20,000 in the concentrations
184 of 0.01%, 0.1%, 1%, 10% and 20% (w/v) until a positive response was reached. Three patients with
185 very strong local responses or systemic urticaria to lower MW PEG were not tested with PEG
186 20,000 for ethical and safety reasons. Prick tests were performed on the forearm with a positive
187 control with histamine 10 mg/ml and a negative control with saline. Duplicates were performed if
188 the test was negative. The controls were tested with all components in duplicate. A positive reaction
189 was defined as a wheal diameter of ≥ 3 mm.

190

191 **Blood sampling and histamine release tests**

192 Prospective blood samples were drawn prior to SPT at both visits. Histamine release test were
193 performed on the day of blood sampling on 10 PEG-allergic patients and 16 healthy controls, using
194 the method previously described by Larsen et al.(16) PEG 300, PEG 3000, PEG 6000, PEG 20,000,
195 Poloxamer 407, Polysorbate 80 (Sigma- Aldrich), anti-IgE (KPL, Gaithersburg, MD, USA) and

phorbol 12-myristate 13-acetate (PMA) + ionomycin (both from Sigma-Aldrich) were all tested in six concentrations. Percent histamine release (HR [%]) equals released histamine of stimuli divided by maximum histamine release induced by PMA + ionomycin stimulation. Histamine release > 10% was considered positive if found in two consecutive concentrations. If anti-IgE response < 10% the test was considered inconclusive. (A detailed description of method of histamine release and passive sensitization histamine release tests is included in appendix 2 in the Online Repository.)

222 Results

223 Six men and four women participated in the study. The median age was 35 years (range 18-64
224 years). Three patients had a history of allergic rhinoconjunctivitis; none had a history of reactions to
225 food, PEG-free drugs, venoms or vaccinations. None of the patients have had a vaccination
226 containing polysorbate 20, polysorbate 80 or PEG since diagnosis.

227 For all patients, median time from first reaction to PEG until diagnosis was 20 months (range 2-120
228 months). Median time from diagnosis to first study visit was 30 months (range, 1-86 months).

229 The most common PEG exposures were oral medications e.g. analgesic tablets, antacids, antibiotic
230 tablets and laxatives, and depot steroid injections. See table 1 for culprit agents. Mean number of
231 reactions before diagnosis were 3, range 2-6. Eight patients had at least one reaction fulfilling the
232 criteria for anaphylaxis and requiring epinephrine. Clinical patient data are reported in detail
233 elsewhere.(17)

235 Skin prick tests

236 In nine patients the diagnosis was made at initial allergy work-up by a positive SPT to PEG 3000
237 and/or PEG 6000 (table I). Patient 4 who had a cardiac arrest after insertion of poloxamer 407-
238 containing bone cement during hand surgery, only tested positive on SPT with the PEG derivatives
239 poloxamer 407 and polysorbate 80 on initial allergy work-up one month after his reaction. He later
240 tested positive to PEGs of varying MW at the first study visit three and a half years later.

241 All patients previously testing positive to PEG 3000 and PEG 6000, and who lost reactivity to these
242 concentrations over time, still tested positive on PEG 20,000. Patients with longer interval since
243 diagnosis (patient 1, 2, 5 and 8) tested negative to lower MW and positive only to the higher
244 concentrations of PEG 20,000 (table I). Three patients (patient 6, 7 and 10) were not tested with
245 PEG 20,000 in the study as they developed systemic urticaria during SPT with lower MW PEG.

246 Patient 6 had tested positive for PEG 20,000 0.01% at the time of diagnosis. Symptoms were treated
247 successfully with PEG-free oral antihistamines in all three patients.

248 All 16 participants in the control group tested negative in all SPT concentrations in duplicate.

249

250 *Changes in skin prick test reactivity to PEG over time*

251 In seven patients, reactivity decreased over time with loss of reactivity to the lower MWs.
252 Decreased reactivity median time was 41 months (range, 26-82 months). In patients 3 and 9,
253 reactivity increased over time after 26 and 16 months, respectively. In patient 10 who was newly
254 diagnosed, reactivity did not change over 9 months.

255

256 *Cross-sensitization*

257 Eight patients showed cross-sensitization to PEG derivatives: All eight to poloxamer 407 and three
258 to polysorbate 80, at some point between diagnosis and last study visit. Patient 1 and 2 who had the
259 longest delays since diagnosis (seven and four years, respectively), tested negative to both
260 derivatives during the study. Neither had been tested with poloxamer 407 and polysorbate 80 before
261 as we had not been aware of the potential for cross-sensitization at the time of their diagnosis.

262

263 **Histamine release test**

264 Blood samples from patients or healthy controls were investigated for basophil reactivity when
265 stimulated with PEGs. Four patients had a HR test performed at time of diagnosis and two (patient
266 1 and 2) tested positive to relevant MW PEGs while two tested negative. Patient 1 and 2, who tested
267 positive in HR test at diagnosis, but tested negative at first study visit, remained positive on skin
268 prick test.

At the first study visit, two out of ten patients tested positive; patient 7 for a relevant MW PEG while patient 4 only showed partial concordance between SPT and HR test (see Table E2 in the Online Repository). Four patients (patient 3, 5, 6 and 10) had inconclusive tests most likely due to non-releasing basophils, a phenomenon found in 10-20 % of the general population where basophils are found to be unresponsive (i.e. histamine is not released) when using IgE dependent stimuli.(18) Three of these patients (patient 3, 6 and 10) had systemic urticarial reactions during SPT in this study. Four patients had a negative HR test to PEG and PEG-derivatives despite having a positive skin test. HR test was not performed at the second study visit.

Passive sensitization histamine release test

To circumvent the problem of non-releasing basophils, the technique of passive sensitization was used, where blood from blood donors with releasing basophils was passively sensitized with IgE from patients or healthy control serum. Passive sensitization HR was performed at both study visits. Only one patient (patient 1) showed a positive response of doubtful clinical relevance. Six patients had negative results and three patients had inconclusive results on samples from the first study visit. Seven patients who had a blood sample analyzed at the second visit all tested negative (see Table E1 in the Online Repository).

HR and passive sensitization HR were negative in all tests in all 16 controls.

294 Discussion

295 In this study of ten patients with PEG allergy, the largest cohort of PEG-allergic patients reported so
296 far, we have shown that skin prick test reactivity to PEGs may decrease over time, but that the
297 diagnosis can still be made by skin prick test with higher MW PEGs. All patients who had lost skin
298 test reactivity over time to low MW PEG (PEG 3000 and/or PEG 6000) tested positive to PEG
299 20,000 in varying concentrations. In seven patients, reactivity decreased over time with loss of
300 reactivity to a lower MW PEG, while reactivity increased over time in two patients and remained
301 stable in one. The two patients (patient 1 and 2) with the longest time interval (seven and four years,
302 respectively) since diagnosis, lost reactivity to the lower MW PEGs and tested positive only to the
303 higher concentrations (10-20%) of PEG 20,000. Two patients (patient 5 and 8) with shorter time
304 intervals (two to three years) since diagnosis had also lost reactivity to lower MW PEGs but tested
305 positive to the lower concentrations (0.1-1%) of PEG 20,000. This indicates that SPT with
306 increasing concentrations of a PEG 20,000 can be used to increase diagnostic sensitivity of SPT
307 even if there is a long delay between clinical reaction and allergy work-up. Despite careful stepwise
308 SPT with increasing concentrations, three patients developed systemic urticaria during testing, even
309 with lower MW PEG (3000) confirming that SPT with PEGs can be hazardous to patients with a
310 history of severe allergic reactions, if not performed with stepwise increasing concentrations.(1,10)
311 Severe systemic reactions on intradermal and provocation testing with PEGs have been reported
312 repeatedly, so avoiding these test modalities would be a safer option.(1,3,7,10–14) Based on the
313 results of our study, we suggest an investigation algorithm based on a titrated stepwise approach of
314 skin prick testing only (Figure 2). If results of SPT with lower MW PEGs are negative and clinical
315 suspicion of PEG allergy is strong, we suggest to test PEG 20,000 in increasing concentrations
316 using a stepwise approach. We believe that this approach will minimize the need for more
317 hazardous test modalities such as intradermal test and graded challenge, which we only recommend

318 if clinical suspicion is strong and the full algorithm has shown negative results. In patients with a
319 low pretest probability of PEG allergy, such as patients with a history of reactions to several drugs,
320 not consistently containing PEGs, we only perform SPT with low MW PEGs, poloxamer 407 and
321 polysorbate 80 without the stepwise approach. In our study, five patients tested positive only to
322 PEG 20,000 at the last study visit although they had previously tested positive to lower MW PEGs.
323 If these patients had been referred with a long delay since their initial reaction, SPT with lower MW
324 PEGs could have turned out falsely negative, and intradermal test or graded challenge might have
325 been performed putting the patients at risk of experiencing systemic reactions on testing.
326 As many health care professionals are unfamiliar with the clinical presentation of PEG allergy, we
327 provide a list of clinical scenarios where allergy to PEGs should be suspected (table II). As the
328 mRNA COVID-19 vaccines contain PEG 2000 it is important that patients with suspected allergy to
329 PEGs are investigated prior to vaccination and we have included PEG 2000 in the new algorithm
330 for this reason.

331

332 Another important finding of this study is that if lower MW SPT tested positive, PEG 20,000 would
333 also test positive suggesting that allergenicity increases with increasing MW (10) and that there is
334 no upper threshold for positivity.(1) This means that if SPT is positive to PEG 3000, further testing
335 with higher MW PEGs is not necessary and may be putting the patient at risk of a systemic reaction.
336 We have included this important information in the algorithm. Whether the threshold on SPT
337 translates into a threshold for clinical reactivity has not been confirmed. Other groups have
338 suggested that a lower threshold can be identified and that patients can use products with PEGs of
339 MWs testing negative on SPT or challenge.(3,10) In our centre, however, we still adopt the more
340 cautious approach of warning against PEGs of all MWs even if lower MWs test negative. This is
341 supported by the results of the current study where two patients showed an increase in reactivity by

testing positive on lower MW at the second study visit. This may be explained by unknown accidental re-exposure to PEG. There is a high risk of accidental re-exposure as PEGs are widely used in daily life and in the healthcare setting. It is possible that a minor asymptomatic exposure, e.g. from soaps, creams, cosmetics or tablet coatings containing PEG can be enough to maintain or increase allergenic reactivity. Finally, a lack of standardized labelling and the possibility of admixture with other MW PEGs means that the MW stated on drugs and other products cannot always be trusted.(1,19)

Recommendations for investigation of patients with suspected hypersensitivity to PEG is generally based on experiences from very few patients making it difficult to assess specificity and sensitivity of individual tests. However, based on negative SPT results in all MW and concentrations in 16 healthy controls in this study; and negative SPT results with PEG 300, PEG 3000, PEG 6000, polysorbate 80 and poloxamer 407 in 314 non-PEG-allergic patients investigated as part of routine allergy work-up in our clinic in the period 2012-2019, specificity of our SPT series with PEG is likely to be high.

Although skin prick testing is the recommended investigation when diagnosing patients with PEG allergy, even this procedure, generally considered very safe for most other allergens, may lead to systemic allergic reactions if performed with too high concentrations in very reactive patients, such as those with very severe reactions or when testing takes place soon after the allergic reaction. In our study, three patients developed systemic urticaria during SPT but responded quickly to treatment with oral antihistamines not containing PEG. This emphasizes the need for a stepwise approach and using this protocol we have never induced anaphylaxis on skin prick testing. We suggest that a 1/10 dilution of our recommended concentrations may be used initially in patients with strong suspicion of PEG allergy and/or very severe or recent reactions. Due to the risk of

366 systemic reactions testing should always be performed in a specialized setting with equipment and
367 expertise in treating immediate-type allergic reactions. It should be ensured that antihistamine
368 tablets without PEG are available for treating early symptoms.(10) On the Danish market, presently
369 only one oral antihistamine is PEG-free.

370

371 Cross-sensitization between PEGs and structurally related polymers have only been rarely
372 investigated.(1,3) Eight patients showed cross-sensitization to PEG derivatives in our study, all
373 eight to poloxamer 407 and three to polysorbate 80. Patient 4 is the only patient in this study with a
374 history of a clinical reaction to poloxamer 407. Another patient from our clinic diagnosed with PEG
375 allergy, who had died prior to this study, did have a clinical reaction to polysorbate 80.(7)

376 Some patients showed a decrease in skin test reactivity to these other polymers over time, while
377 others maintained their reactivity. The clinical relevance of cross-sensitization is unknown, and
378 urgently needs elucidating as polysorbate 80 is used in many drugs (3) and vaccines including some
379 of the upcoming vaccines against COVID-19.

380

381 To our knowledge, the skin test reactivity over time in patients with PEG allergy has not been
382 previously investigated. It is not known whether allergenic reactivity remains dormant until
383 reactivated by re-exposure or if it can disappear permanently. In this study, some patients (patient 2,
384 4 and 5) have only had one reaction and they seem to be less reactive in SPT.(17) It may be that
385 they can tolerate limited exposure to PEG. Others have had repeated severe reactions with years in
386 between and may never lose their reactivity. Whilst there may be individuals who truly loose
387 sensitization to PEG, the risk of severe reactions on re-exposure means that until more affirmative
388 information is available to prove otherwise, in our clinic we tell patients that PEG allergy covers all
389 MW PEGs and is for life.

390

391 If a reliable in vitro test for allergy to PEG was available, the risk of inducing systemic reactions on
392 SPT or other test modalities would be eliminated. However, presently such a test is not available.
393 For other allergens in-vitro test reactivity can decrease or even be lost over time with lack of
394 exposure and this has been shown for IgE to chlorhexidine, ethylene oxide and penicillin.(20–23) It
395 has been suggested, that PEG allergy is caused primarily by an IgE-mediated mechanism.(4,24)
396 Recently an assay for detecting anti-PEG IgE has been reported to show promising results in a small
397 cohort of patients.(25)

398 In this study, we investigated the direct histamine release test (HR) with and without passive
399 sensitization (PS). HR testing is used in some centres in Denmark and shows good results for
400 allergy to e.g. chlorhexidine, peanut and pollen.(16,26,27) Previously our group published
401 promising results on HR and PS for PEG in a single patient (patient 1) on blood taken in close
402 proximity to the clinical reactions.(4) On testing in this study 82 months later she had lost reactivity.
403 In the current study, direct HR was only positive in two patients and another Danish group showed
404 similar results.(15) One of these patients had been diagnosed just one month previously and with
405 proper titration of the PEG-substances, direct HR test may have a place in patients where
406 investigations take place within few months of exposure. Four patients showed inconclusive results
407 very likely due to non-releasing basophils, a well-known limitation of this test.(18) In the present
408 study setting, HR test with passive sensitization was negative in all patients and was not considered
409 helpful in the diagnosis of allergy to PEG. Improved in vitro diagnostic tests for patients with
410 allergy to PEG, and structurally related derivatives, therefore remains to be developed. Besides the
411 potential for improving the sensitivity of biological tests, a serological assay identifying specific
412 IgE to PEGs would be very useful.(4,25) However, at the moment, no commercially validated
413 specific IgE assay for PEGs or structurally related polymers is available.

414

415 In general, optimization of safe diagnostic tests is of great importance to PEG-allergic patients and
416 healthcare personnel. However, there are still many gaps in the current knowledge. The rarity of the
417 allergy and unknown true prevalence makes it difficult to describe the epidemiology and future
418 prognosis. In addition, there is a potential lack of generalizability across health care systems and
419 countries. The pathway to sensitization is unknown and basic immunologic mechanisms are yet to
420 be identified. There is only limited experience with allergy investigation, primarily based in skin
421 prick testing, but data on positive and negative predictive value is sparse. Skin test reagents are not
422 standardized, and the role of intradermal and in-vitro testing is yet to be defined. Total avoidance of
423 PEG causes considerable stress to patients in terms of the large number of products they need to
424 avoid. Developing a safe method for determining a lower threshold for reactivity, potentially
425 allowing exposure to small amounts of PEG, would be very helpful. Very limited information is
426 available on cross-reactivity patterns with polysorbate 80 and other polymers, and this should be
427 addressed as the BioNTech/Pfizer and Moderna mRNA COVID-19 vaccines contains PEG 2000,
428 while most of the other available non-mRNA vaccines contain varying amounts of polysorbate 80.
429 There is therefore an urgent need to identify a COVID-19 vaccine which can be used safely in PEG-
430 allergic patients.

431

432 In conclusion, we have presented novel results of skin test reactivity to PEGs over time and cross-
433 sensitization patterns in ten patients with allergy to PEGs. Based on our past experiences and the
434 results of this study, we suggest an optimized investigation algorithm for patients with suspected
435 allergy to PEGs, based on titrated stepwise skin prick testing with PEGs of increasing MW,
436 utilizing the fact that higher MW PEGs are likely to test positive even after many years. We
437 therefore minimize the need for other tests which carry a high risk of inducing anaphylaxis. Cross-

sensitization between PEGs and Poloxamer 407 and Polysorbate 80 is common, but the clinical implications remain unknown. Whilst in-vitro tests would be the safest option for patients, we confirm the findings of others that in-vitro testing so far has limited use in the investigation of allergy to PEGs.

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519 Table I. Skin prick test results over time with positive skin prick test results **marked in bold (+)** in 10 patients with confirmed PEG allergy.

Patient no., year of diagnosis	Age, sex	Culprit agents	Latest reaction to diagnosis (mths)	SPT at diagnosis (SPT 0)	SPT 0 to SPT A (mths)	SPT at first study visit (SPT A) 2017*	SPT at second study visit (SPT B) 2019
1, 2010	28, F	Intramuscular Depo-Medrol ® (methylprednisolone acetate) injection (PEG 3350) Balancid Novum ® (magnesium hydroxide) reflux tablet (PEG 6000) Effexor ® (venlafaxine) antidepressant tablet (PEG 400)	7	PEG 300 PEG 3350 (+) PEG 6000 (+) Poloxamer and polysorbate not tested	82	PEG 300 PEG 3000 PEG 6000 PEG 20,000 0.01-10 20% (+) Poloxamer 407 Polysorbate 80	Declined
2, 2014	63, F	Intraarticular Depo-Medrol ® (methylprednisolone acetate) injection (PEG 3350)	2	PEG 300 PEG 3000 (+) PEG 6000 (+) Poloxamer and polysorbate not tested	46	PEG 300 PEG 3000 PEG 6000 PEG 20,000 0.01-10 20% (+) Poloxamer 407 Polysorbate 80	PEG 300 PEG 3000 PEG 6000 PEG 20,000 0.01 0.1 10% (+) Poloxamer 407 Polysorbate 80
3, 2014	37, M	Vepicombin ® (phenoxymethylpenicillin) antibiotic tablet (PEG 6000) Vepicombin ® (phenoxymethylpenicillin) antibiotic tablet during drug provocation (PEG 6000) Burana ® (ibuprofen) tablet (PEG 6000) Mucoangin ® (ambroxol) throat lozenge (PEG 6000) Xerodent ® (sodium fluoride) oral tablet (PEG 6000) Balancid Novum ® (magnesium hydroxide) reflux tablet (PEG 6000) Sensodyne® Dental floss (PEG 6000)	4	PEG 300 PEG 3000 PEG 6000 (+) PEG 20,000 0.01% (+) Poloxamer 407 (+) Polysorbate 80	45	PEG 300 PEG 3000 PEG 6000 PEG 20,000 0.01 0.1% (+) Poloxamer 407 (+) Polysorbate 80	PEG 300 PEG 3000 (+) PEG 6000 (+) Poloxamer 407 (+) Polysorbate 80
4, 2014	33, M	Accell Connexus ® DBM putty (Poloxamer 407) during hand surgery	1	PEG 300 PEG 3000 PEG 6000 Poloxamer 407 (+) Polysorbate 80 (+)	41	PEG 300 PEG 3000 (+) PEG 6000 (+) PEG 20,000 0.01 0.1% (+) Poloxamer 407 (+) Polysorbate 80 (+)	PEG 300 PEG 3000 PEG 6000 PEG 20,000 0.01 0.1% (+) Poloxamer 407 Polysorbate 80
5, 2014	53, M	Unidentified perioperative exposure during coronary stent insertion	5	PEG 300 PEG 3000 (+) PEG 6000 (+) PEG 20,000 0.01-10 20% (+) Poloxamer 407 (+) Polysorbate 80	39	PEG 300 PEG 3000 PEG 6000 (+) PEG 20,000 0.01-10 20% (+) Poloxamer 407 Polysorbate 80	PEG 300 PEG 3000 PEG 6000 PEG 20,000 0.01 0.1 1% (+) Poloxamer 407 Polysorbate 80

6, 2016	30, M	Migea ® (telfenamic acid) tablet (PEG 6000) Burana ® (ibuprofene) tablet (PEG 6000) Panodil ® (paracetamol) Zapp tablet (PEG 6000)	5	PEG 300 PEG 3000 (+) PEG 6000 (+) PEG 20,000 0.01% (+) Poloxamer 407 (+) Polysorbate 80	20	PEG 300 PEG 3000 (+) Polysorbate 80 <i>Systemic urticaria</i>	PEG 300 PEG 3000 PEG 6000 (+) Polysorbate 80 <i>Systemic urticaria</i>
7, 2017	37, M	Vepicombin ® (phenoxymethylpenicillin) tablet (PEG 6000) Intraarticular Depo-Medrol ® (methylprednisolone acetate) injection (PEG 3350)	3	PEG 300 (+) PEG 3000 (+) PEG 6000 (+) Poloxamer 407 (+) Polysorbate 80 (+)	1	PEG 300 (+) PEG 3000 (+) PEG 6000 (+) Poloxamer 407 (+) Polysorbate 80 (+)	PEG 300 PEG 3000 (+) Poloxamer 407 (+) Polysorbate 80 (+) <i>Systemic urticaria</i>
8, 2017	22, F	Vepicombin Novum ® (phenoxymethylpenicillin) tablet (PEG 6000) Balancid Novum ® (magnesium hydroxide) tablet (PEG 6000) Movicol ® (macrogol) laxative (PEG 3350) Panodil ® (paracetamol) tablet (PEG and polysorbate 80)	1	PEG 300 PEG 3000 PEG 6000 (+) Poloxamer 407 (+) Polysorbate 80 (+)	1	PEG 300 PEG 3000 PEG 6000 (+) Poloxamer 407 (+) Polysorbate 80 (+)	PEG 300 PEG 3000 PEG 6000 PEG 20,000 0.01 0.1 1% (+) Poloxamer 407 Polysorbate 80
9, 2018	16, M	Movicol ® (macrogol) laxative (PEG 3350) Dulcosoft ® (macrogol) laxative (PEG 4000) Diprosan ® (betamethasone) intraarticular injection (PEG 3350)	27	PEG 300 PEG 3000 PEG 6000 (+) PEG 20,000 0.01 0.1% (+) Poloxamer 407 (+) Polysorbate 80	16	PEG 300 PEG 3000 (+) PEG 6000 (+) PEG 20,000 0.01 0.1% (+) Poloxamer 407 (+) Polysorbate 80	Newly diagnosed, second study visit not possible
10, 2019	33, F	Intraarticular Depo-Medrol ® (methylprednisolone acetate) injection (PEG 3350) Intraarticular Depo-Medrol ® (methylprednisolone acetate) injection (PEG 3350) Sanex ® Bodylotion (PEG 4400)	5	PEG 300 PEG 3000 (+) Poloxamer 407 (+) Polysorbate 80 (+)	8	PEG 300 PEG 3000 (+) Poloxamer 407 (+) Polysorbate 80 (+) <i>Systemic urticaria</i>	Newly diagnosed, second study visit not possible

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521 SPT = Skin prick test. PEG = Polyethylene glycol. F = Female. M = Male. * = Patient 9 in 2018 and patient 10 in 2019

522 Table II. Clinical history where allergy to PEG should be considered.¹⁷

Repeated, severe allergic reactions/anaphylaxis to ≥ 2 structurally different drugs/products e.g. tablets, depot injections, antacids, PEG-based laxatives.

Severe allergic reactions to only some formulations, or doses, of same generic drug.

Severe allergic reaction to drugs, where allergy to the active ingredient has been excluded on testing (e.g. antibiotics, analgesics).

Severe allergic reaction to drugs containing PEG or PEG derivatives (polysorbate 80, poloxamers).

Severe allergic reaction to vaccines containing PEG (mRNA vaccines) or PEG derivatives (polysorbate 80, poloxamers).

Severe allergic reaction to PEGylated drugs, where allergy to the active drug is excluded.

Severe unexplained allergic reactions in connection with surgery or invasive procedures.

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524 PEG = Polyethylene glycol

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Figure legends

Figure 1. Molecular structure and polymerization of polyethylene glycol (PEG) and the derivatives Poloxamer and Polysorbate 80 which share two chemical moieties; $-(OCH_2CH_2)-$ and $-OCH_2CH_2O$. Image reproduced from Wenande et al.¹ with permission from Clinical & Experimental Allergy.

Figure 2. Investigation algorithm for patients with suspected PEG allergy. Stepwise approach should always be used in patients with severe reactions and strong suspicion of PEG allergy. In patients with milder reactions and weak suspicion of PEG allergy several tests can be performed simultaneously after individual risk evaluation.

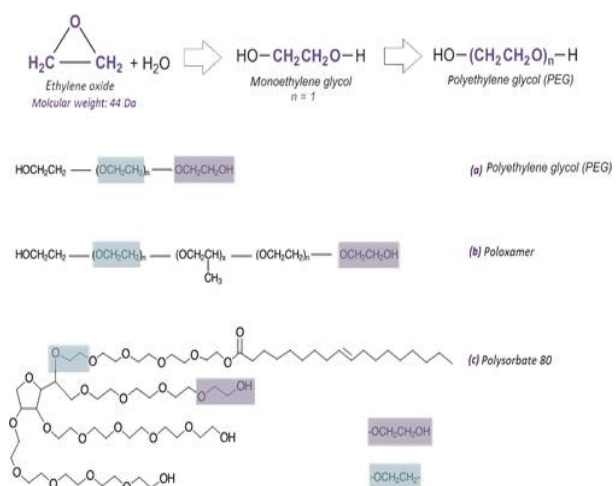
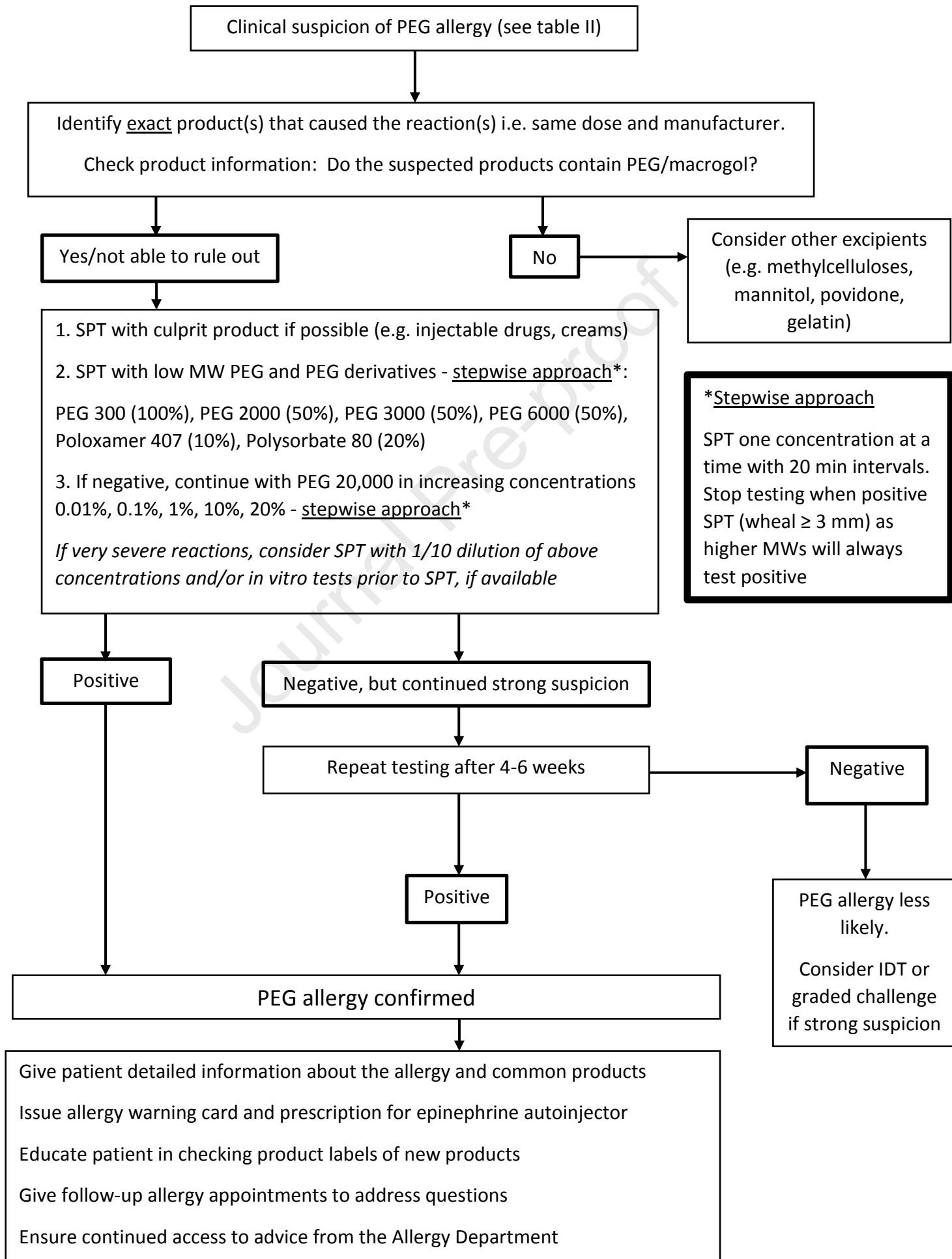


Figure 1.

Figure 2.



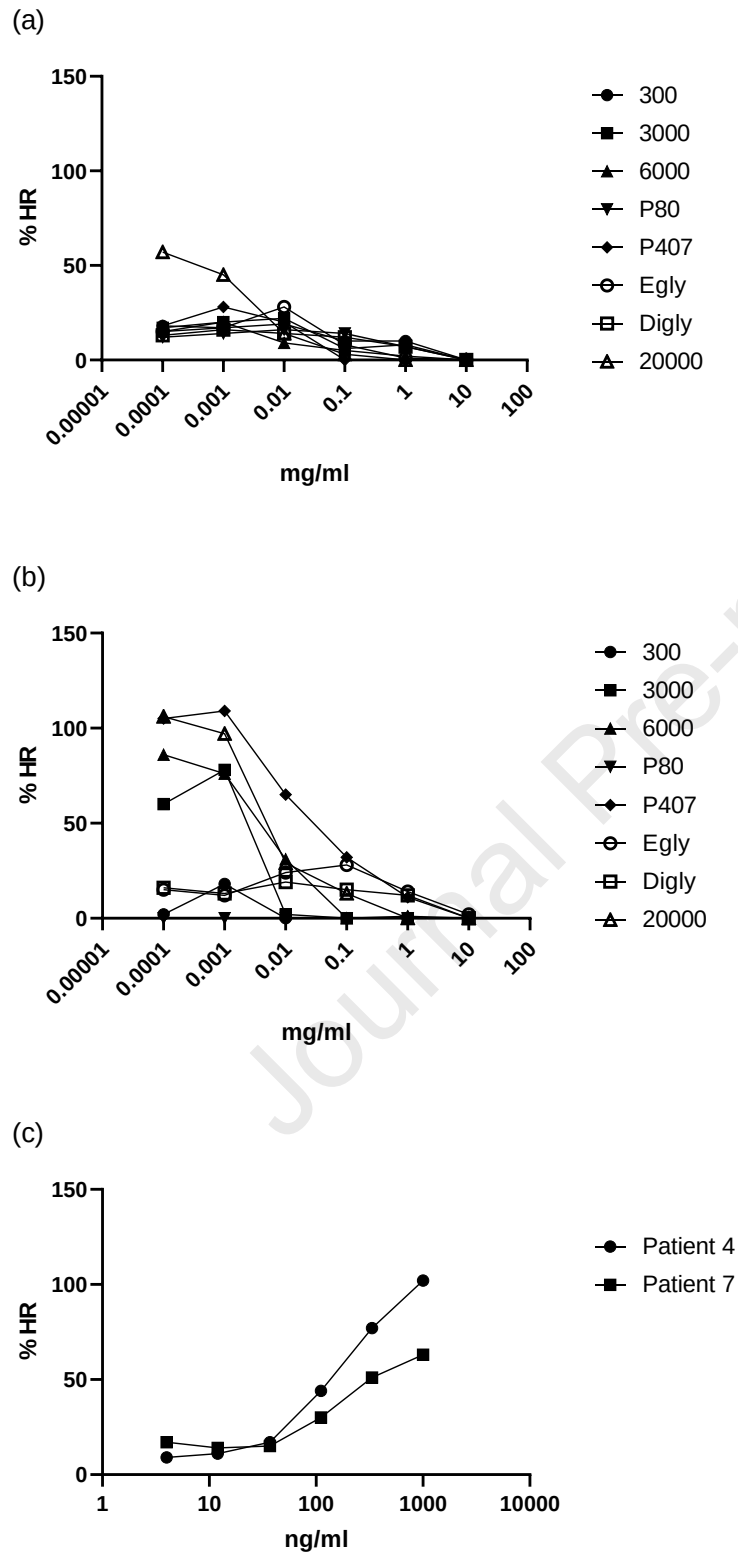


Figure E1.