

Supplementary Data

PICO Question 1: Should proton pump inhibitors be used in patients with esophageal eosinophilia?

PICO Question 2: Should topical glucocorticosteroids be used in patients with EoE?

PICO Question 3: Should systemic glucocorticosteroids be used in patients with EoE?

Forest plot not shown (only 1 study).

PICO Question 4: Should an elemental diet be used in patients with EoE?

PICO Question 5: Should an empiric food elimination diet be used in patients with EoE?

PICO Question 6: Should allergy-based testing be used for the purpose of identifying food triggers in patients with EoE?

PICO Question 7: Should maintenance therapy be recommended in patients with EoE?

Forest Plot not shown (only 1 study).

PICO Question 8: Should esophageal dilation be used in patients with EoE?

PICO Question 9: Should anti-IL-5 therapy be used in patients with EoE?

PICO Question 10: Should anti-IL-13 therapy be used in patients with EoE?

Forest plot not shown (only 1 study)

PICO Question 11: Should anti-IgE therapy be used in patients with EoE?

Forest plot not shown (only 1 study)

PICO Question 12: Should montelukast be used in patients with EoE?

Forest plot not shown (only 1 study)

PICO Question 13: Should cromolyn be used in patients with EoE?

Forest plot not shown (only 1 study)

PICO Question 14: Should anti-TNFs be used in pts with EoE?

Forest plot not shown (only 1 study)

PICO Question 15: Should immunomodulators be used in the treatment of EoE?

Forest plot not shown (only 1 study)

Supplementary Table 1
PICO Questions

Question no.	Question	PICO question				Method
		Population	Intervention(s)	Comparator	Outcome	
1	Should PPIs be used in patients with symptomatic esophageal eosinophilia?	Esophageal eosinophilia, not necessarily meeting EoE criteria	PPI	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
2	Should topical glucocorticosteroids be used in patients with EoE?	Patients with EoE	Topical steroids	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
3	Should systemic glucocorticosteroids be used in patients with EoE?	Patients with EoE	Systemic steroids	Placebo or topical steroids	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
4	Should an elemental diet be used in patients with EoE?	Patients with EoE	Elemental diet	No diet change	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
5	Should an empiric elimination diet be used in patients with EoE?	Patients with EoE	6-food elimination diet 4-food elimination diet 2-food elimination diet Single-food elimination diet	No elimination diet	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
6	Should allergy-based testing be used for the purpose of identifying food triggers in patients with EoE?	Patients with EoE	SPT, sIgE, APT, and/or CRD to direct an elimination diet	No elimination diet	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
7	Is maintenance therapy recommended in patients with EoE?	Patients with EoE who are in clinical and histologic remission	Maintaining therapy	Discontinuing therapy	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
8	Should esophageal dilation be used in patients with EoE?	Patients with EoE	Dilation	No dilation	Adverse events	GRADE
9	Should anti-IL-5 therapy be used in patients with EoE?	Patients with EoE	Anti-IL-5 therapy	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
10	Should anti-IL-13 therapy be used in patients with EoE?	Patients with EoE	Anti-IL-13 therapy	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
11	Should anti-IgE therapy be used in patients with EoE?	Patients with EoE	Anti-IgE therapy	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
12	Should montelukast be used in patients with EoE?	Patients with EoE	Montelukast	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
13	Should cromolyn be used in patients with EoE?	Patients with EoE	Cromolyn	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
14	Should anti-TNFs be used in patients with EoE?	Patients with EoE	Anti-TNF	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE

15	Should immunomodulators be used in patients with EoE?	Patients with EoE	Azathioprine or 6-MP	Placebo	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	GRADE
16	Should repeat EGD be used to assess patients with EoE after a change in treatment?	Patients with EoE	EGD with esophageal biopsy	NA	NA	Narrative
17	What is the management of patients who become asymptomatic on initial PPI treatment?	Patients with esophageal eosinophilia and/or EoE	Repeat EGD, followed by additional therapy if eosinophils still elevated	No EGD, no change in treatment	Failing to achieve histologic remission (<15 eos/hpf) Symptoms Adverse events	Narrative

Abbreviations: ATP, atopy patch test; CRD, component-resolved diagnostics; EGD, esophagogastroduodenoscopy; 6-MP, 6-mercaptopurine; sIgE, specific IgE; SPT, skin-prick test.

Supplementary Table 2

Summary of Eosinophilic Esophagitis Outcomes Considered

Name of outcome	Definition	Minimally important difference	Rating (1–9)	Critical vs important vs nonimportant
Histology	Eosinophil counts <15/hpf in esophagus	Not known	8	Critical
		Response: 30%–50% improvement	6	
Symptoms	DSQ, MDQ, EEsAI, PEES	Remission: absence of symptoms. For EEsAI, score <30 may indicate inactive disease/remission		Important
Endoscopic findings	Eosinophilic esophagitis endoscopic reference score	Response: 30%–50% improvement Remission: normalization	6	Important
Complications of EoE	Stricture	NA	8	Critical
	Food impaction			
	Malnutrition psychiatric			
Quality of life	Pediatric EoE QL Adult EoE QL	Response: 30%–50% improvement as response Remission: baseline for healthy people	6	Important
Biomarkers	Peripheral eos	NA	4	Not important
	Progenitor eos			
	Gene expression			
	Cytosponge			
	EST readout			
Adverse events of medication treatment	Tissue cytokines eosinophil granules			
	Allergy	NA	6	Important
	Weight gain			
	Anaphylaxis			
Complications of endoscopy	Infections			
	Perforation	NA	8	Critical
Costs	Anesthesia complications			
		NA	6	Important

Abbreviations: DSQ, dysphagia symptoms questionnaire; EEsAI, eosinophilic esophagitis activity index; EST, esophageal string test; MDQ, Mayo Dysphagia Questionnaire; NA, not applicable; PEES, Pediatric Eosinophilic Esophagitis Symptom Scores; QL, quality of life.

Supplementary Table 3

Electronic Search Strategies: Eosinophilic Esophagitis–Final Search

Search date: May 13, 2018

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946–Present, Embase Classic+Embase 1947 to 2018 May 11; Wiley Cochrane. Individual systematic review searches were not registered in Prospero, as this technical report represents an umbrella evidence review.

Ovid MEDLINE(R), Embase

No.	Searches	Results
1	exp Eosinophilic Esophagitis/	5991
2	(eosinophilic adj2 (esophagitis or oesophagitis)).ti,ab.	6556
3	1 or 2	7480
4	exp EOSINOPHILIA/	62171
5	exp ESOPHAGITIS/	45445
6	exp ESOPHAGUS/	133201
7	4 and (5 or 6)	2855
8	eo.e.ti,ab.	3588
9	3 and (7 or 8)	4580
10	exp Adrenal Cortex Hormones/ use ppez	376133
11	exp corticosteroid/ use emczd	935731
12	(corticosteroid* or steroid* or prednisone or budesonide or fluticasone).ti,ab.	786701
13	exp Leukotriene Antagonists/ use ppez	2974
14	exp leukotriene receptor blocking agent/ use emczd	18407
15	exp montelukast/ use emczd	8443
16	(montelukast or singulair).mp.	10840
17	exp Proton Pump Inhibitors/ use ppez	16773
18	exp proton pump inhibitor/ use emczd	68622
19	(proton pump inhibitor* or PPI* or omeprazole or Prilosec or Yosprala or lansoprazole or Prevacid or dexlansoprazole or Dexilent or rabeprazole or Aciphex or pantoprazole or Protonix or esomeprazole or Nexium or Vimovo or Zegerid).ti,ab.	88470
20	exp monoclonal antibody/ use emczd	480638
21	exp Antibodies, Monoclonal, Humanized/ use ppez	39896
22	exp Interleukin-5/ai [Antagonists & Inhibitors]	293
23	exp Receptors, Interleukin-5/ai [Antagonists & Inhibitors]	31
24	exp interleukin 5/ use emczd	25332
25	(anti-il-5* or Interleukin-5 or Mepolizumab or nucala or Reslizumab or Cinqair or Benralizumab or fasenra).ti,ab.	6850
26	exp Interleukin-13/ai [Antagonists & Inhibitors]	219
27	interleukin 13/ use emczd	20432
28	exp Interleukin-4/ai [Antagonists & Inhibitors]	501
29	exp interleukin 4/ use emczd	71100
30	(Dupilumab or Dupixent or anti-il-13* or anti-il-4* or Interleukin-13 or Interleukin-4).ti,ab.	26804
31	exp Immunoglobulin E/ai [Antagonists & Inhibitors]	20
32	immunoglobulin e/ use emczd or immunoglobulin e antibody/ use emczd	80681
33	(anti-IgE or Omalizumab or Xolair).mp.	14248
34	exp Dilatation/ use ppez	10447
35	exp esophagus dilatation/ use emczd	3265
36	(dilation or dilatation).ti,ab.	210743
37	exp Immunologic Factors/ use ppez	1274605
38	exp immunomodulating agent/ use emczd	1045440
39	immunomodulator*.ti,ab.	93101
40	exp Mercaptopurine/	46362
41	(6-Mercaptopurine or 6-MP or Purinethol or Purixan or azothioprine or Azathioprine or Azasan or Imuran).ti,ab.	46642
42	exp Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]	14168
43	tumor necrosis factor inhibitor/ use emczd	10354
44	(Infliximab or remicade or adalimumab or humira or golimumab or simponi or vedolizumab or entyvio or tofacitinib or Xeljanz or Jakvinsus).ti,ab.	45437
45	exp Cromolyn Sodium/ use ppez	4044
46	exp cromoglycate disodium/ use emczd	15471
47	cromolyn.ti,ab.	2968
48	Food Hypersensitivity/di [Diagnosis]	6271
49	exp Protein Array Analysis/ use ppez	7467
50	exp IMMUNOASSAY/ use ppez	475054
51	exp allergy test/ use emczd or exp food allergy/ use emczd	35286
52	(Component Resolved Diagnostic Testing or crd).ti,ab.	6533
53	(test* adj2 (allerg* or hypersensitiv*).ti,ab.	17189
54	or/10-53	4631827
55	9 and 54	2875
56	(Randomized Controlled Trial or Pragmatic Clinical Trial or meta-analysis).pt.	550035
57	exp Randomized Controlled Trials as Topic/	263799
58	“Randomized Controlled Trial (topic)”/	145282
59	Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/	1420748
60	meta-analysis/ or systematic review/ or meta-analysis as topic/ or “meta analysis (topic)”/ or “systematic review (topic)”/ or exp technology assessment, biomedical/	416180
61	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3100357
62	((singl* or doubl*) adj (blind* or dumm* or mask*).ti,ab,hw,kf,kw.	491550
63	((tripl* or trebl*) adj (blind* or dumm* or mask*).ti,ab,hw,kf,kw.	1696
64	((systematic* adj3 (review* or overview*) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	303565
65	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	19173
66	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*).ti,ab,kf,kw.	49299

(continued on next page)

Supplementary Table 3 (continued)

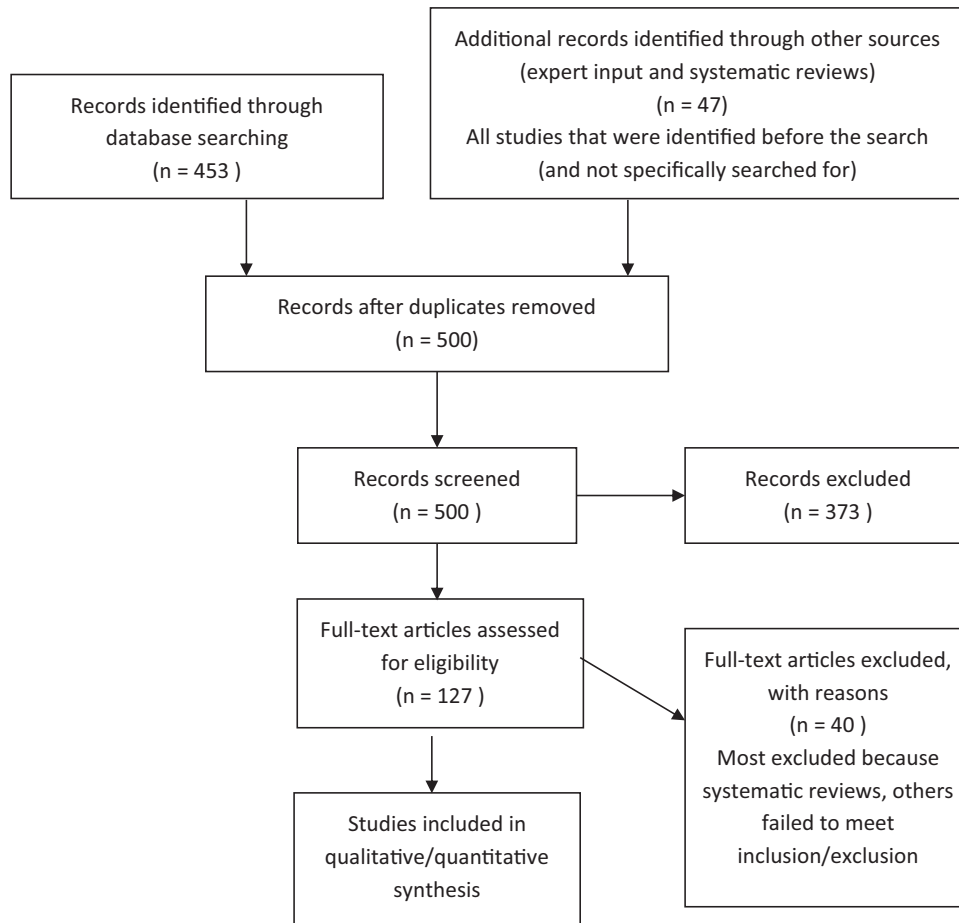
No.	Searches	Results
67	(data syntheses* or data extraction* or data abstraction* or handsearch* or hand search or mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square* or met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal* or meta regression* or metaregression* or outcomes research or relative effectiveness).ti,ab,kf,kw.	151747
68	(cochrane or (health adj2 technology assessment) or evidence report).jw.	44072
69	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	594805
70	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	387579
71	(meta-analysis or systematic review).md.	0
72	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	27349
73	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.	4938
74	or/56-73	3749981
75	55 and 74	420
76	exp diet therapy/	380595
77	(diet* adj2 (6 food or six food or elimination or elemental)).ti,ab.	5676
78	76 or 77	385128
79	9 and 78	875
80	75 or 79	1166
81	animals/ not (humans/ and animals/)	5768520
82	80 not 81	1163
83	limit 82 to (case reports or comment or editorial or letter or conference abstract or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	418
84	case report/	4211687
85	82 not (83 or 84)	722
86	remove duplicates from 85	496
Wiley Cochrane		
ID	Search Hits	
#1	MeSH descriptor: [Eosinophilic Esophagitis] explode all trees	26
#2	(eosinophilic near/2 (esophagitis or oesophagitis)).ti,ab	126
#3	#1 or #2	128
#4	MeSH descriptor: [Eosinophilia] explode all trees	240
#5	MeSH descriptor: [Esophagitis] explode all trees	680
#6	MeSH descriptor: [Esophagus] explode all trees	1282
#7	#4 and (#5 or #6)	36
#8	eoe:ti,ab	86
#9	#3 or #7 or #8 131	
#10	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 13563	
#11	(corticosteroid* or steroid* or prednisone or budesonide or fluticasone).ti,ab 35079	
#12	MeSH descriptor: [Leukotriene Antagonists] explode all trees	439
#13	(montelukast or singulair).ti,ab 1269	
#14	MeSH descriptor: [Proton Pump Inhibitors] explode all trees	1302
#15	(proton pump inhibitor* or PPI* or omeprazole or Prilosec or Yosprala or lansoprazole or Prevacid or dexlansoprazole or Dexilent or rabeprazole or Aciphex or pantoprazole or Protonix or esomeprazole or Nexium or Vimovo or Zegerid).ti,ab	6841
#16	MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees	3971
#17	MeSH descriptor: [Interleukin-5] explode all trees	159
#18	MeSH descriptor: [Receptors, Interleukin-5] explode all trees	9
#19	(anti-il-5* or Interleukin-5 or Mepolizumab or nucala or Reslizumab or Cinqair or Benralizumab or fasenra).ti,ab	806
#20	MeSH descriptor: [Interleukin-13] explode all trees	81
#21	MeSH descriptor: [Interleukin-4] explode all trees	332
#22	(Dupilumab or Dupixent or anti-il-13* or anti-il-4* or Interleukin-13 or Interleukin-4).ti,ab	873
#23	MeSH descriptor: [Immunoglobulin E] explode all trees 1287	
#24	(anti-IGE or Omalizumab or Xolair).ti,ab	704
#25	MeSH descriptor: [Dilatation] explode all trees 420	
#26	(dilation or dilatation).ti,ab	6065
#27	MeSH descriptor: [Immunologic Factors] explode all trees	8197
#28	immunomodulator*.ti,ab	2491
#29	MeSH descriptor: [Mercaptopurine] explode all trees	1304
#30	(6-Mercaptopurine or 6-MP or Purinethol or Purixan or azothioprine or Azathioprine or Azasan or Imuran).ti,ab	2101
#31	MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees	3094
#32	(Infliximab or remicade or adalimumab or humira or golimumab or simponi or vedolizumab or entyvio or tofacitinib or Xeljanz or Jakvinus).ti,ab	3531
#33	MeSH descriptor: [Cromolyn Sodium] explode all trees 705	
#34	cromolyn:ti,ab 332	
#35	MeSH descriptor: [Food Hypersensitivity] explode all trees	731
#36	MeSH descriptor: [Protein Array Analysis] explode all trees	34
#37	MeSH descriptor: [Immunoassay] explode all trees	4804
#38	(Component Resolved Diagnostic Testing or crd).ti,ab 166	
#39	(test* near/2 (allerg* or hypersensitivit*)).ti,ab	756
#40	MeSH descriptor: [Diet Therapy] explode all trees	5354
#41	(diet* near/2 (6 food or six food or elimination or elemental)).ti,ab	306
#42	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41	86910
#43	#9 and #42	103

Supplementary Table 4
Additional Evidence Profile

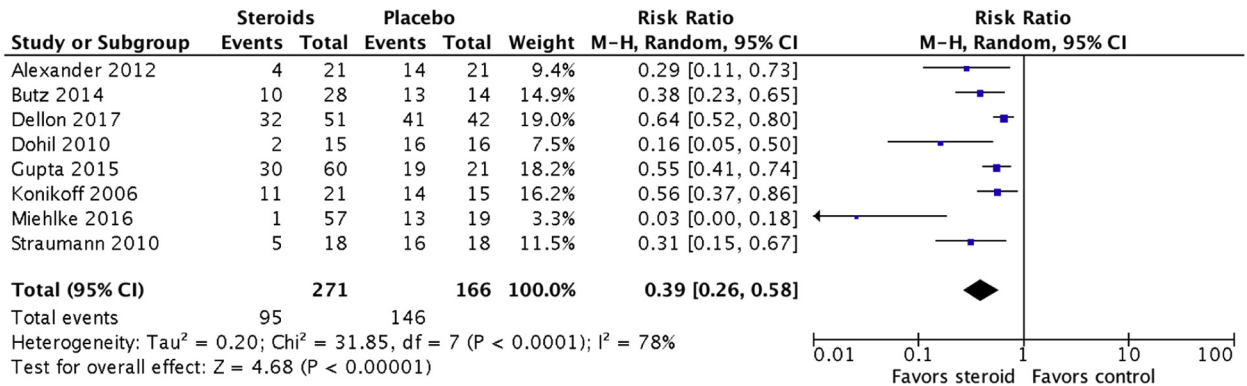
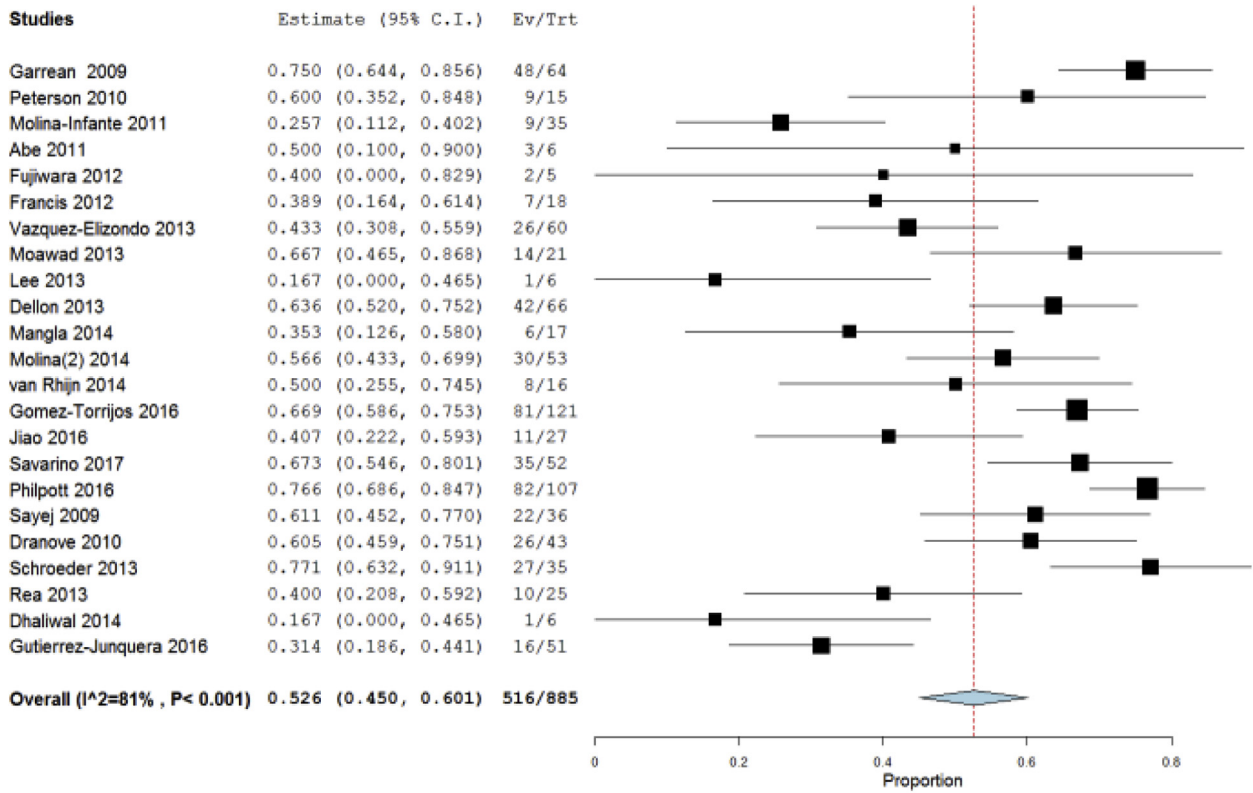
Failure to achieve histologic response (assessed with: <15 Eos/hpf)												
Certainty assessment							Patients, n (%)		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical Steroids	PPI	Relative, RR (95% CI)	Absolute (95% CI)		
2 ^{27,33}	Randomized trials	Not serious	Not serious	Serious ^a	Serious ^b	None	53/88 (60.2)	55/88 (62.5)	0.96 (0.76–1.22)	25 fewer per 1000 (from 137 more to 150 fewer)	⊕⊕○○ LOW	CRITICAL

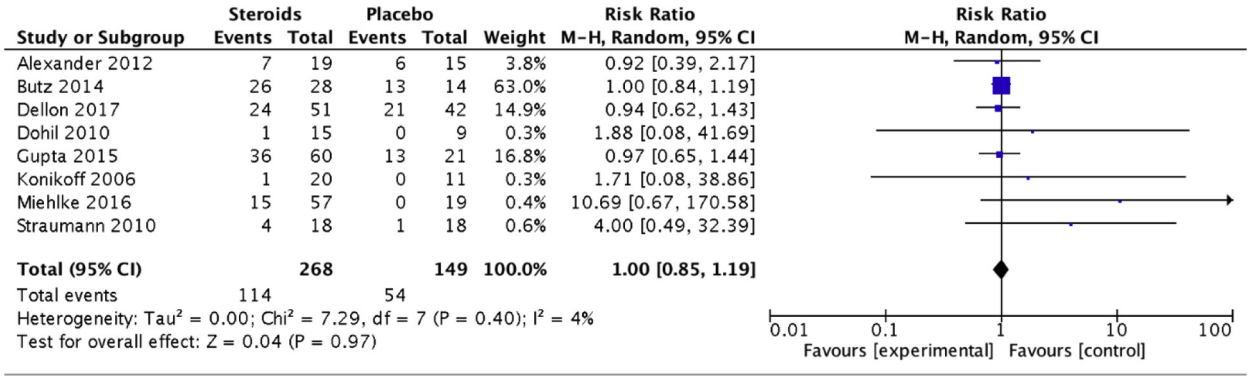
^aNo PPI trial before steroids (so GERD is possible confounder).

^bClinical management would vary at ends of CI.

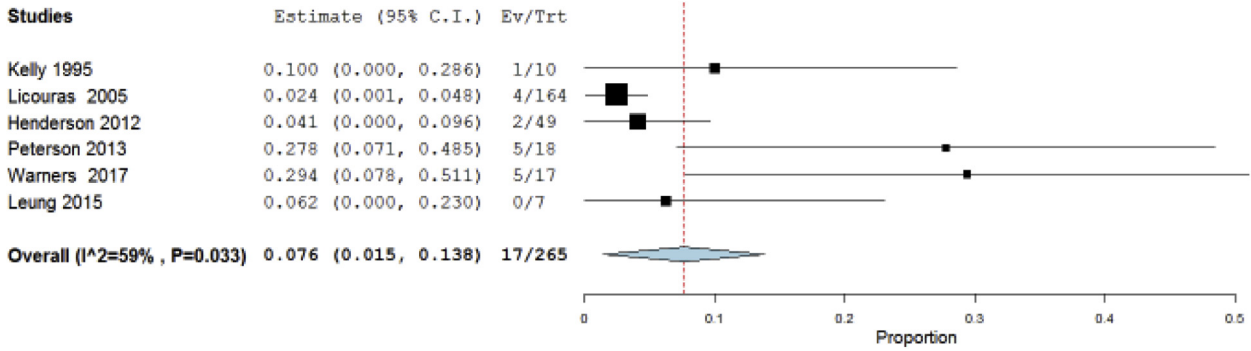


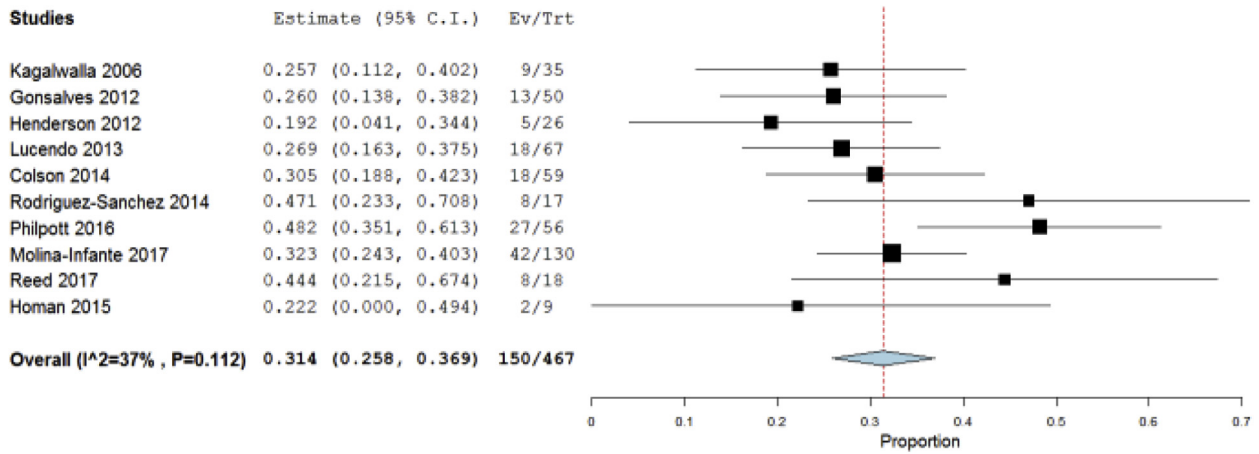
Supplementary Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



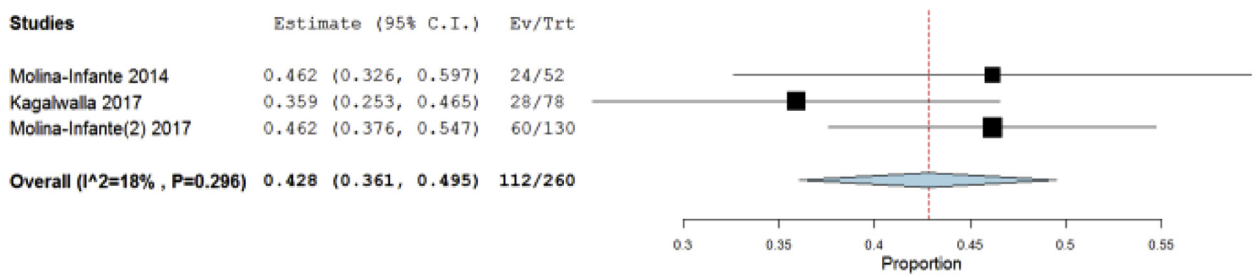


Adverse events in topical steroids compared to placebo

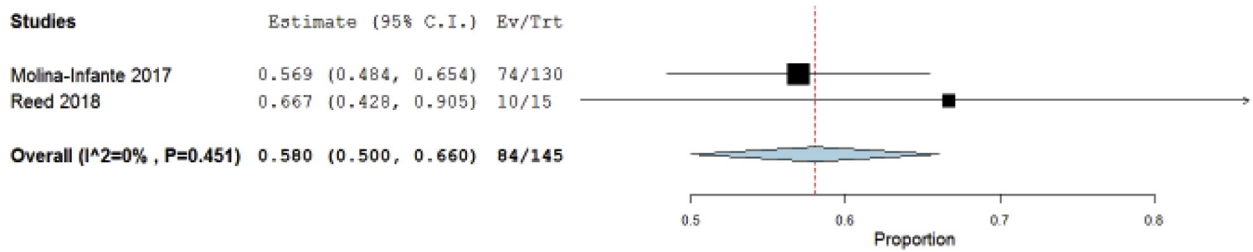




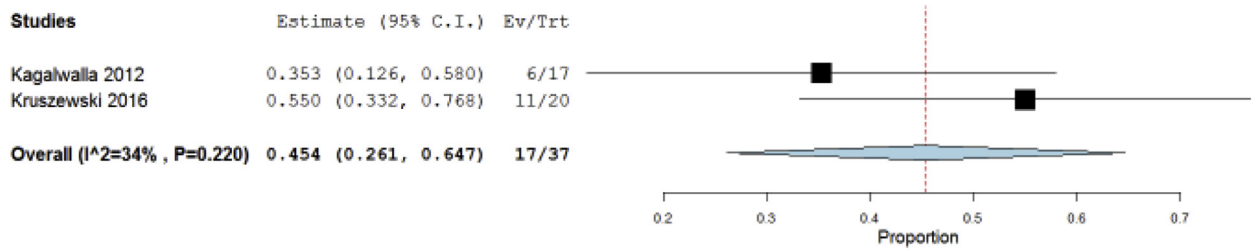
PICO Question 5a: 6-food elimination



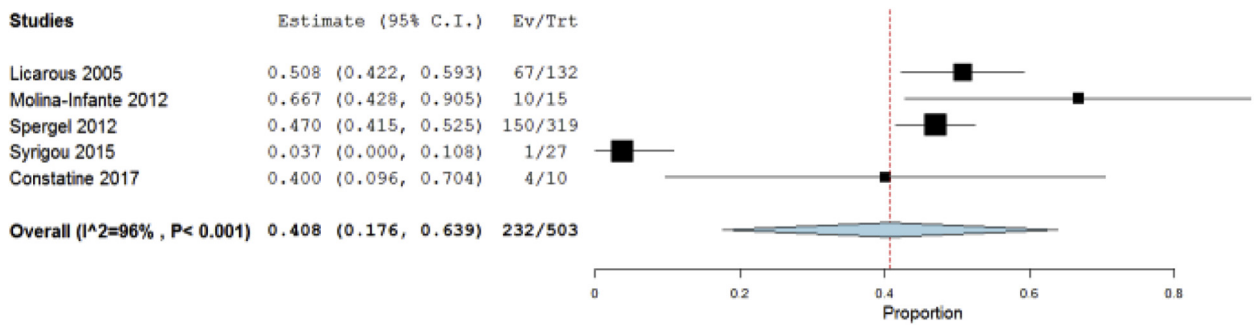
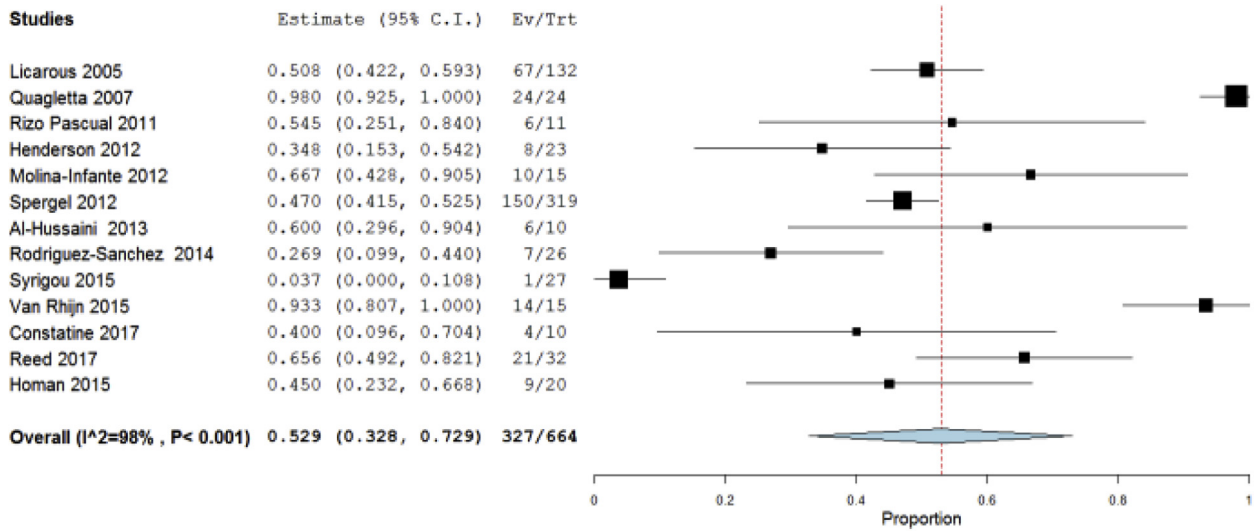
PICO Question 5b: 4-food elimination



PICO Question 5c: 2-food elimination

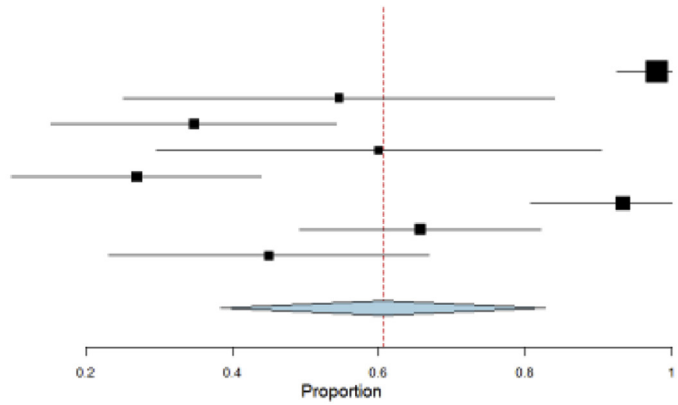


PICO Question 5d: Single-food elimination



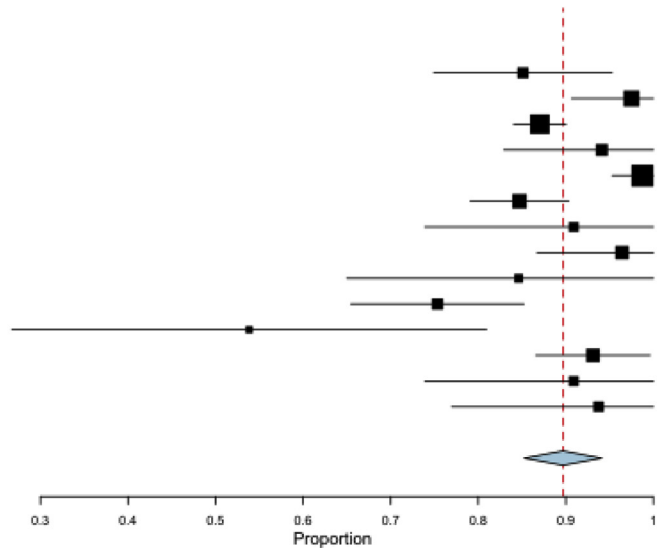
Studies including patch testing

Studies	Estimate (95% C.I.)	Ev/Trt
Quagletta 2007	0.980 (0.925, 1.000)	24/24
Rizo Pascual 2011	0.545 (0.251, 0.840)	6/11
Henderson 2012	0.348 (0.153, 0.542)	8/23
Al-Hussaini 2013	0.600 (0.296, 0.904)	6/10
Rodriguez-Sanchez 2014	0.269 (0.099, 0.440)	7/26
Van Rhijn 2015	0.933 (0.807, 1.000)	14/15
Reed 2017	0.656 (0.492, 0.821)	21/32
Homan 2015	0.450 (0.232, 0.668)	9/20
Overall (I²=94% , P< 0.001)	0.605 (0.384, 0.827)	95/161

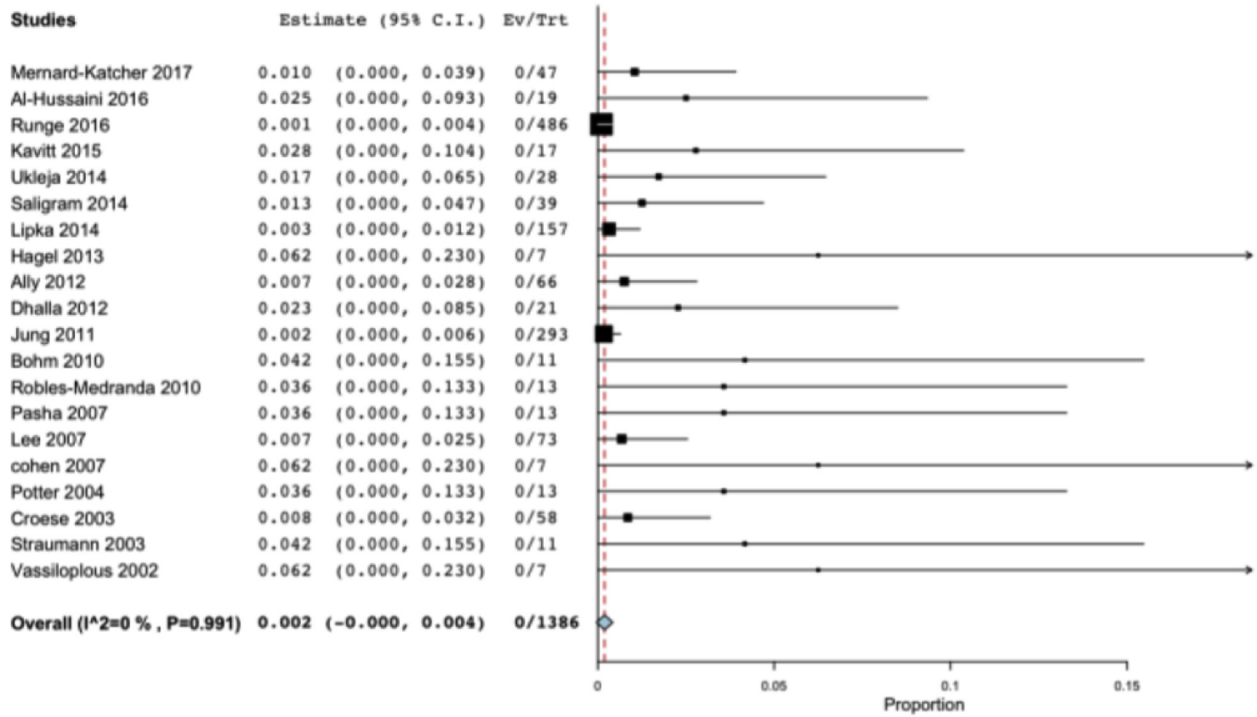


Studies not using patch testing

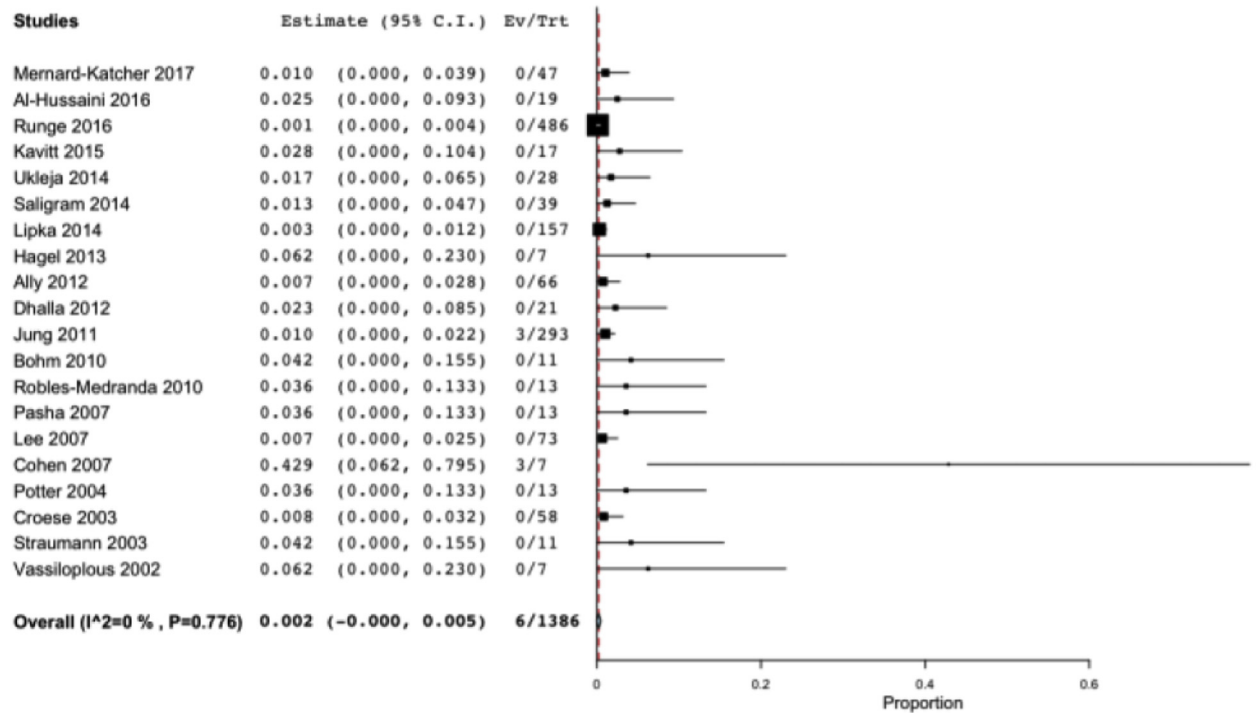
Studies	Estimate (95% C.I.)	Ev/Trt
Mernard-Katcher 2017	0.851 (0.749, 0.953)	40/47
Al-Hussaini 2016	0.975 (0.907, 1.000)	19/19
Runge 2016	0.870 (0.841, 0.900)	423/486
Kavitt 2015	0.941 (0.829, 1.000)	16/17
Saligram 2014	0.988 (0.953, 1.000)	39/39
Lipka 2014	0.847 (0.791, 0.903)	133/157
Bohm 2010	0.909 (0.739, 1.000)	10/11
Robles-Medranda 2010	0.964 (0.867, 1.000)	13/13
Pasha 2007	0.846 (0.650, 1.000)	11/13
Lee 2007	0.753 (0.655, 0.852)	55/73
Potter 2004	0.538 (0.267, 0.809)	7/13
Croese 2003	0.931 (0.866, 0.996)	54/58
Straumann 2003	0.909 (0.739, 1.000)	10/11
Vassilopoulos 2002	0.938 (0.770, 1.000)	7/7
Overall (I²=7638 % , P< 0.001)	0.897 (0.852, 0.941)	837/964



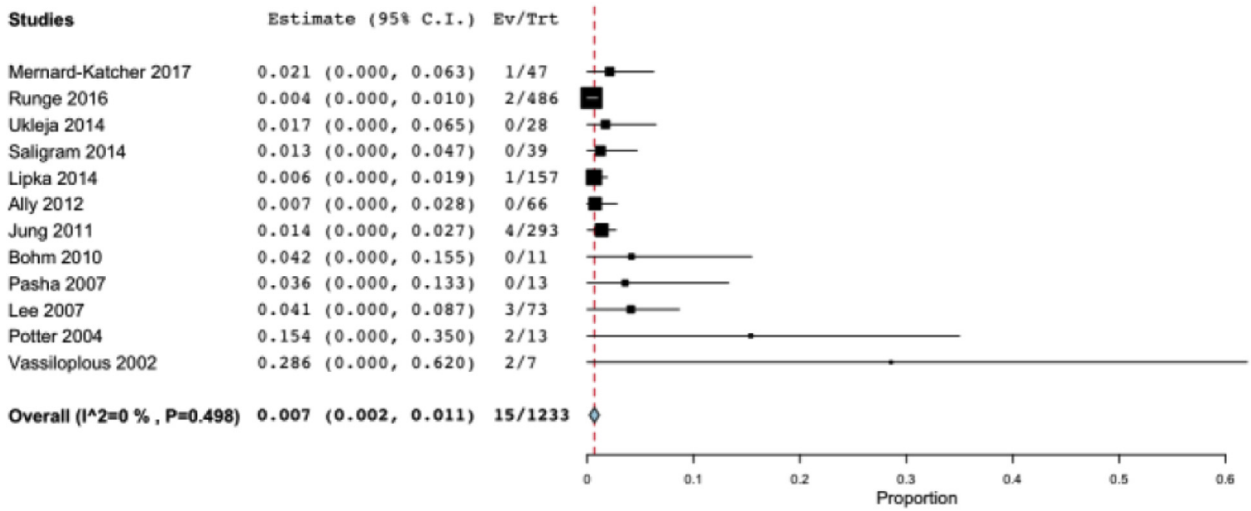
Clinical improvement



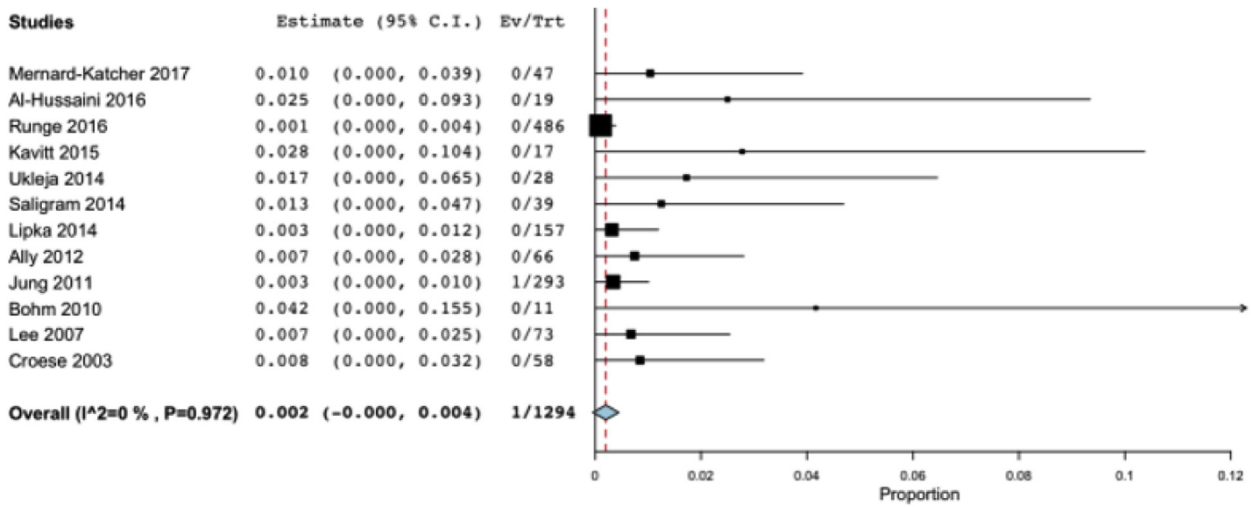
Mortality



Perforation



Hospitalizations



Hemorrhage

