NCGC National Clinical Guideline Centre

Crohn's disease

Appendix G

Clinical Guideline <...>

Forest plots

10 October 2012

NICE's original guidance on Crohn's disease: management in adults, children and young people was published in October 2012; it was partially updated in May 2016 when a new recommendation on inducing remission was added. It has now undergone a further partial update published in May 2019. The full, current recommendations can be found on the NICE website.

This document preserves evidence for areas of the guideline that have not been updated in 2019. Black shading indicates text from 2012 replaced by the 2019 update.

Commissioned by the National Institute for Health and Clinical Excellence











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1 Forest plots

1.1 Key

5-aminosalicylates = 5-ASA = 5-asa = ASA

Azathioprine = AZA = aza

Mercaptopurine = MP

Conventional glucocorticosteroid = CGCS

Methotrexate = Mtx

1.2 Induction of remission

1.2.1 Conventional glucocorticosteroid

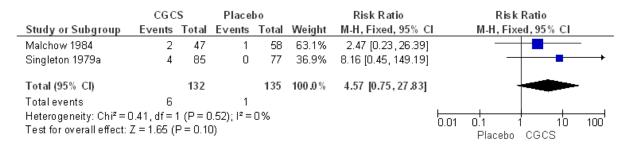
1.2.2 Conventional glucocorticosteroid versus placebo

Figure 1: Induction of remission (follow-up 15 weeks)

	CGC	S	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Malchow 1984	39	47	22	58	48.4%	2.19 [1.54, 3.12]	-
Summers 1979	40	85	20	77	51.6%	1.81 [1.17, 2.81]	-
Total (95% CI)		132		135	100.0%	1.99 [1.51, 2.64]	•
Total events	79		42				
Heterogeneity: Chi²= Test for overall effect:				0%			

Source: Benchimol El, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.

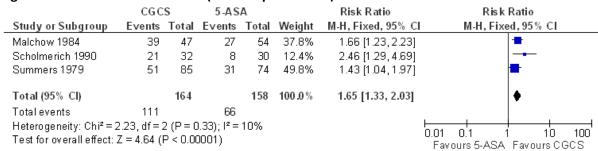
Figure 2: Withdrawal due to adverse events (follow-up 17-18 weeks)



Source: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.

1.2.3 Conventional glucocorticosteroid versus 5-aminosalicylate

Figure 3: Induction of remission (follow-up 15 weeks)



Source: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.

Figure 4: Withdrawal due to adverse events (follow-up 15 weeks)

	CGC	S	5-AS	Α		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-H, Fixed, 95% CI
Gross 1995	1	16	1	15	7.6%	0.94 [0.06 , 13.68]		+
Malchow 1984	1	58	1	52	7.8%	0.90 [0.06, 13.97]		
Martin 1990	3	28	2	22	16.5%	1.18 [0.22, 6.45]		
Prantera 1999	5	31	1	63	4.9%	10.16 [1.24,83.27]		
Scholmerich 1990	2	32	2	30	15.2%	0.94 [0.14, 6.24]		
Singleton 1979a	4	85	5	46	47.9%	0.43 [0.12, 1.53]		
Total (95% CI)		250		228	100.0%	1.18 [0.61, 2.29]		•
Total events	16		12					
Heterogeneity: Chi² = 6		•		24%			0.01	0.1 1 10 100
Test for overall effect: 2	Z = 0.49 (1	P = 0.63	2)					5-ASA CGCS

Source: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.

Figure 5: Adverse events – all doses [fixed effects] (follow-up 15 weeks)

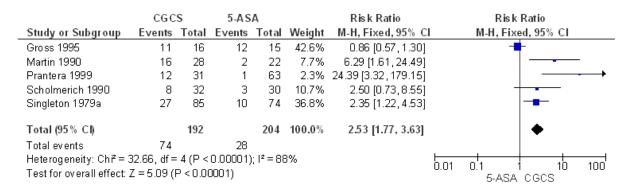
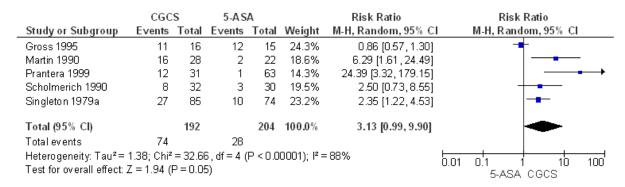


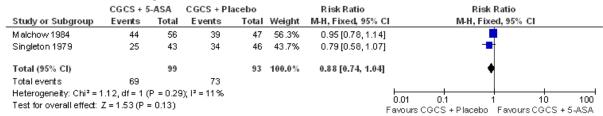
Figure 6: Adverse events – all doses [random effects] (follow-up 15 weeks)



Source: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.

1.2.4 Conventional glucocorticosteroid plus 5-aminosalicylate (sulfasalazine) versus conventional glucocorticosteroid

Figure 7: Conventional glucocorticosteroid plus 5-aminosalicylate (sulfasalazine) versus conventional glucocorticosteroid for induction of remission



1.2.5 Adjunctive azathioprine versus placebo

Figure 8: AZA/MP +/-glucocorticosteroid vs conventional glucocorticosteroid +/- placebo for induction of remission [fixed effect] (follow-up mean 16 weeks)

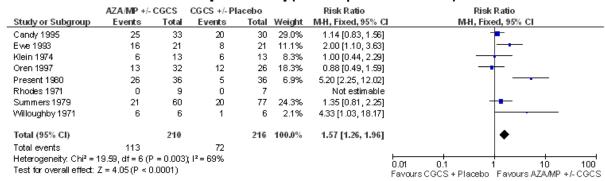


Figure 9: AZA/MP +/-glucocorticosteroid vs conventional glucocorticosteroid +/- placebo for induction of remission [random effect] (follow-up mean 16 weeks)

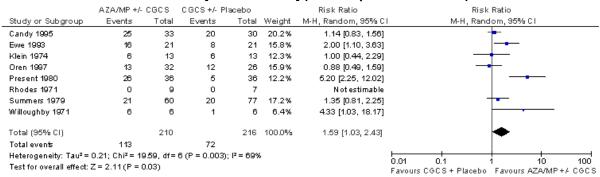


Figure 10: AZA/MP + glucocorticosteroid vs. placebo + glucocorticosteroid for glucocorticosteroidsparing [fixed effect] (follow-up mean 16 weeks)

	AZA/MP+	CGCS	CGCS + PI	acebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	MH, Fixed, 95% (CI M-H, Fixed, 95% CI
Candy 1995	25	33	20	30	52.0%	1.14 [0.83, 1.56]	+
E we 1993	16	21	8	21	19.8%	2.00 [1.10, 3.63]	- • -
Klein 1974	2	13	2	13	5.0%	1.00 [0.16, 6.07]	·
Piresent 1980	28	44	6	39	15.8%	4.14 [1.92, 8.93]	
Willoughby 1971	5	6	3	6	7.4%	1.67 [0.69, 4.00]	·
Total (95% CI)		117		109	100.0%	1.81 [1.38, 2.38]	•
Total events	76		39				
Heterogeneity: Chi² = 1	13.26, df = 4 (P = 0.01), I ² = 70%				0.01 0.1 1 10 100
Test for overall effect:	Z = 4.28 (P <	0.0001)					0.01 0.1 1 10 100 Favours CGCS + Placebo Favours AZA/MP + CGCS

Figure 11: AZA/MP + glucocorticosteroid vs. placebo + glucocorticosteroid for glucocorticosteroidsparing [random effect] (follow-up mean 16 weeks)

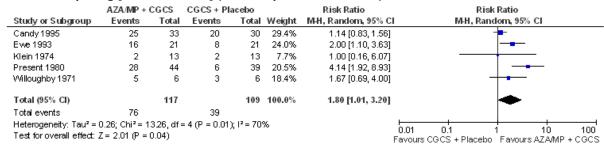
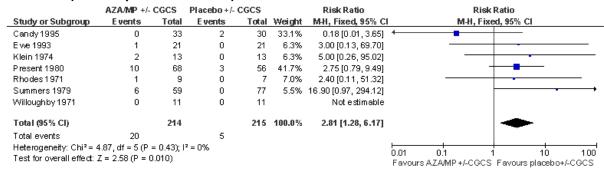


Figure 12: AZA/MP + glucocorticosteroid vs. placebo + glucocorticosteroid for fistula healing (follow-up mean 16 weeks)

	AZA/MP +	CGCS	CGCS + PI	acebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	MHH, Fixed, 95% C	I M-H, Fixed, 95% CI
Klein 1974	4	5	2	5	73.7%	2.00 [0.63, 6.38]	- -
Rhodes 1971	2	4	0	1	26.3%	2.00 [0.16, 25.75]	
Willoughby 1971	0	2	0	1		Not estimable	
Total (95% CI)		11		7	100.0%	2.00 [0.67, 5.93]	
Total events	6		2				
Heterogeneity, Chi ² = 1	0.00, df = 1 (P)	(00.1 = 1	l² = 0%				100
Test for overall effect:	Z = 1.25 (P =	0.21)					0.01 0.1 1 10 100 Favours CGCS + Placebo Favours AZAMP + CGCS

Figure 13: AZA/MP +/- glucocorticosteroid vs. placebo +/- glucocorticosteroid for adverse events (follow-up mean 16 weeks)



1.2.6 Adjunctive methotrexate versus placebo

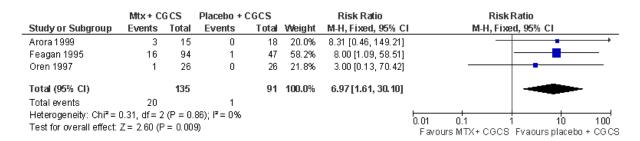
Figure 14: Methotrexate + glucocorticosteroid vs. placebo + glucocorticosteroid for induction of remission [fixed effect] (follow-up 16 weeks)



Figure 15: Methotrexate + glucocorticosteroid vs. placebo + glucocorticosteroid for induction of remission [random effect] (follow-up 16 weeks)

	Mtx + C	GCS	Placebo+	CGCS		Risk Ratio		Ri	sk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ra	ndom, 95	% CI	
Arora 1999	10	15	16	18	40.0%	0.75 [0.51, 1.11]			-		
Feagan 1995	37	94	9	47	34.7%	2.06 [1.09, 3.89]			-		
Oren 1997	5	26	6	26	25.4%	0.83 [0.29, 2.39]		_	-		
Total (95% CI)		135		91	100.0%	1.09 [0.48, 2.47]			-		
Total events	52		31								
Heterogeneity: Tau ² =	0.39; Chi²	= 9.33,	df = 2(P = 0)	.009); I ² =	- 79%					+	
Test for overall effect:	Z = 0.21 (P	= 0.83)				0.01 voursPl	0.1 acebo + CGC	า S Favou	10 rs Mtx+(100 CGCS

Figure 16: Methotrexate + glucocorticosteroid vs. placebo + glucocorticosteroid for withdrawal due to adverse events (follow-up 18 months)



1.2.7 Budesonide

1.2.7.1 Budesonide versus placebo

Figure 17: Induction of remission (CDAI ≤ 150) (follow-up eight weeks)

	Budeso	nide	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Greenberg 1994	31	61	13	66	46.4%	2.58 [1.49, 4.45]	-
Tremaine 2002	78	159	13	41	53.6%	1.55 [0.96, 2.49]	
Total (95% CI)		220		107	100.0%	1.96 [1.19, 3.23]	•
Total events	109		26				
Heterogeneity: Tau²=	0.06; Chi²	= 1.91,	df = 1 (P :	= 0.17);	I= 48%		0.01 0.1 1 10 100
Test for overall effect:	Z = 2.64 (F	P = 0.00	8)				Favours Placebo Favours Budesonide

Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009 Copyright Cochrane Collaboration, reproduced with permission.

Figure 18: Withdrawal due to adverse events (follow-up 8-10 weeks)

	Budeso	nide	Place	bo		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95%	6 CI	
Greenberg 1994	3	61	3	66	37.1%	1.08 [0.23, 5.16]		_		
Tremaine 2002	14	159	3	41	62.9%	1.20 [0.36, 3.99]		-		
Total (95% CI)		220		107	100.0%	1.16 [0.45, 2.99]		-		
Total events	17		6							
Heterogeneity: Tau² = I				= 0.92);	$ ^2 = 0\%$	ŀ	0.01	0.1	16	100
Test for overall effect: 2	Z = 0.30 (F	² =0.76)					Placebo Budeso	nide	

Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009 Copyright Cochrane Collaboration, reproduced with permission

Figure 19: Change in IBDQ score [fixed effect] (follow-up 8 – 10 weeks)

	Bud	esoni	de	PI	acebo			Mean Difference	Mear	Differer	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, F	ixed, 95%	6 CI	
Irvine 2000	40.1	37.3	61	11.7	31.5	66	55.3%	28.40 [16.34, 40.46]		\neg	_	
Tremaine 2002	34.1	35.2	79	29.3	35.7	41	44.7%	4.80 [-8.60, 18.20]		+		
Total (95% CI)			140			107	100.0%	17.84 [8.88, 26.81]		•		
Heterogeneity: Chi² = (Test for overall effect:		,		•	i%				-100 -50 Favours Place	0 bo Favo	50 ours Bud	100 esonide

Figure 20: Change in IBDQ score [random effects] (follow-up 8 - 10 weeks)

	Bud	esoni	de	PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI
Irvine 2000	40.1	37.3	61	11.7	31.5	66	50.8%	28.40 [16.34, 40.46]	-
Tremaine 2002	34.1	35.2	79	29.3	35.7	41	49.2%	4.80 [-8.60, 18.20]	-
Total (95% CI)			140			107	100.0%	16.79 [-6.34, 39.91]	
Heterogeneity: Tau² = Test for overall effect:				if=1 (P	= 0.0	1); I² = 1	85%		-100 -50 0 50 100 Favours Placebo Favours Budesonide

1.2.7.2 Budesonide versus conventional glucocorticosteroid

Figure 21: Induction of remission (follow-up eight weeks)

	Budeso	nide	CGC	S		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	I M-H, Random, 95% CI
Bar-Meir 1998	51	100	56	101	23.8%	0.92 [0.71, 1.19]	+
Campieri 1997	61	119	35	58	21.7%	0.85 [0.65, 1.12]	+
Escher 2004	12	22	17	26	7.2%	0.83 [0.52, 1.34]	+
Gross 1995	19	34	24	33	12.1%	0.77 [0.53, 1.11]	
Levine 2003	8	19	6	14	2.5%	0.98 [0.44, 2.19]	+
Rutgeerts 1994	45	88	56	88	24.1%	0.80 [0.62, 1.04]	-
Tursi 2006	10	15	8	15	4.6%	1.25 [0.69, 2.26]	+-
Van Ierssel 1995	5	9	8	9	4.1%	0.63 [0.33, 1.17]	
Total (95% CI)		406		344	100.0%	0.85 [0.75, 0.97]	•
Total events	211		210				
Heterogeneity: Tau2 = 0	0.00; Chi ² :	= 3.52, 0	df = 7 (P:	= 0.83);	$ ^2 = 0\%$		0.01 0.1 1 10 100
Test for overall effect: 2	Z = 2.51 (F	= 0.01))			Fa	avours Budesonide Favours CGCS

Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009 Copyright Cochrane Collaboration, reproduced with permission

Figure 22: Induction of remission (follow-up 12 weeks)

	Budeso	nide	CGS	C		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Campieri 1997	66	119	31	58	67.8%	1.04 [0.78, 1.39]	
Escher 2004	12	22	14	26	20.8%	1.01 [0.60, 1.71]	+
Levine 2003	9	19	7	14	11.4%	0.95 [0.47, 1.92]	+
Total (95% CI)		160		98	100.0%	1.02 [0.81, 1.30]	•
Total events	87		52				
Heterogeneity: Tau² =	0.00; Chi ² :	= 0.06,	df = 2 (P:	= 0.97);	$ ^2 = 0\%$	<u> </u>	1 01 1 10 1
Test for overall effect:	Z = 0.18 (F	0.86)				rs Budesonide Favours CGCS

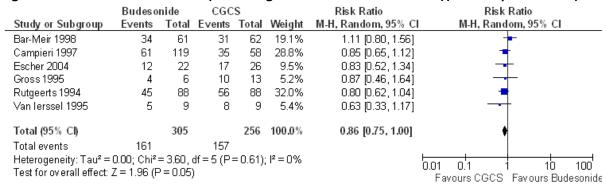
Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009 Copyright Cochrane Collaboration, reproduced with permission

Figure 23: Induction of clinical remission at eight weeks (in people with severe disease at trial entry, CDAI ≥ 300)



Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009 Copyright Cochrane Collaboration, reproduced with permission

Figure 24: Induction of remission (ileal or right-sided ileocolonic disease)(follow-up not stated)



Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009 Copyright Cochrane Collaboration, reproduced with permission

Figure 25: Change in CDAI [fixed effect] (follow-up 8-12 weeks)

	Buc	desonic	le	1	CGCS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bar-Meir 1998	123.7	73.31	100	126.6	73.09	101	34.3%	-2.90 [-23.14, 17.34]	—
D'Haens 1998	74	79.9	16	131	114	13	2.6%	-57.00 [-130.30, 16.30]	
Escher 2004	90	75.29	22	179	71.04	26	8.1%	-89.00 [-130.66, -47.34]	
Gross 1995	145	61.49	34	167	73.08	33	13.4%	-22.00 [-54.39, 10.39]	
Rutgeerts 1994	98	61.3	88	148	69.1	88	37.7%	-50.00 [-69.30, -30.70]	
Van Ierssel 1995	104	67.01	9	164	63	9	3.9%	-60.00 [-120.09, 0.09]	· · ·
Total (95% CI)			269			270	100.0%	-33.83 [-45.68, -21.97]	•
Heterogeneity: Chi2=	20.03, df	f = 5 (P	= 0.001	1); $I^2 = 7$	5%				-100 -50 0 50 10
Test for overall effect:	Z = 5.59	(P < 0.	00001)						Favours CGCS Favours Budesoni

Figure 26: Change in CDAI [random effect] (follow-up 8-12 weeks)

	Bu	desonid	le		CGCS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bar-Meir 1998	123.7	73.31	100	126.6	73.09	101	22.3%	-2.90 [-23.14, 17.34]	
D'Haens 1998	74	79.9	16	131	114	13	9.0%	-57.00 [-130.30, 16.30]	
Escher 2004	90	75.29	22	179	71.04	26	16.0%	-89.00 [-130.66, -47.34]	
Gross 1995	145	61.49	34	167	73.08	33	18.7%	-22.00 [-54.39, 10.39]	
Rutgeerts 1994	98	61.3	88	148	69.1	88	22.5%	-50.00 [-69.30, -30.70]	
Van Ierssel 1995	104	67.01	9	164	63	9	11.4%	-60.00 [-120.09, 0.09]	•
Total (95% CI)			269			270	100.0%	-42.27 [-69.67, -14.86]	-
Heterogeneity: Tau ² =	770.37;	-100 -50 0 50 10							
Test for overall effect:		Favours CGCS Favours Budesoni							

Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009 Copyright Cochrane Collaboration, reproduced with permission

Budesonide CGCS Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Bar-Meir 1998 4 100 4 101 47.6% 1.01 [0.26, 3.93] Escher 2004 26.7% 22 7 26 0.17 [0.02, 1.27] 1 Gross 1995 1 34 0 33 12.3% 2.91 [0.12,69.08] Rutgeerts 1994 0 88 2 88 13.4% 0.20 [0.01, 4.11] Tursi 2006 0 15 0 15 Not estimable Total (95% CI) 259 263 100.0% 0.57 [0.18, 1.84] Total events 6 13 Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 3.62$, df = 3 (P = 0.31); $I^2 = 17\%$ 0.01 100 0.1 10 Test for overall effect: Z = 0.93 (P = 0.35) Budesonide CGCS

Figure 27: Withdrawal due to adverse events (follow-up 8 – 12 weeks)

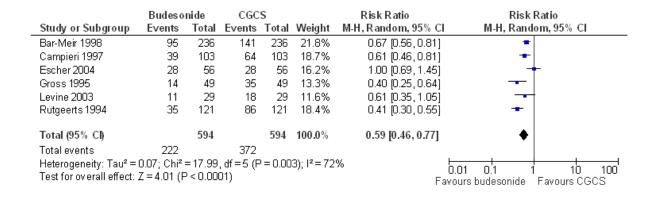
Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.

Figure 28: Glucocorticosteroid-related adverse events [fixed effect] (follow-up 8 – 12 weeks) - adults and children

	Budeso	nide	CGC	S	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95 % CI
Bar-Meir 1998	95	236	141	236	37.9%	0.67 [0.56, 0.81] •
Campieri 1997	39	103	64	103	17.2%	0.61 [0.46, 0.81	-
Escher 2004	28	56	28	56	7.5%	1.00 [0.69, 1.45	<u>+</u>
Gross 1995	14	49	35	49	9.4%	0.40 [0.25, 0.64	<u></u>
Levine 2003	11	29	18	29	4.8%	0.61 [0.35, 1.05] -
Rutgeerts 1994	35	121	86	121	23.1 %	0.41 [0.30, 0.55] -
Total (95% CI)		594		594	100.0%	0.60 [0.53, 0.67]	ı •
Total events	222		372				
Heterogeneity: Chi ² = 1	17.99, df=	5(P = 0)	0.003); I ² :	=72%			0.01 0.1 1 10 100
Test for overall effect: 2	Z = 8.28 (F	9 < 0.000	001)			1	Favours budesonide Favours CGCS

Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis

Figure 29: Glucocorticosteroid-related adverse events [random effects] (follow-up 8 – 12 weeks) – adults and children



Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis

Figure 30: Glucocorticosteroid-related adverse events [fixed effect] (follow-up 8 – 12 weeks) – adults only

	•									
	Budeso	nide	CGC	S		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI	M-H, Fixe	ed, 95% CI	
Bar-Meir 1998	95	236	141	236	43.3%	0.67 [0.56, 0.81]]			
Campieri 1997	39	103	64	103	19.6%	0.61 [0.46, 0.81]]	-		
Gross 1995	14	49	35	49	10.7%	0.40 [0.25, 0.64]]	-		
Rutgeerts 1994	35	121	86	121	26.4%	0.41 [0.30, 0.55]]	-		
Total (95% CI)		509		509	100.0%	0.56 [0.49, 0.64]		♦		
Total events	183		326							
Heterogeneity: Chi ² =	10.26, df =	3(P = 0)).02); I ² =	71%		0.04	01	1 10	100	
Test for overall effect:	Z = 8.47 (F	o < 0.000	001)	F	0.01 avours ex	0.1 perimental	1 10 Favours cor	100 ntrol		

Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis

Figure 31: Glucocorticosteroid-related adverse events [random effects] (follow-up 8 – 12 weeks) – adults only

	Budeso	nide	CGC	S		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	dom, 95% CI
Bar-Meir 1998	95	236	141	236	31.4%	0.67 [0.56, 0.81]	=	
Campieri 1997	39	103	64	103	26.0%	0.61 [0.46, 0.81]	-	
Gross 1995	14	49	35	49	17.3%	0.40 [0.25, 0.64]		
Rutgeerts 1994	35	121	86	121	25.4%	0.41 [0.30, 0.55]	-	
Total (95% CI)		509		509	100.0%	0.53 [0.40, 0.69]	•	
Total events	183		326					
Heterogeneity: Tau ² =	0.05; Chi ²	= 10.26	, df = 3 (P	= 0.02); I ² = 71%		0.04	1 10 100
Test for overall effect:	Z = 4.60 (F	o < 0.00	001)			Fa	0.01 0.1 avours experimental	1 10 100 Favours control

Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis

1.2.7.3 Budesonide versus 5-aminosalicylates

Figure 32: Budesonide vs. mesalazine - induction of remission [fixed effects] (follow-up eight weeks)

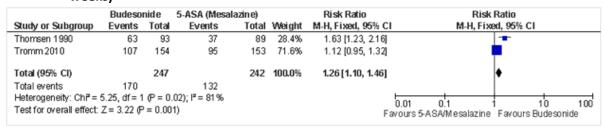


Figure 33: Budesonide vs. mesalazine - induction of remission [random effects] (follow-up eight weeks)

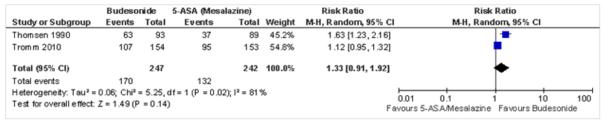
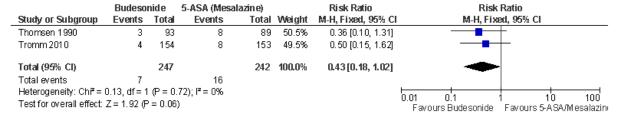


Figure 34: Budesonide vs. mesalazine - withdrawal due to adverse events (follow-up eight weeks)



1.2.7.4 Budesonide in children

Budesonide vs. conventional glucocorticosteroid

Figure 35: Induction of remission in children: eight weeks

	Budeso	nide	CGC	S		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Escher 2004	12	22	17	26	69.3%	0.83 [0.52 , 1.34]	-
Levine 2003	8	19	6	14	30.7%	0.98 [0.44, 2.19]	-
Total (95% CI)		41		40	100.0%	0.88 [0.58, 1.33]	•
Total events	20		23				
Heterogeneity: Chi² = 0				1%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.61 (F	y = 0.54)				Favours CGCS Favours Budesonide

Figure 36: Induction of remission in children: 12 weeks

	Budesonide		CGCS		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Escher 2004	12	22	14	26	61.4%	1.01 [0.60 , 1.71]	-
Levine 2003	9	19	7	14	38.6%	0.95 [0.47 , 1.92]	+
Total (95% CI)		41		40	100.0%	0.99 [0.65, 1.50]	+
Total events	21		21				
Heterogeneity: Chi² = 0 Test for overall effect: .		•)%			0.01 0.1 1 10 100
real for overall effect.	2 - 0.00 (1	-0.55,	,				Favours CGCS Favours Budesonide

Figure 37: Glucocorticosteroid-related adverse events in children: eight weeks

	Budesonide		CGCS		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Escher 2004	11	22	20	26	61.4%	0.65 [0.41, 1.04]	-
Levine 2003	6	19	10	14	38.6%	0.44 [0.21, 0.93]	-
Total (95% CI)		41		40	100.0%	0.57 [0.38, 0.85]	•
Total events	17		30				
Heterogeneity: Chi ² = 0	0.76, df = 1	(P = 0.5)	38); I² = 0	1%			0.01 0.1 1 10 100
Test for overall effect:	Z = 2.78 (P	= 0.00	5)			F	avours Budesonide Favours CGCS

1.2.8 5-aminosalicylates

1.2.8.1 5-aminosalicylates versus placebo

Figure 38: Induction of remission (follow-up 6-18 weeks)

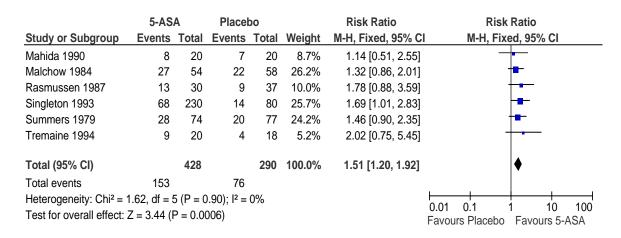


Figure 39: Adverse events (follow-up 16 weeks)

	5-ASA		Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Rasmussen 1987	17	30	23	37	48.6%	0.91 [0.61, 1.36]	•
Singleton 1979	10	74	5	77	11.6%	2.08 [0.75, 5.80]	+-
Tremaine 1994	16	20	16	18	39.8%	0.90 [0.68, 1.18]	†
Total (95% CI)		124		132	100.0%	1.04 [0.80, 1.36]	•
Total events	43		44				
Heterogeneity: Chi² = 3	3.29, df = 1	2 (P = 0	0.19); I² =	39%			0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.30 (F	P = 0.70	6)				0.01 0.1 1 10 100 Favours 5-ASA Favours placebo

Figure 40: Withdrawal for any reason (follow-up 6-18 weeks)

	5-AS	5-ASA		bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Mahida 1990	7	20	4	20	3.0%	1.75 [0.61, 5.05]	+-
Malchow 1984	54	117	58	110	44.8%	0.88 [0.67, 1.14]	=
Rasmussen 1987	4	30	10	37	6.7%	0.49 [0.17, 1.42]	
Singleton 1993	115	230	41	80	45.5%	0.98 [0.76, 1.25]	•
Total (95% CI)		397		247	100.0%	0.92 [0.77, 1.10]	♦
Total events	180		113				
Heterogeneity: Chi² = 3	3.10, df = 3		0.01 0.1 1 10 100				
Test for overall effect: 2	Z = 0.90 (F	P = 0.3°	7)				Favours 5-ASA Favours placebo

1.2.8.2 5-aminosalicylates versus azathioprine/mercaptopurine

Figure 41: Induction of remission [fixed effect] (follow-up 16-30 weeks)

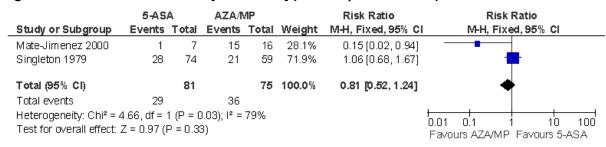


Figure 42: Induction of remission [random effect] (follow-up 16 - 30 weeks)

	5-AS	Α	AZ A/N	ИP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Mate-Jimenez 2000	1	7	15	16	40.5%	0.15 [0.02 , 0.94]	
Summers 1979	28	74	21	59	59.5%	1.06 [0.68 , 1.67]	*
Total (95% CI)		81		75	100.0%	0.48 [0.07, 3.53]	
Total events	29		36				
Heterogeneity: Tau² = 1				P = 0.03); I² = 79 %		0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.72 (1	P = 0.47	7)				Favours AZA/MP Favours 5-ASA

1.2.9 Azathioprine/mercaptopurine

1.2.9.1 Azathioprine/mercaptopurine versus methotrexate

Figure 43: Induction of remission (follow-up 24-36 weeks)

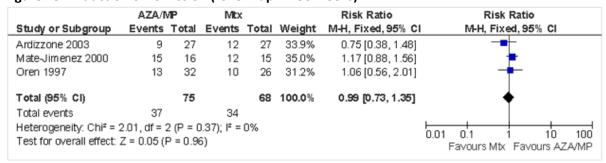


Figure 44: Withdrawal due to adverse events (follow-up 24 – 36 weeks)

	AZA/I	VIP .	Mtx			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Ardizzone 2003	3	27	3	27	48.6%	1.00 [0.22, 4.52]	
Mate-Jimenez 2000	1	16	2	15	33.5%	0.47 [0.05, 4.65]	
Oren 1997	1	32	1	26	17.9%	0.81 [0.05, 12.37]	
Total (95% CI)		75		68	100.0%	0.79 [0.25, 2.44]	
Total events	5		6				
Heterogeneity: Chi² = (0.29, df = 1	2 (P = 0	0.86); l² =	0%			
Test for overall effect: 3	Z = 0.41 (0.01 0.1 1 10 100 Favours AZA/MP Favours Mtx				

1.3 Maintenance

1.3.1 Conventional glucocorticosteroid

1.3.1.1 Conventional glucocorticosteroid versus placebo

Figure 45: Relapse or failure of remission (follow-up one year)

	CGC	CGCS Pla		bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95 % CI
Malchow 1984	25	66	26	52	69.7%	0.76 [0.50 , 1.14]	=
Smith 1978	3	32	0	26	1.3%	5.73 [0.31, 106.11]	
Summers 1979	9	33	17	60	28.9%	0.96 [0.48 , 1.91]	+
Total (95% CI)		131		138	100.0%	0.88 [0.62, 1.25]	•
Total events	37		43				
Heterogeneity: Chi² = 2	2.17 , df = 2	2(P = 0)).34); I ² =	8%			10 10 100
Test for overall effect:							0.01 0.1 1 10 100 Favours CGCS Favours Placebo

Figure 46: Relapse or failure of remission (follow-up two years)

	CGC	S	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Malchow 1984	22	42	25	39	63.6%	0.82 [0.56, 1.19]	=
Smith 1978	5	25	4	24	10.0%	1.20 [0.37 , 3.94]	
Summers 1979	9	28	10	24	26.4%	0.77 [0.38 , 1.58]	-
Total (95% CI)		95		87	100.0%	0.84 [0.61, 1.17]	•
Total events	36		39				
Heterogeneity: Chi² = 0	0.42 , df = 3	2 (P = 0).81); I² =	0%			0.01 0.1 1 10 100
Test for overall effect: .	Z = 1.02 ($P = 0.3^{\circ}$	1)				Favours CGCS Favours Placebo

1.3.2 Budesonide

1.3.2.1 Budesonide versus placebo

Figure 47: Relapse at one year [fixed effect]; budesonide 6 mg vs. placebo

•					• •		
	Budesonid	e 6mg	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ferguson 1998	10	22	14	27	14.4%	0.88 [0.49, 1.57]	_ -
Greenberg 1996	22	36	24	36	27.6%	0.92 [0.65, 1.30]	
Hanauer 2005	26	55	32	55	36.8%	0.81 [0.57, 1.16]	
Lofberg 1996	15	32	17	27	21.2%	0.74 [0.47, 1.19]	
Total (95% CI)		145		145	100.0%	0.84 [0.68, 1.03]	•
Total events	73		87				
Heterogeneity: Chi ² =	0.55, $df = 3$ (P	= 0.91);	$I^2 = 0\%$			<u>⊢</u>	
Test for overall effect:	Z = 1.69 (P =	0.09)				0.0 Favours	01 0.1 1 10 100 s Budesonide 6mg Favours Placebo

Figure 48: Relapse at one year budesonide 3 mg vs. placebo

	Budesonide	3 mg	Placel	bo		Risk Ratio	Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI		
Ferguson 1998	11	26	14	27	12.1%	0.82 [0.46, 1.45]	_	+		
Greenberg 1996	23	33	24	36	20.3%	1.05 [0.76, 1.44]		 -		
Gross 1998	56	84	62	95	51.5%	1.02 [0.83, 1.26]		+		
Lofberg 1996	21	31	17	27	16.1%	1.08 [0.74, 1.57]		+		
Total (95% CI)		174		185	100.0%	1.01 [0.86, 1.18]		•		
Total events	111		117							
Heterogeneity: Chi ² =	0.69, df = 3 (P :	= 0.88); (l²=0%				L	<u>.</u>		400
Test for overall effect:	Z = 0.13 (P = 0)	.90)				Favo	0.01 0.1 urs Budesonide 3 mg	1 1 Favours PI	_	100

Figure 49: Relapse + withdrawal at one year budesonide 6 mg

	Budesonide	6 mg	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ferguson 1998	13	22	14	27	18.1%	1.14 [0.69, 1.88]	-
Hanauer 2005	30	55	35	55	50.5%	0.86 [0.63, 1.17]	+
Lofberg 1996	18	32	20	27	31.3%	0.76 [0.52, 1.11]	
Total (95% CI)		109		109	100.0%	0.88 [0.71, 1.09]	•
Total events	61		69				
Heterogeneity: Chi ^z =	1.62, df = 2 (P :	= 0.44); 1	z = 0%				0.01 0.1 1 10 100
Test for overall effect: Z = 1.17 (P = 0.24)						Favi	0.01 0.1 1 10 100 ours Budesonide 6 mg Favours Placebo

Figure 50: Relapse + withdrawal at one year budesonide 3 mg

	Budesonide	3 mg	Placel	00		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Ferguson 1998	12	26	14	27	12.9%	0.89 [0.51, 1.55]	+
Gross 1998	64	84	76	95	67.0%	0.95 [0.81, 1.11]	
Lofberg 1996	22	31	20	27	20.1%	0.96 [0.70, 1.32]	+
Total (95% CI)		141		149	100.0%	0.95 [0.82, 1.09]	•
Total events	98		110				
Heterogeneity: Chi ^z =	0.06, df = 2 (P =	: 0.97); I	²= 0%				0.01 0.1 10 100
Test for overall effect: $Z = 0.78$ (P = 0.44)						Fav	ours Budesonide 3 mg Favours Placebo

Figure 51: Withdrawal due to adverse events at one year budesonide 6 mg

	Budesonide	6 mg	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ferguson 1998	1	22	0	27	3.4%	3.65 [0.16, 85.46]	-
Hanauer 2005	10	55	10	55	76.0%	1.00 [0.45, 2.21]	—
Lofberg 1996	0	32	2	27	20.6%	0.17 [0.01, 3.39] 🛨	•
Total (95% CI)		109		109	100.0%	0.92 [0.45, 1.88]	•
Total events	11		12				
Heterogeneity: Chr =	2.00, df = 2 (P =	= 0.37);1	²= 0%			F	.01 0.1 1 10 100
Test for overall effect:	Z = 0.23 (P = 0)	.82)				-	rs Budesonide 6mg Favours placebo

Figure 52: Withdrawal due to adverse events at one year budesonide 3 mg

	Budesonide	3 mg	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ferguson 1998	1	26	0	27	7.1%	3.11 [0.13, 73.09]	-
Gross 1998	2	84	4	95	54.3%	0.57 [0.11, 3.01]	
Lofberg 1996	0	31	2	27	38.6%	0.17 [0.01, 3.49]	
Total (95% CI)		141		149	100.0%	0.60 [0.18, 1.98]	
Total events	3		6				
Heterogeneity: Chr =	1.70, df = 2 (P = 1.70)	= 0.43);1	l²= 0%			<u>⊢</u>	4 10 100
Test for overall effect:	Z = 0.85 (P = 0	.40)				0.0 Favours	1 0.1 1 10 100 Budesonide 3mg Favours placebo

1.3.3 5-aminosalicylate maintenance

1.3.3.1 5-aminosalicylate versus placebo

Figure 53: Relapse at one year [fixed effect]

	5-ASA Plac		Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Arber 1995	6	28	15	31	7.1%	0.44 [0.20, 0.98]	
IMSG 1990	29	125	44	123	22.0%	0.65 [0.44, 0.96]	-
Mahmud 2001	55	167	59	161	29.9%	0.90 [0.67, 1.21]	+
Prantera 1992	19	64	32	61	16.3%	0.57 [0.36, 0.88]	-
Thomson 1995	33	138	38	148	18.2%	0.93 [0.62, 1.40]	+
Wellman 1988	10	31	14	35	6.5%	0.81 [0.42, 1.55]	
Total (95% CI)		553		559	100.0%	0.76 [0.64, 0.90]	•
Total events	152		202				
Heterogeneity: Chi² = 6	6.28, df =	5 (P = 0	0.28); I² =	20%			0.01 0.1 1 10 100
Test for overall effect: 2	Z = 3.13 (I	⊃ = 0.00	02)				Favours 5-ASA Favours placebo

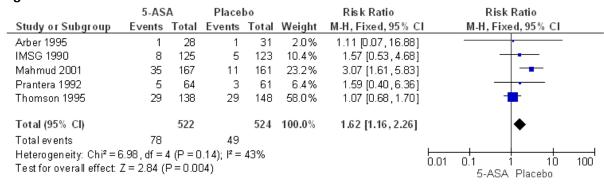
Figure 54: Relapse + withdrawal at one year [fixed effect]

	5-AS	Α	Place	bo		Risk Ratio		F	Risk Rati	io	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H,	Fixed, 9	5% CI	
Arber 1995	12	28	19	31	5.9%	0.70 [0.42, 1.17]			-		
IMSG 1990	61	125	67	123	22.1%	0.90 [0.70, 1.14]			+		
Mahmud 2001	110	167	86	161	28.7%	1.23 [1.03, 1.48]			-		
Prantera 1992	29	64	37	61	12.4%	0.75 [0.53, 1.05]			-		
Thomson 1995	85	138	84	148	26.6%	1.09 [0.90, 1.32]			•		
Wellman 1988	10	31	14	35	4.3%	0.81 [0.42, 1.55]			+		
Total (95% CI)		553		559	100.0%	1.01 [0.91, 1.12]			♦		
Total events	307		307								
Heterogeneity: Chi ² = 1		-			+	400					
Test for overall effect:	0.01 Fav	0.1 ours 5-	ASA Fa	10 vours Pl	100 acebo						

Figure 55: Relapse + withdrawals at one year [random effect]

	5-AS	Α	Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Arber 1995	12	28	19	31	9.1%	0.70 [0.42, 1.17]	-
IMSG 1990	61	125	67	123	20.7%	0.90 [0.70, 1.14]	+
Mahmud 2001	110	167	86	161	24.7%	1.23 [1.03, 1.48]	•
Prantera 1992	29	64	37	61	15.4%	0.75 [0.53, 1.05]	-= +
Thomson 1995	85	138	84	148	23.9%	1.09 [0.90, 1.32]	<u>+</u>
Wellman 1988	10	31	14	35	6.3%	0.81 [0.42, 1.55]	+
Total (95% CI)		553		559	100.0%	0.96 [0.80, 1.15]	•
Total events	307		307				
Heterogeneity: Tau² = I	0.03; Chi²	= 11.70), df = 5 (P = 0.0	4); $1^2 = 579$	% <u></u>	.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.46 (1	P = 0.68	5)			U.	5-ASA Placebo

Figure 56: Withdrawals due to adverse events at 12 months



1.3.4 Azathioprine/mercaptopurine

1.3.4.1 Azathioprine versus placebo

Figure 57: Relapses at 12 months

	AZA/I	/IP	Place	bo		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
Lemann 2006	2	40	7	43	44.3%	0.31 [0.07 , 1.39]		_	_	
O'Donoghue 1978	1	24	9	27	55.7%	0.13 [0.02, 0.92]	_			
Total (95% CI)		64		70	100.0%	0.21 [0.06, 0.68]		•		
Total events	3		16							
Heterogeneity: Chi² = 0	0.51 , df = 1	1 (P = 0).47); l² =	0%			0.01		10	100
Test for overall effect: .	Z = 2.60 (1)	P = 0.00	09)				0.01	AZA/MP		100

Figure 58: Relapses + withdrawals at 12 months

	AZA/N	ΛP	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lemann 2006	6	40	8	43	42.7%	0.81 [0.31, 2.12]	
O'Donoghue 1978	4	24	11	27	57.3%	0.41 [0.15, 1.12]	-
Total (95% CI)		64		70	100.0%	0.58 [0.29, 1.15]	•
Total events	10		19				
Heterogeneity: Chi² = (0.91, df =	1 (P = 0	0.34); I² =	0%			0.01 0.1 1 10 100
Test for overall effect: 2	Z = 1.56 (F	P = 0.10	2)				Favours AZA/MP Favours Placebo

Figure 59: Withdrawal due to adverse events at 12 months

	AZA/N	1P	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lemann 2006	1	40	1	43	67.1%	1.07 [0.07, 16.62]	
O'Donoghue 1978	1	24	0	27	32.9%	3.36 [0.14, 78.79]	-
Total (95% CI)		64		70	100.0%	1.83 [0.25, 13.38]	
Total events	2		1				
Heterogeneity: Chi² = 0).29, df = 1	I (P = 0).59); I ² =	0%			
Test for overall effect: 2	Z = 0.59 (F	P = 0.55	5)				0.01 0.1 1 10 100 Favours AZA/MP Favours Placebo

Figure 60: Adverse events at 12 months

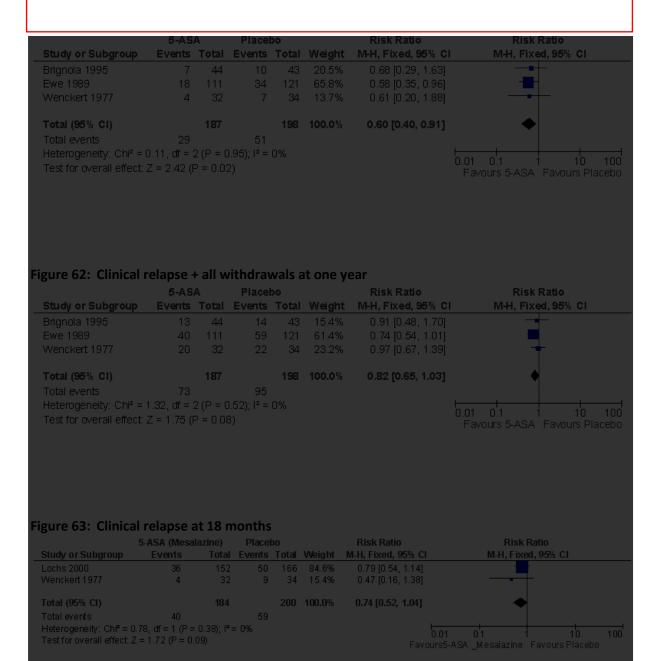
	AZA/N	VIP	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lemann 2006	2	40	1	43	67.1%	2.15 [0.20, 22.81]	- •
O'Donoghue 1978	1	24	0	27	32.9%	3.36 [0.14, 78.79]	- •
Total (95% CI)		64		70	100.0%	2.55 [0.39, 16.72]	
Total events	3		1				
Heterogeneity: Chi² = 0	0.05, df =	1(P = 0)	0.82); I² =	0%			0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.97 (F	P = 0.33	3)				Favours AZA/MP Favours Placebo

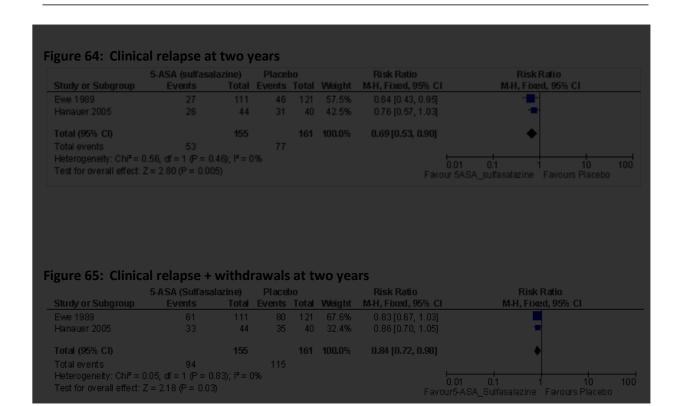
1.4 Maintaining remission after surgery





Please note that evidence on treatments for post-surgical maintenance of remission in Crohn's disease was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.





1.4.2 (5-aminosalicylates versus azathioprine)

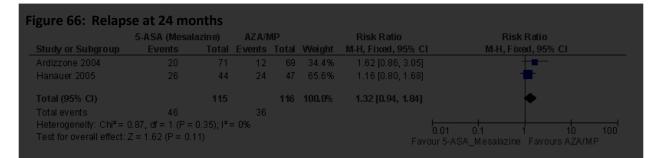


Figure 67: Relapse + withdrawal at 24 months

	5-ASA (Mesala	rzin e)	AZAA	1P		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ardizzone 2004		71	31	69	50.4%	0.94 [0.65, 1.37]	•
Hanauer 2005	33	44	32	47	49.6%	1.10 [0.85, 1.43]	†
Total (95% CI)		115		116	100.0%	1.02 [0.81, 1.28]	.
Total events	63		63				
Heterogeneity: ChF = Test for overall effect:			= 0%			Favo	0.01 0.1 1 10 100 ur 5-ASA (Mesalazine) Favour AZA/MP

Figure 68: Withdrawal due to adverse events at 24 months

	5-ASA (Mesala	izin e)	AZAM	(P		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ardizzone 2004	6	71	15	69	63.6%	0.39 [0.16, 0.94]	_
Hanauer 2005	6	44	9	47	36.4%	0.71 [0.28, 1.84]	
Total (95% CI)		115		116	100.0%	0.51 [0.27, 0.96]	•
Total events	12		24				
Heterogeneity: Chif = 0	0.84, $df = 1$ (P = 0.84	0.36); l ^a :	= 0%			<u> </u>	1 0.1 1 10 100
Test for overall effect: 2	Z= 2.08 (P = 0.0	4)				0.0	5-ASA (Mesalazine) Favours AZA/MP

1.4.3 Budesonide

(1.4.3.1) (Budesonide versus placebo)

Figure 69: Recurrence based on CDAI at one year

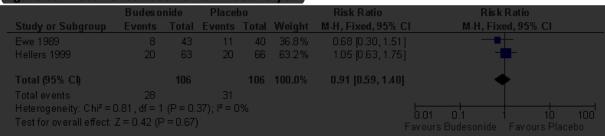


Figure 70: Withdrawal due to adverse events at one year

	Budeso	nide	Placel	00		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI
Ewe 1989	1	43	1	40	17.5%	0.93 [0.06], 14.38	· · · · · · · · · · · · · · · · · · ·
Hellers 1999	5	63	5	66	82.5%	1.05 [0.32, 3.45]	i —
Total (95% CI)		106		106	100.0%	1.03 [0.34, 3.06]	•
Total events	6		6				
Heterogeneity: Chi² = I	0.01, $df = 1$	(P = 0.	94); $I^2 = 0$				0.01 0.1 1 10 100
Test for overall effect:	Z = 0.05 (F	9 = 0.96					Favours Budesonide Favours Placebo

Figure 71: Withdrawal for any reason at one year [fixed effect]

	Budeso	nide	Placel	00		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI
Ewe 1989	14	43	17	40	50.0%	0.77 [0.44, 1.34]] -
Hellers 1999	23	63	18	66	50.0%	1.34 [0.80, 2.23	i T
Total (95% CI)		106		106	100.0%	1.05 [0.72, 1.53]	ı +
Total events	37						
Heterogeneity: Chi² = 2	2.08, df = 1	(P = 0.	15); $I^2 = 5$	2%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.27 (P	= 0.79)				Favours Budesonide Favours Placebo

Figure 72: Withdrawal for any reason at one year Irandom effect

	Budeso	nide	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Ewe 1989	14	43	17	40	47.8%	0.77 [0.44, 1.34]	-
Hellers 1999	23	63	18	66	52.2%	1.34 [0.80, 2.23]	-
Total (95% CI)		106		106	100.0%	1.03 [0.59, 1.77]	•
Total events	37						
Heterogeneity: Tau² = Test for overall effect:				= 0.15)	; I² = 52%		0.01 0.1 10 100 vours Budesonide Favours Placebo

1.5 Enteral nutrition - induction of remission

1.5.1 Enteral nutrition versus conventional glucocorticosteroid

Figure 73: Induction of remission by CDAI or PCDAI [fixed effect] (follow-up 4-10 weeks)

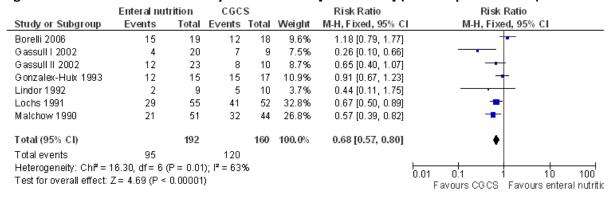


Figure 74: Induction of remission by CDAI or PCDAI [random effect] (follow-up 4-10 weeks)

	Enteral nut	rition	CGC	S		RiskRatio	RiskRatio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Borelli 2006	15	19	12	18	17.1%	1.18 [0.79, 1.77]	 -
Gassull I 2002	4	20	7	9	6.7%	0.26 [0.10, 0.66]	
Gassull II 2002	12	23	8	10	14.4%	0.65 [0.40, 1.07]	-• -
Gonzalex-Huix 1993	12	15	15	17	19.9%	0.91 [0.67, 1.23]	+
Lindor 1992	2	9	5	10	3.7%	0.44 [0.11, 1.75]	
Lochs 1991	29	55	41	52	20.5%	0.67 [0.50, 0.89]	-
Malchow 1990	21	51	32	44	17.8%	0.57 [0.39, 0.82]	
Total (95% CI)		192		160	100.0%	0.70 [0.53, 0.93]	•
Total events	95		120				
Heterogeneity: Tau ² =	0.08; Chi ^z = 1	6.30, df	= 6 (P = 0)	0.01); I ^a	e 63%		0.01 0.1 1 10 100
Test for overall effect: 2	Z = 2.46 (P =	0.01)					Favours CGCS Favours enteral nutritic

Figure 75: Induction of remission - adults by CDAI [fixed effect] (follow-up 4-10 weeks)

	Enteral nut	rition	CGC	S		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Gassull I 2002	4	20	7	9	8.3%	0.26 [0.10, 0.66]	
Gassull II 2002	12	23	8	10	9.6%	0.65 [0.40, 1.07]	
Gonzalex-Huix 1993	12	15	15	17	12.1%	0.91 [0.67, 1.23]	+
Lindor 1992	2	9	5	10	4.1%	0.44 [0.11, 1.75]	
Lochs 1991	29	56	41	52	36.5%	0.66 [0.49, 0.88]	-
Malchow 1990	21	51	32	44	29.5%	0.57 [0.39, 0.82]	-
Total (95% CI)		174		142	100.0%	0.62 [0.52, 0.74]	◆
Total events	80		108				
Heterogeneity: Chr = 9	9.96, df = 5 (P	' = 0.08)	; I² = 50%				0.01 0.1 1 10 100
Test for overall effect: 2	Z= 5.25 (P ≤	0.00001)				Favours CGCS Favours enteral nutritic

Figure 76: Induction of remission - adults by CDAI [random effect] (follow-up 4-10 weeks)

	Enteral nut	rition	CGC	S		RiskRatio	RiskRatio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Gassull I 2002	4	20	7	9	6.6%	0.26 [0.10, 0.66]	
Gassull II 2002	12	23	8	10	16.3%	0.65 [0.40, 1.07]	
Gonzalex-Huix 1993	12	15	15	17	25.4%	0.91 [0.67, 1.23]	+
Lindor 1992	2	9	5	10	3.4%	0.44 [0.11, 1.75]	
Lochs 1991	29	55	41	52	26.5%	0.67 [0.50, 0.89]	-
Malchow 1990	21	51	32	44	21.8%	0.57 [0.39, 0.82]	-
Total (95% CI)		173		142	100.0%	0.64 [0.49, 0.84]	◆
Total events	80		108				
Heterogeneity: Tau² =	0.05; Chi ^z = 9	9.90, df=	5 (P = 0.	08); l² :	= 50%		0.01 0.1 1 10 100
Test for overall effect: 2	Z = 3.25 (P =	0.001)					ours enteral nutrition Favours CGCS

1.6 Monitoring

1.6.1 Monitoring for early relapse

Figure 77: Faecal calprotectin – prediction of relapse

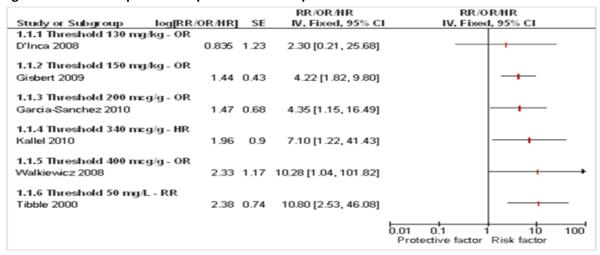


Figure 78: CRP - prediction of relapse

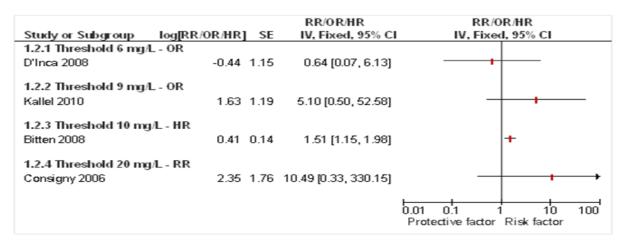


Figure 79: ESR - prediction of relapse

