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Systematic Review and Meta-analysis: Optimal Salvage Therapy in Acute Severe Ulcerative Colitis

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Background: Infliximab is an effective salvage therapy in acute severe ulcerative colitis; however, the optimal dosing strategy is unknown. We performed a systematic review and meta-analysis to examine the impact of infliximab dosage and intensification on colectomy-free survival in acute severe ulcerative colitis.

Methods: Studies reporting outcomes of hospitalized steroid-refractory acute severe ulcerative colitis treated with infliximab salvage were identified. Infliximab use was categorized by dose, dose number, and schedule. The primary outcome was colectomy-free survival at 3 months. Pooled proportions and odds ratios with 95% confidence intervals were reported.

Results: Forty-one cohorts (n = 2158 cases) were included. Overall colectomy-free survival with infliximab salvage was 79.7% (95% confidence interval [CI], 75.48% to 83.6%) at 3 months and 69.8% (95% CI, 65.7% to 73.7%) at 12 months. Colectomy-free survival at 3 months was superior with 5-mg/kg multiple (\geq 2) doses compared with single-dose induction (odds ratio [OR], 4.24; 95% CI, 2.44 to 7.36; *P* < 0.001). However, dose intensification with either high-dose or accelerated strategies was not significantly different to 5-mg/kg standard induction at 3 months (OR, 0.70; 95% CI, 0.39 to 1.27; *P* = 0.24) despite being utilized in patients with a significantly higher mean C-reactive protein and lower albumin levels.

Conclusions: In acute severe ulcerative colitis, multiple 5-mg/kg infliximab doses are superior to single-dose salvage. Dose-intensified induction outcomes were not significantly different compared to standard induction and were more often used in patients with increased disease severity, which may have confounded the results. This meta-analysis highlights the marked variability in the management of infliximab salvage therapy and the need for further studies to determine the optimal dose strategy.

Key Words: acute severe ulcerative colitis, infliximab, colectomy

INTRODUCTION

Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition that has historically resulted in emergency colectomy in 30% of patients within 3 months of presentation.¹ Twenty-five percent of patients with ulcerative colitis

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Conflicts of interest: M.C.C. has received travel and educational grants from Abbvie, Ferring, Shire, Orphan, and Takeda; has served as a speaker for DiaSorin; and received research support from Janssen. G.R.S. has served as a consultant, an advisory board member, or a speaker for AbbVie, Ferring, Janssen, Shire, Protagonist, Pfizer, and Takeda Pharmaceuticals. T.B. has served as a speaker for Janssen, Abbvie, Takeda, Pendopharm, Shire, and Ferring; as a consultant for Janssen, Abbvie, Takeda, and Pfizer; and received research support from Janssen, Pentax, and Abbvie. develop ASUC during their disease course, and 15% have 2 or more episodes.² Corticosteroids represent firstline therapy for ASUC; however, approximately one-third of patients do not respond.¹ Infliximab (IFX) and cyclosporine have demonstrated equivalent efficacy as medical salvage therapies in

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ASUC in randomized controlled trials (RCTs); however, nonrandomized studies have suggested a better treatment response and reduced risk of colectomy at 12 months with IFX.³

The standard induction schedule for IFX, which comprises 3 doses at 5 mg/kg given at weeks 0, 2, and 6, has been derived from studies in Crohn's disease and moderate to severe outpatient ulcerative colitis.^{4, 5} However, these conditions differ in their biology and inflammatory disease burden from ASUC. New insights into the pharmacokinetics of IFX in the setting of ASUC that have shown increased drug clearance,⁶ low serum levels,⁷ and fecal drug loss⁸ have led to an interest in dose intensification. In a survey of gastroenterologist members of the International Organization for the Study of Inflammatory Bowel Diseases, the majority preferred dose-intensified or accelerated-schedules⁹ to standard-schedule induction; however, the evidence to support such an approach is conflicting.^{10–14}

Despite conflicting data, we hypothesized that IFX dose intensification either via higher-dose therapy or shorter dose intervals would result in a reduction in colectomy rates. In this meta-analysis, we sought to examine the efficacy of IFX induction in ASUC and the impact of dosage, dose number, and dose intensification on colectomy-free survival (CFS).

METHODS

Search Strategy

A systematic literature search was performed independently by 2 investigators (M.C.C., D.S.) in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Supplementary Appendix 1). A broad search strategy was utilized, using Medical Subject Headings (MeSH) and key words related to ASUC and treatment with IFX therapy (Supplementary Appendix 2).

Studies were identified from the PubMed/MEDLINE, EMBASE, and CENTRAL databases from January 1999 to July 2018. The reference lists of included articles were manually reviewed, and a hand-search of the main gastroenterology conference abstract directories was performed to identify additional studies for inclusion. Relevant abstracts from British Society of Gastroenterology/Digestive Diseases Week/European Crohn's and Colitis Organisation/United European Gastroenterology Week conferences from the 2014 to July 2018 were included. Discrepancies with regards to article inclusion were resolved by consensus in consultation with the senior authors.

Inclusion and Exclusion Criteria

Studies were included if they met the following selection criteria: (1) observational or interventional design; (2) patients were hospitalized or had acute severe flares of UC refractory to oral or intravenous (IV) corticosteroids; and (3) treatment with IFX as rescue therapy was administered. Furthermore, to be eligible for inclusion, criteria for IFX use, dosing, and schedule of IFX administration and CFS had to be reported. Studies were excluded if patients had been treated previously with a rescue therapy (eg, cyclosporine, tacrolimus) during the same presentation of ASUC. Studies were also excluded if there was concomitant *Clostridium difficile* infection or cytomegalovirus colitis as these represent distinct clinical entities that have a different clinical course and have traditionally been excluded from both clinical trials and observational studies. Pediatric studies and studies that focused primarily on chronic active colitis were also excluded. Conference abstracts that had not been published as full-text articles within the last 4 years (before 2014) were excluded.

Outcomes of Interest

The primary outcome was CFS at 3 months after commencement of IFX therapy. Secondary outcomes included CFS survival at 1 and 12 months, adverse drug events, mortality, and postoperative complications.

The use of IFX was categorized by dosage (5 mg/kg or 10 mg/kg), dose number (single- or multiple-dose induction), and dose schedule. Dose schedule was defined as follows: (1) standard-schedule induction: 3 IFX doses at weeks 0, 2, and 6; (2) accelerated-schedule induction: 3 doses within 4 weeks; (3) dose-intensified induction: use of either multiple 10-mg/kg doses or an accelerated schedule with 5 mg/kg (incorporating [2]). The IFX schedule was classified on the basis of the reported intention-to-treat (ITT) strategy.

Data Extraction and Quality Assessment

Data were extracted from included studies by 2 reviewers independently (M.C.C., D.S.). In studies with multiple treatment arms, data extraction was performed in IFX-treated populations only. Corresponding authors were contacted to obtain additional data where required. Risk of bias and study quality were evaluated independently by 2 reviewers (M.C.C., D.S.), and any discrepancies were resolved in consultation with senior authors. Single-arm/extracted cohort studies that described proportions of CFS cases were treated as prevalence studies and assessed with a critical appraisal tool designed by the Joanna-Briggs Institute.¹⁵ The quality of nonrandomized studies was assessed with the Newcastle Ottawa Scale.¹⁶ The quality of randomized studies was assessed with the Cochrane risk of bias table.

Statistical Analysis

Data were analyzed on ITT principles. A random-effects model for these analyses was selected to provide a more conservative estimate than a fixed-effects model. Weighted pooled proportions of CFS were derived from studies by combining individual proportions and 95% confidence intervals (CIs) using the Freeman-Tukey double arcsine transformation method. Subgroups of IFX strategy were determined from studies that contained sufficient discriminatory information. Analysis of comparative studies that contained combinations of individual treatment groups was performed by converting binary data into pooled odds ratios (ORs).

Potential confounding covariates such as age, disease duration, IV steroid therapy, baseline C-reactive protein (CRP), and albumin levels were also examined. Continuous variables were reported as mean \pm SD. Reported medians and interquartile ranges or ranges were converted to means and SDs according to formulae provided by Wan et al.¹⁷ Where required, means and variances of treatment groups within studies were pooled for analyses.

Analyses were performed with MIX 2.0 Pro (MIX 2.0 – Professional software for meta-analysis in Excel. Version 2.0.1.5. BiostatXL, 2016. https://www.meta-analysis-made-easy.com. Mountain View, California, USA) to derive pooled proportions and RevMan 5.3 (Review Manager [RevMan], version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark) to determine ORs in comparative studies and mean covariate differences. A 2-tailed *P* value <0.05 was considered statistically significant.

Heterogeneity and Publication Bias

Heterogeneity was assessed with the I^2 test.¹⁸ The I^2 statistic estimates the percentage of variation across studies that is due to heterogeneity rather than chance. Following Higgins et al.,¹⁸ we considered I^2 values of 25%, 50%, and 75% to be low, moderate, and high. These categories do not refer to the absolute amount of observed heterogeneity, but rather to the proportion of the observed effect variance that would remain if the sampling error were to be eliminated. Subgroup analyses were performed if there was moderate or high heterogeneity in pooled effect estimates. Publication bias was assessed with Egger's test.¹⁹

RESULTS

Search Results

The literature search identified 1944 citations (Fig. 1), of which 105 met the criteria for full-text review. A total of 62 studies were subsequently excluded (Fig. 1): 12 were in non-ASUC cohorts; 5 reported on already included cohorts; 1 examined primary nonresponders to IFX; 1 investigated IFX maintenance therapy; and 1 investigated the postoperative setting. Three studies were excluded due to comorbid CMV colitis. There was insufficient information regarding IFX dosing and/or timing of administration in 10 studies. Four studies did not adequately report clinical outcomes. Nineteen studies were excluded on the basis of pooled outcome reporting without exclusion of patients with moderately severe UC and/or chronic active UC. The full-text versions of 4 studies were not available. One abstract was not published as full text within 4 years, and 1 was not in English.

Overall, 43 full-text articles were included for meta-analysis.^{10–12, 14, 20–58} Two articles published by Laharie et al.^{37, 38} and similar articles published by Jarnerot et al.³³ and Gustavsson et al.²⁹ reported outcomes on the same respective cohorts and were therefore merged for quantitative analysis. Thus, a total of 2158 patients across 41 separate study cohorts were included.

Characteristics of Included Studies

There were 5 RCTs, 30 retrospective and 6 prospective observational cohorts. Study characteristics and considerations for analyses are outlined in Table 1. Of the 5 RCT populations, 3 reported on IFX vs placebo^{28, 33, 48} and 2 reported on IFX vs cyclosporine.^{37, 38, 54} Only the IFX-treated arms from these RCTs were extracted for this review. Additional data were obtained from 12 studies by correspondence.^{10–12, 20, 22, 24, 26, 27, 30, 40, 47, 53} Unadjusted data were utilized for the analysis.

Twelve study populations reported on single-dose induction, ^{22–24, 29, 31, 33, 34, 36, 48, 50, 51, 53} and 35 studies reported on multiple-dose IFX induction.^{10–12, 14, 20–22, 25–28, 30, 32, 35–47, 49–54, 56–58} Dose-intensified induction strategies were employed in 11 studies.^{10–12, 14, 20, 22, 32, 49, 56–58} Of these, 10 studies utilized an accelerated dosing schedule,^{10–12, 20, 22, 32, 49, 56–58} 4 utilized 10-mg/kg dose induction therapy,^{11, 12, 14, 32} and 4 studies investigated accelerated induction in conjunction with high-dose IFX.^{11, 12, 32, 58} One study was a single dose finding RCT.⁴⁸ One abstract assessed standard vs accelerated-schedule induction.¹⁴ However, as both arms contained patients who were treated with a combination of 5- and 10-mg/kg dosing, this study was excluded from the comparative meta-analysis. Extracted data for the analysis are detailed in Table 1 and Supplementary Appendix 3.

Pooled Colectomy-Free Survival

The overall pooled colectomy-free survival following IFX therapy for ASUC from all included studies was 79.7% (95% CI, 75.5% to 83.6%; P = 77%; 36 studies, 1659/2129 cases) at 3 months. Pooled CFS at 1 month was 85.7% (95% CI, 82.0% to 89.0%; P = 70.6%; 36 studies, 1550/1860 cases), and 69.8% (95% CI, 65.7% to 73.7%; P = 67%; 33 studies, 1357/1943 cases) at 12 months (Fig. 2).

Pooled CFS with 5-mg/kg single-dose induction was 67.3% (95% CI, 57.1% to 76.8%; P = 55.1%; 10 studies, 200/307 cases) at 3 months, 78.8% (95% CI, 68.4% to 88.0%; P = 40.2%; 9 studies, 127/168 cases) at 1 month, and 57.0% (95% CI, 40.7% to 72.7%; P = 60.2%; 6 studies, 75/127 cases) at 12 months.

Pooled CFS with 5-mg/kg standard week 0, 2, and 6 induction was 84.0% (95% CI, 78.3% to 89.1%; P = 80.5%; 25 studies, 923/1152 cases) at 3 months, 89.4% (95% CI, 83.9% to 93.9%; P = 81.5%; 24 studies, 882/1038 cases) at 1 month, and 73.8% (95% CI, 67.9% to 79.4%; P = 74.6%; 24 studies, 772/1080 cases) at 12 months.

Pooled CFS with dose-intensified induction was 78.5% (95% CI, 70.8% to 85.4%; P = 49.2%; 11 studies, 254/325 cases) at 3 months, 84.8% (95% CI, 78.0% to 90.6%; P = 46.1%; 11

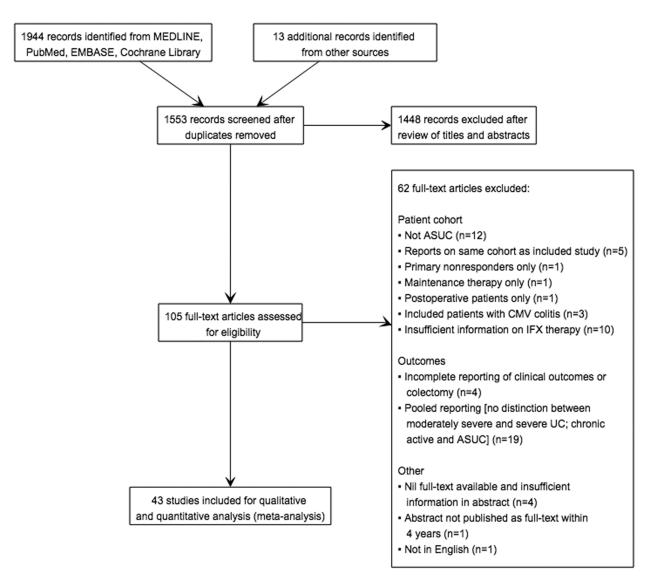


FIGURE 1. PRISMA flowchart.

studies, 274/325 cases) at 1 month, and 70.1% (95% CI, 60.2% to 79.2%; P = 65.9%; 10 studies, 231/321 cases) at 12 months.

CFS proportions by IFX strategy are described in Table 2.

Comparative Cohort Meta-analysis

5-mg/kg multiple-dose induction vs 5-mg/kg single-dose induction

Among comparative studies, 5-mg/kg multiple-dose induction was superior to 5-mg/kg single-dose induction with respect to CFS at 3 months (OR, 4.24; 95% CI, 2.44 to 7.36; P < 0.001; P = 0%; 5 studies) (Fig. 3A).^{22, 50, 51, 53, 59} Multiple-dose induction was numerically superior at 1 and 12 months, but this did not reach statistical significance.

Dose-intensified induction vs standard induction

Dose intensification was not found to be significantly different than standard induction with CFS at 3 months (OR, 0.70; 95% CI, 0.39 to 1.27; P = 0.24; $I^2 = 48\%$; 8 studies, 736 cases) (Fig. 3B).^{10, 12, 20, 49, 56–58, 60} CFS was also not significantly different at 1 month (OR, 0.76; 95% CI, 0.34 to 1.68; P = 0.49; $I^2 = 54\%$) or 12 months (OR, 0.83; 95% CI, 0.55 to 1.25; P = 0.31; $I^2 = 20\%$).

Subanalyses

Subanalyses were performed to examine 5-mg/kg standard induction compared with individual treatment strategies of 5-mg/kg accelerated, 10-mg/kg standard, and 10-mg/kg accelerated induction.

										IFX			CFS (N)		
				Abstract						Dose	IFX Dose				Considerations
Author	Үеаг	Country	Type of Study	or Full Text	Definition of Severity	Eligibility for Rescue Therany	Sample Size		Subgroups IFX Dose	Number (TT)	Strategy (ITT)	Month 1	Month Month Month 1 3 12		for the Meta-analysis
Al Khoury	2017	Ca Ca	Retrospective	Abstract	Mayo severity score 6–12 with Mayo endoscopic	IV steroid- refractory (Oxford criteria)						69	67		
					score 22			37	5 mg/kg	6	Standard	36	35	33	
								35	10 mg/kg	б	Standard	30	30	29	
								5	10 mg/kg	ю	Accelerated		7	7	
An	2017	2017 Australia	Retrospective	Abstract	Abstract TLW criteria	IV steroid- refractory	4		5 mg/kg			38	35	34	
								16		3	Standard	15	13	13	
								28		3	Accelerated	23	22	21	
Aratari	2008	2008 Italy	Retrospective	Full text	TLW criteria and Powell Tuck	IV steroid-r- efractory	11		5 mg/kg	ς	Standard	11	11	10	
Beswick	2016	2016 Australia	Prospective observational	Abstract	TLW criteria	IV steroid- refractory	24		5 mg/kg			22	22	19	
								3	5 mg/kg	1	Single dose	3	з	ю	
								6	5 mg/kg	≥2	Standard	6	6	6	
								12	5 mg/kg	≥2	Accelerated	10	10	7	
Bressler	2008	2008 Canada	Retrospective	Full text	Hospitalized UC	IV steroid- refractory	21		5 mg/kg	1	Single dose	16	13	NS	
Croft	2013	2013 Australia	Prospective observational	Full text ul	TLW criteria	IV steroid- refractory	38		5 mg/kg	1	Single dose	31	28	24	
Dean	2011	New Zealand	Retrospective	Full text	Hospitalized UC	IV steroid- refractory	19		5 mg/kg	1-5	Single or multiple dose	NS	15	12	
Duijvis	2016	Netherlands	2016 Netherlands Retrospective	Full text	Hospitalized UC	IV or oral steroid- refractory	22		5 mg/kg	ξ	Standard	21	16	12 N	Mixture of moder- ate-severe and severe patients
Fernandes	2016	2016 Portugal	Retrospective	Full text	TLW criteria	IV steroid-re- fractory (Oxford criteria)	25		5 mg/kg	ŝ	Standard	20	20	19	
Florhomen	2011	2011 Norway	RCT	Full text	TLW criteria	IV steroid-re-	13		5 mg/kg	С	Standard	1,	1,	SZ	

										IFX			CFS (N)		
				Abstract						Dose	IFX Dose				Considerations
			Type of	or Full	Definition of	Eligibility for	Sample			Number	er Strategy	Month	Month Month	Month	for the
Author	Year (Country	Study	Text	Severity	Rescue Therapy	Size	Subgroup.	Subgroups IFX Dose	(ITT)	(ITT)		3	12	Meta-analysis
Gibson	2015 Ireland	land	Retrospective	Full text	Hospitalized UC	IV steroid- refractory	50					36	32	29	
								35	5 mg/kg	б	Standard	22	20	18	
Gibson	2018 Ireland	land	Retrospective	Abstract	Abstract Hospitalized	IV steroid-	145	15	5 mg/kg	б	Accelerated	14	12	11	
					0	refractory		87 58	5 mg/kg 5 mg/kg	<i>რ</i> ო	Standard Accelerated	71	66 49	60 44	
Govani	2016 USA	V:	Retrospective	Abstract	Abstract Hospitalized	IV steroid-re-	55	2	0	•			42	33	Mixture of
					nc	fractory									5 mg/kg and 10 mg/ kg given to patients in both accel- erated and high-dose cohorts, unable to include into the meta-analysis
								17	10 mg/kg starting dose	б	NA	10	6	6	
								38	5 mg/kg starting dose	ŝ	NA	34	33	24	
Jarnerot/ Gustavsson	2005/ Sweden 2010	eden	RCT/ retrospective	Full text	Seo index	IV steroid-re- fractory (fail- ure to improve according to Seo index)	24		4-5 mg/kg	-	Single dose	17	17	14	Jarnerot and Gustavsson cohorts merged; mix- ture of mod- erate-severe and severe patients
Halpin	2013 UK	~	Retrospective	Full text	TLW criteria	IV steroid- refractory	4		5 mg/kg	ŝ	Standard	34	34	31	IV steroid-re- fractory
Но	2009 UK	٤/Scotland	2009 UK/Scotland Prospective observational	Full text ul	TLW criteria	IV steroid- refractory (Oxford criteria or Ho index)	21		5 mg/kg	1	Single dose	10	NS	NS	
Hulkower	2016 USA	P.	Prospective observational	Abstract	Abstract Hospitalized UC/Mayo score >9	IV steroid- refractory	4		10 mg/kg	2–3	Accelerated	4	4	NS	

										IFX		J	CFS (N)		
			Tyne of	Abstract or Full	Definition of	Elioihility for S	Samule			Dose	IFX Dose Strateov	Month	Month Month Month		Considerations
Author	Year	Country	Study	Text	Severity			Subgroups IFX Dose		(TTI)	(ITT)	1	3	12	Meta-analysis
Kaser	2001	2001 Austria	Prospective observational	Full text	Hospitalized UC	IV steroid- refractory	9	5 n	5 mg/kg	1	Single dose	9	9	NS	
Kim	2015	2015 South Korea Retrospective	Retrospective	Full text	Hospitalized UC	IV steroid- refractory	33	5 n	5 mg/kg	б	Standard	33	33	32	
Kohn	2007	2007 Italy	Retrospective	Full text	TLW criteria	IV steroid- refractory	83	5 n	5 mg/kg			NS	12	SZ	2-mo analysed as 3-mo outcomes; mixture of moder- ate-severe and severe patients
								26 57		1 ≥2	Single dose Weeks 0, 2, 4, or 0,	NS NS	17 54	NS NS	
Laharie	201 <i>2/</i> 2017	France	RCT	Full text	Full text Lichtiger score IV steroid->10 refractor	IV steroid- refractory	55	S n	5 mg/kg	m	2, 0 Standard	SZ	4	38	Laharie 2012/2017 cohorts merged; 2 patients excluded as receired CyA; 12-mo outcome derived % estimate
Lees	2007 UK	UK	Retrospective	Full text	Full text TLW criteria	IV steroid- refractory	39	5 n	5 mg/kg	1–3	Single or multiple dose	26	26	24	
Llao	2016	Spain	Retrospective	Full text	Montreal clas- IV steroid- sification/ refractoi TLW	IV steroid- refractory	14	5 n	5 mg/kg	б	Standard	14	14	11	
Lowenberg	2014	2014 Netherlands Retrospective	Retrospective	Full text	TLW criteria	IV steroid- refractory (Oxford criteria)	16	5 n	5 mg/kg	ς	Standard	15	12	10	
Mocciaro	2012	2012 Italy	Retrospective	Full text	TLW criteria	IV steroid- refractory	30	5 n	5 mg/kg	б	Standard	25	25	25	
Monterubbianesi		2014 Italy	Retrospective	Full text	TLW criteria (modified by Chapman)	IV steroid- refractory	113	5 п	5 mg/kg	3	Standard	96	91	83	
Mortensen	2011	2011 Denmark	Retrospective	Full text	+	IV or oral ste-	56	5 n	5 mg/kg	1_{-9}	Single or	46	39	NS	

TABLE 1. (Continued	_													
										IFX			CFS (N)	_	
				Abstract						Dose	IFX Dose				Considerations
			Type of	or Full	Definition of	Eligibility for	Sample			Number	Strategy	Month	Month Month	Month	for the
Author	Year C	Country	Study	Text	Severity	Rescue Therapy	Size	Subgroup.	Subgroups IFX Dose	(ITT)	(ITT)	-	3	12	Meta-analysis
Nalagatla	2018 USA	×.	Retrospective	Full text	Hospitalized UC	IV steroid-re- fractory	213								
								132	5 mg/kg	>2	Standard	121	113	96	
								81	5-10 mg/kg	>2	Accelerated/ intensified	74	65	58	
Ordas	2017 Spain	in	Retrospective	Full text	Hospitalized UC	IV steroid- refractory	131		5 mg/kg	1 or 3	Single or standard	NS	112	100	
Regueiro	2006 USA	Ā	Retrospective	Full text	Partial Mayo score ≥9	IV steroid- refractory	11		5 mg/kg	б	Standard	7	4	7	
Ribaldone	2017 Italy	y	Retrospective	Full text	TLW criteria	IV steroid- refractory	20		5 mg/kg	б	Standard	19	19	15	
Sands	2001 USA	¥	RCT	Full text	TLW criteria/ Lichtiger score	IV steroid- refractory	11					٢	4	NS	
								б	5 mg/kg	1	Single dose	3	1	NS	
								б	10 mg/kg	1	Single dose	2	1	NS	
								2	20 mg/kg	1	Single dose	7	7	NS	
Seah	2017 Australia	stralia	Retrospective	Full text	TLW criteria	IV steroid- refractory	41		5 mg/kg	б		37	36	30	
								30			Standard	28	28	24	
								10			Accelerated	6	8	9	
Shah	2018 USA	A	Retrospective	Full text	Hospitalized UC	IV or oral ste- roid-refractory	126			б		106	67	89	
								89	5 mg/kg		Standard	78	72	65	
								23	5 mg/kg		Accelerated	16	14	14	
								8	10 mg/kg		Standard	9	5	4	
								9	10 mg/kg		Accelerated	9	9	9	
Shepherd	2014 Australia	stralia	Retrospective	Abstract	TLW criteria	IV steroid-re- fractory	15		5 mg/kg	1–3		12	10	9	
								11		1	Single dose	8	9	4	
								4		≥2	Multiple dose	4	4	7	
Sjoberg	2013 Sweden	sden	Retrospective	Full text	TLW criteria	IV steroid-re- fractory (fulminant colitis index-	211		5 mg/kg			153	149	133	
						Lindgren 1998 or Seo index)									
								124 87		1 2–3	Single dose Standard	NS NS	76 73	NS NS	

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TABLE 1. Continued	ntinued													
									IFX			CFS (N)		
			Abstract						Dose	IFX Dose				Considerations
		Type of	or Full	Definition of	or Full Definition of Eligibility for Sample	Sample		4	Vumber	Number Strategy Month Month Month for the	Month	Month	Month	for the
Author	Year Country	y Study	Text	Severity	Rescue Therapy Size Subgroups IFX Dose (ITT)	Size	Subgroup	s IFX Dose	(ITT)	(ITT)	1	3	12	Meta-analysis
Sly	2017 USA	Retrospective	Abstract	Abstract Hospitalized IV steroid-re- UC fractory	IV steroid-re- fractory	41								
							18	5 mg/kg	3	Standard	16	16	13	
							23	5-10 mg/kg	3	Accelerated	16	14	11	
Sood	2014 India	Retrospective	Full text	Full text Lichtiger score IV steroid-re- fractory	: IV steroid-re- fractory	28		5 mg/kg	3	Standard	25		19	
Van Langenberg 2015 Australia	2015 Australia	Retrospective	Abstract	Abstract TLW criteria IV steroid-re- fractory	IV steroid-re- fractory	88		5 mg/kg			80	76	67	
							41		1	Single dose	33	31	28	
							47		≥2	Standard	47	45	39	
Williams	2016 UK	RCT	Full text	TLW criteria or clinical judgment	IV steroid-re- fractory	135		5 mg/kg	ŝ	Standard	106	96	88	Moderate- severity TLW in 27%
Yamamoto- Furusho	2008 Mexico	Prospective observational		Full text TLW criteria IV steroid-re- fractory	IV steroid-re- fractory	10		5 mg/kg	1	Single dose	NS	7	7	
Abbreviations: NS,	Abbreviations: NS, not stated; TLW, Truelove and Witt's.	selove and Witt's.												

Month 1

Internet 1											
Author	Year	Sample size	Measure (95% CI)	Weight %							
An	2017	44	0.86 (0.74 to 0.95)	3.15%						_	
Florhomen	2011	13	1 (0.87 to 1)	1.81%					I-		
Jarnerot/Gustavsson	2005/10	24	0.71 (0.51 to 0.88)	2.5%							
Sands	2001	11	0.64 (0.33 to 0.9)	1.64%						_	
Al Khoury	2017	72	0.96 (0.9 to 0.99)	3.6%							
Aratari	2008	11	1 (0.85 to 1)	1.64%							
Beswick	2016	24	0.92 (0.76 to 1)	2.5%							
Bressler	2008	21	0.76 (0.55 to 0.92)	2.35%						-	
Croft	2013	38	0.82 (0.67 to 0.93)	3%				-		-	
Duijvis	2016	22	0.95 (0.82 to 1)	2.4%							
Fernandes	2016	25	0.8 (0.62 to 0.94)	2.54%						_	
Gibson	2015	50	0.72 (0.59 to 0.84)	3.28%							
Gibson	2018	145	0.86 (0.79 to 0.91)	4.05%							
Govani	2016	55	0.8 (0.68 to 0.9)	3.37%				-			
Halpin	2013	44	0.77 (0.64 to 0.89)	3.15%							
Ho	2009	21	0.48 (0.26 to 0.69)	2.35%							
Hulkower	2016	4	1 (0.61 to 1)	0.82%							
Kaser	2001	6	1 (0.73 to 1)	1.1%							
Kim	2015	33	1 (0.95 to 1)	2.85%							
Lees	2007	39	0.67 (0.51 to 0.81)	3.03%							
Llao	2016	14	1 (0.88 to 1)	1.89%					I –		
Lowenberg	2014	16	0.94 (0.75 to 1)	2.04%							
Mocciaro	2012	30	0.83 (0.68 to 0.95)	2.75%				_		_	
Monterubbianesi	2014	113	0.85 (0.78 to 0.91)	3.92%							
Mortensen	2011	56	0.82 (0.71 to 0.91)	3.38%							
Nalagatla	2018	213	0.92 (0.87 to 0.95)	4.22%					- 1	-	
Reguerio	2006	11	0.64 (0.33 to 0.9)	1.64%							
Ribaldone	2017	20	0.95 (0.8 to 1)	2.29%					-+-	-	
Seah	2017	41	0.9 (0.79 to 0.98)	3.08%						<u> </u>	
Shah	2017	126	0.84 (0.77 to 0.9)	3.98%							
Shepherd	2014	15	0.8 (0.55 to 0.97)	1.97%					7		
Sjoberg	2013	211	0.73 (0.66 to 0.78)	4.22%				_			
Sly	2017	41	0.78 (0.64 to 0.9)	3.08%							
Sood	2014	28	0.89 (0.75 to 0.99)	2.67%							
Van Langenberg	2015	88	0.91 (0.84 to 0.96)	3.75%						-	
Williams	2016	135	0.79 (0.71 to 0.85)	4.02%						_	
Synthesis		1860	0.86 (0.82 to 0.89)	100%					- 🕹		
					0	0.2	0.4	0.6	0.8	1	1.2
					0	0.2	0.4		0.0	1	1.2
								Р			
Month 3											
Month 3											
	Veee	Convolucion	Manager (05%/ Cl)	M-:-ka 0/							
Author	Year	Sample size	Measure (95% CI)	Weight %	I				•		
Author An	2017	44	0.8 (0.66 to 0.9)	2.85%				_	+_		
Author An Florhomen	2017 2011	44 13	0.8 (0.66 to 0.9) 1 (0.87 to 1)	2.85% 1.76%							
Author An	2017	44 13 24	0.8 (0.66 to 0.9) 1 (0.87 to 1) 0.71 (0.51 to 0.88)	2.85% 1.76% 2.34%							
Author An Florhomen Jarnerot/Gustavsson Laharie Sands	2017 2011 2005/10 2012/17 2001	44 13 24 55 11	0.8 (0.66 to 0.9) 1 (0.87 to 1) 0.71 (0.51 to 0.88) 0.82 (0.7 to 0.91) 0.36 (0.1 to 0.67)	2.85% 1.76% 2.34% 3.01% 1.61%							
Author An Florhomen Jarnerot/Gustavsson Laharie	2017 2011 2005/10 2012/17 2001 2017	44 13 24 55 11 72	0.8 (0.66 to 0.9) 1 (0.87 to 1) 0.71 (0.51 to 0.88) 0.82 (0.7 to 0.91) 0.36 (0.1 to 0.67) 0.93 (0.86 to 0.98)	2.85% 1.76% 2.34% 3.01% 1.61% 3.18%						∎	
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari	2017 2011 2005/10 2012/17 2001 2017 2008	44 13 24 55 11 72 11	0.8 (0.66 to 0.9) 1 (0.87 to 1) 0.71 (0.51 to 0.88) 0.82 (0.7 to 0.91) 0.36 (0.1 to 0.67) 0.93 (0.86 to 0.98) 1 (0.85 to 1)	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61%			•				
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Beswick	2017 2011 2005/10 2012/17 2001 2017 2008 2016	44 13 24 55 11 72 11 24	0.8 (0.66 to 0.9) 1 (0.87 to 1) 0.71 (0.51 to 0.88) 0.82 (0.7 to 0.91) 0.36 (0.1 to 0.67) 0.93 (0.86 to 0.98) 1 (0.85 to 1) 0.92 (0.76 to 1)	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34%							
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Beswick Bressler	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008	44 13 24 55 11 72 11 24 21	0.8 (0.66 to 0.9) 1 (0.87 to 1) 0.71 (0.51 to 0.88) 0.82 (0.7 to 0.91) 0.36 (0.1 to 0.67) 0.93 (0.86 to 0.98) 1 (0.85 to 1) 0.92 (0.76 to 1) 0.62 (0.4 to 0.82)	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34% 2.21%			•				
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Beswick Bressler Croft	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013	44 13 24 55 11 72 11 24 21 38	0.8 (0.66 to 0.9) 1 (0.87 to 1) 0.71 (0.51 to 0.88) 0.82 (0.7 to 0.91) 0.36 (0.1 to 0.67) 1 (0.85 to 1) 0.92 (0.76 to 1) 0.62 (0.4 to 0.82) 0.74 (0.58 to 0.87)	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34% 2.21% 2.73%			•				
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Beswick Bressler Croft Dean	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013 2011	44 13 24 55 11 72 11 24 21 38 19	$\begin{array}{c} 0.8 (0.66 {\rm to} 0.9) \\ 1 (0.87 {\rm to} 1) \\ 0.71 (0.51 {\rm to} 0.88) \\ 0.82 (0.7 {\rm to} 0.81) \\ 0.36 (0.1 {\rm to} 0.67) \\ 1.0 0.31 (0.85 {\rm to} 0.98) \\ 1 (0.85 {\rm to} 1) \\ 0.92 (0.76 {\rm to} 1) \\ 0.62 (0.7 {\rm to} 0.82) \\ 0.74 (0.58 {\rm to} 0.87) \\ 0.79 (0.57 {\rm to} 0.95) \end{array}$	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34% 2.21% 2.73% 2.12%			-•				
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Beswick Bressler Croft Dean Duijvis	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013 2011 2016	44 13 24 55 11 72 11 24 21 38 19 22	$\begin{array}{c} 0.8 \ (0.66 \ to \ 0.9) \\ 1 \ (0.87 \ to \ 1) \\ 0.71 \ (0.51 \ to \ 0.88) \\ 0.82 \ (0.7 \ to \ 0.91) \\ 0.36 \ (0.1 \ to \ 0.67) \\ 1 \ (0.85 \ to \ 1) \\ 0.92 \ (0.85 \ to \ 0.98) \\ 1 \ (0.85 \ to \ 1) \\ 0.62 \ (0.7 \ to \ 0.87) \\ 0.79 \ (0.57 \ to \ 0.87) \\ 0.79 \ (0.57 \ to \ 0.91) \\ 0.73 \ (0.52 \ to \ 0.9) \end{array}$	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34% 2.71% 2.73% 2.12% 2.26%			•				
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Beswick Bressler Croft Dean Dujivis Fernandes	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013 2011 2016 2016 2015	44 13 24 55 11 72 11 24 21 38 19 22 25	$\begin{array}{c} 0.8 \left(0.66 \ to \ 0.9 \right) \\ 1 \left(0.87 \ to \ 1 \right) \\ 0.71 \left(0.51 \ to \ 0.88 \right) \\ 0.82 \left(0.7 \ to \ 0.91 \right) \\ 0.36 \left(0.1 \ to \ 0.77 \right) \\ 0.39 \left(0.86 \ to \ 0.79 \right) \\ 1 \left(0.85 \ to \ 1 \right) \\ 0.92 \left(0.76 \ to \ 1 \right) \\ 0.52 \left(0.76 \ to \ 1 \right) \\ 0.74 \left(0.58 \ to \ 0.87 \right) \\ 0.73 \left(0.57 \ to \ 0.95 \right) \\ 0.73 \left(0.57 \ to \ 0.9 \right) \\ 0.8 \left(0.22 \ to \ 0.9 \right) \\ 0.8 \left(0.22 \ to \ 0.9 \right) \\ 0.8 \left(0.22 \ to \ 0.9 \right) \\ 0.8 \left(0.22 \ to \ 0.9 \right) \\ 0.8 \left(0.22 \ to \ 0.9 \right) \\ 0.8 \left(0.22 \ to \ 0.9 \right) \\ 0.8 \left(0.22 \ to \ 0.9 \right) \\ \end{array}$	2.85% 1.76% 2.34% 3.01% 1.61% 1.61% 2.34% 2.21% 2.73% 2.12% 2.26% 2.37%			-•				
Author An Florhomen Jarnerot/Gustavsson Jarnerot/Gustavsson Jarnerot/Gustavsson Al Khoury Al Khoury Al Khoury Al Khoury Bressler Croft Dean Duijvis Fernandes Gibson	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013 2011 2016 2016 2015	44 13 24 55 11 72 11 24 21 23 8 8 9 22 25 50 25 50 145	$\begin{array}{c} 0.8 \left(0.66 \pm 0.9 \right) \\ 1 \left(0.87 \pm 0.1 \right) \\ 0.71 \left(0.51 \pm 0.88 \right) \\ 0.82 \left(0.7 \pm 0.91 \right) \\ 0.36 \left(0.1 \pm 0.67 \right) \\ 0.37 \left(0.85 \pm 0.1 \right) \\ 0.52 \left(0.75 \pm 0.1 \right) \\ 0.52 \left(0.75 \pm 0.1 \right) \\ 0.52 \left(0.75 \pm 0.1 \right) \\ 0.74 \left(0.55 \pm 0.87 \right) \\ 0.79 \left(0.57 \pm 0.95 \right) \\ 0.73 \left(0.52 \pm 0.94 \right) \\ 0.54 \left(0.52 \pm 0.94 \right) \\ 0$	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34% 2.71% 2.73% 2.12% 2.26%			-•				
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Al Khoury Asswick Bessier Croft Dean Duijvis Fernandes Gibson Gibson Govani	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013 2011 2016 2016 2015 2015 2018 2016	44 13 24 55 11 72 11 24 21 38 19 22 25 50 145 55	$\begin{array}{c} 0.8 \left(0.66 \ to \ 0.9 \right) \\ 1 \left(0.87 \ to \ 1 \right) \\ 0.71 \left(0.51 \ to \ 0.88 \right) \\ 0.82 \left(0.7 \ to \ 9.1 \right) \\ 0.36 \left(0.1 \ to \ 6.7 \right) \\ 0.36 \left(0.85 \ to \ 9.7 \right) \\ 0.37 \left(0.85 \ to \ 9.7 \right) \\ 0.52 \left(0.75 \ to \ 1 \right) \\ 0.52 \left(0.75 \ to \ 1 \right) \\ 0.52 \left(0.75 \ to \ 1.52 \ to \ 9.7 \right) \\ 0.74 \left(0.55 \ to \ 9.7 \right) \\ 0.73 \left(0.52 \ to \ 9.7 \right) \\ 0.8 \left(0.62 \ to \ 9.4 \right) \\ 0.54 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.65 \ to \ 9.7 \right) \\ 0.76 \left(0.55 \ to \ 9.7 \right) \\ 0.76 \left(0$	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.24% 2.21% 2.73% 2.22% 2.37% 2.26% 2.37% 3.5% 3.01%			•	-			
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Bessiler Croft Dean Duijvis Fernandes Gibson Gibson Govani Halpin	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013 2011 2016 2016 2015 2015 2018 2013 2013 2015 2013	44 13 24 55 11 12 21 23 38 9 9 22 25 50 25 50 145 55 44	$\begin{array}{c} 0.8 \left(0.66 \ to \ 0.9\right) \\ 1 \left(0.87 \ to \ 1\right) \\ 0.71 \ \left(0.51 \ to \ 0.88\right) \\ 0.82 \ \left(0.7 \ to \ 0.91\right) \\ 0.36 \ \left(0.1 \ to \ 0.67\right) \\ 0.37 \ \left(0.85 \ to \ 1\right) \\ 0.22 \ \left(0.75 \ to \ 1\right) \\ 0.42 \ \left(0.75 \ to \ 1\right) \\ 0.42 \ \left(0.75 \ to \ 1.9\right) \\ 0.73 \ \left(0.52 \ to \ 0.91\right) \\ 0.46 \ \left(0.57 \ to \ 0.91\right) \\ 0.75 \ \left(0.64 \ to \ 0.87\right) \\ 0.77 \ \left(0.64 \ to \ 0.87\right) \\ 0.77 \ \left(0.54 \ to \ 0.87\right) \\ 0.75 \ \left(0.54 \ to \ 0.87\right) \ \left(0.55 \ to \ 0.87\right) \\ 0.75 \ \left(0.55 \ to \ 0.87\right) \ \left(0.5$	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34% 2.34% 2.73% 2.73% 2.75% 2.27% 2.37% 2.37% 2.35% 3.01% 3.01%			•				
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Al Khoury Al Khoury Al Khoury Bressler Croft Dean Duijvis Fernandes Gibson Gibson Gibson Govani Halpin Hulkower	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2016 2016 2016 2015 2018 2016 2015 2018 2016 2013 2016 2013 2016	44 13 24 55 11 72 11 24 21 38 19 22 25 50 145 55 44 4	$\begin{array}{c} 0.8 \left(0.66 \ to \ 0.9\right) \\ 1 \left(0.87 \ to \ 1\right) \\ 0.71 \left(0.51 \ to \ 0.88\right) \\ 0.82 \left(0.7 \ to \ 0.91\right) \\ 0.36 \left(0.1 \ to \ 0.67\right) \\ 0.36 \left(0.85 \ to \ 0.98\right) \\ 1 \left(0.85 \ to \ 1.9\right) \\ 0.52 \left(0.76 \ to \ 1\right) \\ 0.52 \left(0.76 \ to \ 1\right) \\ 0.52 \left(0.58 \ to \ 0.87\right) \\ 0.74 \left(0.55 \ to \ 0.87\right) \\ 0.74 \left(0.55 \ to \ 0.87\right) \\ 0.73 \left(0.52 \ to \ 0.94\right) \\ 0.64 \left(0.55 \ to \ 0.87\right) \\ 0.76 \left(0.52 \ to \ 0.94\right) \\ 0.64 \left(0.56 \ to \ 0.77\right) \\ 0.77 \left(0.56 \ to \ 0.87\right) \\ 0.76 \left(0.56 \ t$	2.85% 1.76% 3.01% 1.61% 3.18% 1.61% 2.34% 2.21% 2.73% 2.12% 2.26% 2.37% 2.26% 2.37% 3.01% 2.85% 0.84%							
Author An Florhomen Jarnerot/Gustavsson Laharie Sands Al Khoury Aratari Bessiler Croft Dean Duijvis Fernandes Gibson Gibson Gibson Govani Halpin Hulkower	2017 2011 2005/10 2012/17 2001 2017 2008 2018 2018 2018 2016 2016 2016 2016 2018 2018 2016 2013 2016 2013 2016 2013 2016	44 13 24 55 11 72 11 24 21 23 89 22 25 50 145 55 55 44 4 6	$\begin{array}{l} 0.8 \left(0.66 \ {\rm to} \ 0.9 \right) \\ 1 \left(0.87 \ {\rm to} \ 1 \right) \\ 0.71 \left(0.51 \ {\rm to} \ 0.88 \right) \\ 0.82 \left(0.7 \ {\rm to} \ 0.91 \right) \\ 0.36 \left(0.1 \ {\rm to} \ 0.67 \right) \\ 0.36 \left(0.85 \ {\rm to} \ 0.98 \right) \\ 1 \left(0.85 \ {\rm to} \ 1.9 \right) \\ 0.52 \left(0.75 \ {\rm to} \ 1.9 \right) \\ 0.52 \left(0.55 \ {\rm to} \ 0.87 \right) \\ 0.75 \left(0.55 \ {\rm to} \ 0.87 \right) \\ 0.76 \left(0.54 \ {\rm to} \ 0.87 \right) \\ 0.77 \left(0.64 \ {\rm to} \ 0.87 \right) \\ 0.77 \left(0.64 \ {\rm to} \ 0.87 \right) \\ 1 \left(0.64 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.64 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.64 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.64 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.64 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.64 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.54 \ {\rm to} \ 1.9 \right) \\ 1 \left(0.73 \ {\rm to} \ 1$	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.34% 2.24% 2.75% 2.27% 2.37% 2.37% 2.37% 2.37% 3.5% 3.01% 2.85% 0.84% 1.11%			•	- 			
Author An Florhomto Jarnerot/Gustavsson Laharie Sands Ai Khoury Aratari Beswick Brester Dean Dean Duijvis Fernandes Gibson Gibson Gibson Govani Halpin Hulkower Kaser Kim	2017 2011 2005/10 2012/17 2001 2017 2008 2016 2008 2013 2016 2016 2016 2015 2018 2016 2015 2018 2016 2013 2016 2013 2016 2013 2016 2013 2016 2013	44 13 24 55 11 72 11 24 21 38 19 22 25 50 145 55 44 4 4 6 33	$\begin{array}{c} 0.8 \left(0.66 \ to \ 0.9 \right) \\ 1 \left(0.87 \ to \ 1 \right) \\ 0.71 \left(0.51 \ to \ 0.88 \right) \\ 0.82 \left(0.7 \ to \ 9.1 \right) \\ 0.36 \left(0.1 \ to \ 0.67 \right) \\ 0.36 \left(0.88 \ to \ 9.8 \right) \\ 1 \left(0.85 \ to \ 1.9 \right) \\ 0.52 \left(0.76 \ to \ 1 \right) \\ 0.52 \left(0.76 \ to \ 1 \right) \\ 0.52 \left(0.76 \ to \ 1 \right) \\ 0.52 \left(0.76 \ to \ 1 \right) \\ 0.74 \left(0.55 \ to \ 0.87 \right) \\ 0.73 \left(0.52 \ to \ 0.94 \right) \\ 0.64 \left(0.55 \ to \ 0.77 \right) \\ 0.77 \left(0.52 \ to \ 0.94 \right) \\ 0.76 \left(0.52 \ to \ 0.94 \right) \\ 0.76 \left(0.56 \ to \ 1.7 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 0.76 \left(0.56 \ to \ 0.77 \right) \\ 1 \left(0.73 \ to \ 1 \right) \\ 1 \left(0.73 \ to \ 1 \right) \\ 1 \left(0.75 \ to \ 1 \right) \\ 1 \left(0.55 \ to \ 1 \right) \end{array}$	2.85% 1.76% 2.34% 3.01% 1.61% 3.18% 1.61% 2.24% 2.23% 2.22% 2.37% 2.22% 2.37% 3.01% 2.85% 0.84% 1.11% 2.62%			•				
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FIGURE 2. Forest plot using random-effects model for overall pooled colectomy-free survival (proportions).

5-mg/kg standard vs 5-mg/kg accelerated induction.

Five studies (391 patients)^{10, 20, 49, 56, 60} reported the outcomes of patients treated with 5-mg/kg standard-schedule and 5-mg/kg accelerated-schedule induction. Colectomy-free survival was not statistically different between the 2 groups at 1 month (OR, 1.04; 95% CI, 0.29 to 3.69; P = 0.96; $I^2 = 66\%$), 3 months (OR, 0.93; 95% CI, 0.39 to 2.22; P = 0.87; $I^2 = 56\%$), or 12 months (OR, 0.96; 95% CI, 0.52 to 1.78; P = 0.89; $I^2 = 32\%$).

5-mg/kg standard vs 10-mg/kg standard induction dose.

Two studies (169 patients)^{12, 60} reported the outcomes of 5-mg/kg standard vs 10-mg/kg standard induction. Colectomyfree survival was not statistically different between the 2 groups at 1 month (OR, 0.30; 95% CI, 0.08 to 1.15; P = 0.08; $I^2 = 0\%$), 3 months (OR, 0.37; 95% CI, 0.12 to 1.16; P = 0.09; $I^2 = 0\%$), or 12 months (OR, 0.53; 95% CI, 0.19 to 1.45; P = 0.21; $I^2 = 0\%$), favoring 5-mg/kg standard induction. Month 12

Author	Year	Sample size	Measure (95% CI)	Weig
An	2017	44	0.77 (0.64 to 0.89)	3.219
Jarnerot/Gustavsson	2005/10	24	0.58 (0.38 to 0.77)	2.449
Laharie	2012/17	55	0.69 (0.56 to 0.81)	3.489
Al Khoury	2017	72	0.89 (0.8 to 0.95)	3.789
Aratari	2008	11	0.91 (0.65 to 1)	1.529
Beswick	2016	24	0.79 (0.6 to 0.93)	2.449
Croft	2013	38	0.63 (0.47 to 0.78)	3.039
Dean	2011	19	0.63 (0.4 to 0.84)	2.149
Duijvis	2016	22	0.55 (0.33 to 0.75)	2.339
Fernandes	2016	25	0.76 (0.57 to 0.91)	2.499
Gibson	2015	50	0.58 (0.44 to 0.71)	3.379
Gibson	2018	145	0.72 (0.64 to 0.79)	4.4%
Govani	2016	55	0.6 (0.47 to 0.73)	3.489
Halpin	2013	44	0.7 (0.56 to 0.83)	3.219
Kim	2015	33	0.97 (0.87 to 1)	2.859
Lees	2007	39	0.62 (0.46 to 0.76)	3.069
Llao	2016	14	0.79 (0.53 to 0.97)	1.789
Lowenberg	2014	16	0.63 (0.37 to 0.85)	1.939
Mocciaro	2012	30	0.83 (0.68 to 0.95)	2.729
Monterubbianesi	2014	113	0.73 (0.65 to 0.81)	4.219
Nalagatla	2018	213	0.72 (0.66 to 0.78)	4.65%
Ordas	2017	131	0.76 (0.69 to 0.83)	4.339
Reguerio	2006	11	0.18 (0 to 0.47)	1.529
Ribaldone	2017	20	0.75 (0.53 to 0.92)	2.219
Seah	2017	41	0.73 (0.58 to 0.86)	3.129
Shah	2017	126	0.71 (0.62 to 0.78)	4.3%
Shepherd	2014	15	0.4 (0.16 to 0.66)	1.869
Sjoberg	2013	211	0.63 (0.56 to 0.69)	4.649
Sly	2017	41	0.59 (0.43 to 0.73)	3.129
Sood	2014	28	0.68 (0.49 to 0.84)	2.649
Van Langenberg	2015	88	0.76 (0.67 to 0.85)	3.989
Williams	2016	135	0.65 (0.57 to 0.73)	4.359
Yamamoto-Furusho	2008	10	0.2 (0.01 to 0.51)	1.429
Synthesis		1943	0.7 (0.66 to 0.74)	1009

FIGURE 2. Continued.

5-mg/kg standard induction vs 10-mg/kg accelerated dose.

Two studies (137 patients)^{12, 60} reported the outcomes of 5-mg/kg standard vs 10-mg/kg accelerated induction. Colectomy-free survival was not statistically different between the 2 groups at 1 month (OR, 0.27; 95% CI, 0.01 to 13.07; P = 0.51; $I^2 = 74\%$), 3 months (OR, 0.32; 95% CI, 0.00 to 31.34; P = 0.62; $I^2 = 84\%$), or 12 months (OR, 0.56; 95% CI, 0.01 to 41.34; P = 0.79; $I^2 = 83\%$), favoring 5-mg/kg standard induction.

Influence of Covariates and Confounders

Covariate analysis was performed to assess the relationship of demographic and biochemical factors to outcomes between dose-intensified induction vs standard induction. A metaregression was not performed due to the small number of studies available. Dose-intensified induction patients had a higher mean CRP compared with standard induction (mean difference, 14.78 mg/L; 95% CI, 7.91 to 21.65; P < 0.001) and lower serum albumin (mean difference, -1.95 g/L; 95% CI, -2.81 to -1.09; P < 0.001). There was no significant difference in age, disease duration, or IV steroid duration between the 2 groups (Fig. 4).

A narrative synthesis was performed on other studies reporting on the impact of confounders. Hypoalbuminemia was noted to be an independent poor prognostic factor and was associated with colectomy risk.^{10, 23, 39, 51, 60} Elevated CRP at baseline was associated with risk of colectomy^{22, 30, 43, 44, 60} and a lower likelihood of achieving mucosal healing.²⁰ Fecal calprotectin was predictive of poor outcome, with a level of >1922.5 mcg/g associated with an 87% risk of colectomy at 1 year.⁶¹ Endoscopic features were also prognostic, with the presence of severe endoscopic lesions found to be associated with a higher risk of colectomy by Monterubbianesi et al. (RR, 7.0; 95% CI, 1.09 to 44.7).⁴³ Conversely, achievement of mucosal healing with induction therapy was associated with increased long-term CFS.²⁹ These risk factors were not addressed with dose intensification in these studies.

Multiple studies analyzed outcomes according to IFX strategy. In studies that reported on IFX dose number, single induction was found to have an increased risk of colectomy in 2 studies,^{36, 53} with a relative risk of 5.76 (95% CI, 1.54 to 21.62; P = 0.005) reported by Kohn et al.,³⁶ although no significant difference was found in a third study by Sjoberg et al.⁵¹ Although the study by Govani et al. was not included in our formal analysis due to mixed 5-mg/kg and 10-mg/kg dosing within standard-schedule and accelerated-schedule cohorts, they found that an accelerated-schedule induction had higher 90-day colectomy rates compared with standard-schedule induction (47.1% vs 12.5%; P = 0.01).¹⁴ However, accelerated-schedule patients also had a higher baseline CRP (58 mg/L ± 39 vs 37 mg/L ± 3.0; P = 0.06).

Of the studies that reported dose intensification, none documented a strategy of a priori dose intensification for all patients. Seven of these studies had reported that the decision for dose acceleration was based on insufficient clinical or biochemical response to the first infliximab dose.^{10, 14, 20, 32, 49, 58, 62} The reason for dose escalation was not reported in the remaining 4 studies.^{12, 56, 57, 60} In the study by Nalagatla et al., an initial dose of 10 mg/kg was selected in

	Month 1	Month 3	Month 12
Overall colectomy free-survival	85.7%	79.7%	69.8%
	(82.0%–89.0%; <i>I</i> ² = 70.6%; 36	(75.48%–83.6%; <i>P</i> = 77%; 36	(65.7%–73.7%; <i>P</i> = 67%; 33
	studies, 1550/1860 cases)	studies, 1659/2129 cases)	studies, 1357/1943 cases)
5-mg/kg single dose	78.8%	67.3%	57.0%
	(68.4%–88.0%; <i>I</i> ² = 40.2%; 9	(57.1%–76.8%; <i>I</i> ² = 55.1%; 10	(40.7%–72.7%; <i>I</i> ² = 60.2; 6
	studies, 127/168 cases)	studies, 200/307 cases)	studies, 75/127 cases)
5-mg/kg multiple dose	90.0%	85.1%	72.8%
	(86.1%–93.3%; <i>I</i> ² = 67.7%; 25	(80.9%–89.0%; <i>I</i> ² = 71.7%; 28	(68.2%–77.2%; <i>I</i> ² = 60.2%; 25
	studies, 1027/1189 cases)	studies, 1125/1379 cases)	studies, 881/1231 cases
5-mg/kg standard 026 induction	89.4%	84.0%	73.8%
	(83.9%–93.9%; <i>P</i> = 81.5%; 24	(78.3%–89.1%; <i>P</i> = 80.5%; 25	(67.9%–79.4%; <i>I</i> ² = 74.6%; 24
	studies, 882/1038 cases)	studies, 923/1152 cases)	studies, 772/1080 cases)
5-mg/kg accelerated induction	86.3%	79.7%	71.2%
	(78.5%–92.8%; <i>I</i> ² = 21.7%; 6	(72.3%–86.2%; <i>I</i> ² = 0%; 6	($63.1\%-78.6\%$; $P = 0\%$; 5
	studies, 125/145 cases)	studies, 115/145 cases)	studies, 103/145 cases)
Dose-intensified induction	84.8%	78.5%	70.1%
	(78.0%–90.6%; <i>I</i> ² = 46.1%; 11	(70.8%–85.4%; <i>I</i> ² = 49.2%; 11	(60.2%-79.2%; <i>I</i> ² = 65.9%; 10
	studies, 274/325 cases)	studies, 254/325 cases)	studies, 231/321 cases)
10-mg/kg multiple-dose induction	81.0%	76.7%	69.6%
	(65.4%–93.2%; <i>P</i> = 39.9%; 4	(59.1%–91.1%; <i>P</i> = 48.3%; 4	(54.0%–83.3%; <i>P</i> = 37.3%; 3
	studies, 59/75 cases)	studies, 56/75 cases)	studies, 50/71 cases)
10-mg/kg standard schedule	84.9%	79.4%	71.5%
	(71.6%–95.0%; <i>I</i> ² = 0%; 2	(53.9%–97.1%; <i>I</i> ² = 50.1%; 2	(36.4%–96.9%; <i>I</i> ² = 69.7%; 2
	studies, 36/43 cases)	studies, 35/43 cases)	studies, 33/43 cases)
10-mg/kg accelerated schedule	92.7%	88.3%	78.8%
	(60.3%–100%; <i>I</i> ² = 43.7%; 3	(63.5%–100%; <i>I</i> ² = 68.9%; 3	(8.3%–100%; $I^2 = 81.7\%$; 2
	studies, 13/15 cases)	studies, 12/15 cases)	studies, 8/11 cases)

TABLE 2. Pooled Colectomy-Fre	ee Survival (Random-Effects	Model), Expressed as N% (95% CI)
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patients with more severe clinical, biochemical, or endoscopic disease activity, and among the subgroup of patients who were dose accelerated, an upfront dose of 10 mg/kg was associated with a lower risk of colectomy compared with those who first received 5 mg/kg.⁵⁸

In individual studies, the use of maintenance therapy with IFX⁴³ and/or immunomodulators²⁸ after induction was associated with reduced colectomy compared with no maintenance (hazard ratio, 0.26; 95% CI, 0.09 to 0.85; P = 0.02).⁴³ Subanalysis to assess the effect of maintenance therapy among our included cohorts could not be performed due to the highly variable combinations of aminosalicylates, thiopurines, and infliximab (Supplementary Appendix 3).

Adverse Events, Postoperative Complications, and Mortality

The pooled adverse drug event rate was 26.1% (344/1319) from 24 studies, the pooled postoperative complication rate was 42.2% (155/367) from 13 studies, and the mortality rate was 1.0% (13/1342) from 22 studies. There were insufficient data to make meaningful comparisons on adverse events, postoperative complications, and mortality between dose-intensified and standard-dose induction across studies. Only 1 study provided data on adverse drug event rates and postoperative complication

rates between 5-mg/kg and 10-mg/kg patients.¹¹ The adverse drug event rate was 42.9% (48/112) in those treated with 5-mg/ kg induction vs 28.6% (4/14; P = 0.394) in those treated with 10-mg/kg induction. The postoperative complication rate was 78.8% (26/33) among those treated with 5-mg/kg induction vs 0% (0/4) in those treated with 10-mg/kg induction (P = 0.005).

Study Quality, Heterogeneity, and Publication Bias

In all studies, cases were representative of hospitalized steroid-refractory ASUC, and colectomy was utilized as an objective outcome measure. However, the majority of studies were uncontrolled with respect to case selection and disease severity on admission. There were recurrent issues of incomplete outcome reporting and inconsistency in reporting of relevant data (demographics/biochemistry and complication rates). A quality assessment utilizing the Newcastle Ottawa Scale and the Cochrane risk of bias table demonstrated that the majority of included studies in the meta-analysis were of poor quality. Details of study quality assessment can be found in Supplementary Appendix 4.

In our heterogeneity assessment, we identified variability regarding the definitions of disease severity and steroid

Study or Subgroup	5-mg/kg Eve		Total	Events		al Weig	Odds Ratio ht M-H, Random, 95%	6 CI	M-H, Rand	om, 95% Cl	
Beswick 2016		19	21	3		3 30.5				-	
Shepherd 2014		4	4	8		1 31.7					
/an Langenberg 2014		4	4	33			3% 24.10 (1.34 to 432				
ran Langenberg 2015		47	47	22	4	1 57.0	24.10 (1.54 (0 452	.09)		-	
Total (95% CI)			72		-	5 100.0	% 5.22 (0.82 to 33	14)			
		70	12		5	5 100.0			-		
Fotal events		70		44							
Heterogeneity: Tau ² =			f = 2 (P =	$(0.34); I^2 = 7\%$				0.01	0.1	1 10	10
Test for overall effect:	Z = 1.75 (P	P = 0.08)						0.01		Favours Multiple dose	10.
					_						
Study or Subgroup	5-mg/kg Eve		Dose 5- Total	-mg/kg Single Events		l Weigh	Odds Ratio nt M-H, Random, 95%	S CI	Odds M-H, Rand		
Beswick 2016		19	21	3		3 2.9				*	
(ohn 2007		54	57	17	2						
hepherd 2014		4	4	6	1						
joberg 2013		73	87	76	12						
/an Langenberg 2015		45	47	31	4	1 12.1	% 7.26 (1.49 to 35.	44)			
Total (95% CI)			216		20	5 100.0	% 4.24 (2.44 to 7.	36)			
otal events	1	195		133	20	5 10010		,			
leterogeneity: Tau ² =			_ A (D_					L			
				(0.55), T = 0%				0.01	0.1	i 1'0	100
est for overall effect:	Z = 5.12 (P	< 0.0000	(1)						Favors Single Dose	Favours Multiple Dose	
5-	-mg/kg/ka	Multiple	Dose 5	-mg/kg Single	e Dose		Odds Ratio		Odds	Ratio	
Study or Subgroup	Eve		Total	Events		al Weigh	nt M-H, Random, 95%	i CI	M-H, Rand		
Beswick 2016		16	21	3		3 8.1			•		
Shepherd 2014		2	4	4	1						
Van Langenberg 2015		39	47	28	4				_		
van Langenberg 2015		22	47	20	4	1 //.3	2.20 (0.85 10 6.	19)			
Total (95% CI)			72		F	5 100.0	% 1 91 /0 70 +~ 4	62)	-		
		E 7	12	25	5	5 100.0	% 1.91 (0.79 to 4.	02)			
Total events	0.00. CL-2	57		35				L			
Heterogeneity: Tau ² =			= 2 (P =	0.60 ; $I^* = 0\%$				0.01	0.1	1 10	100
Test for overall effect:	Z = 1.43 (F	r = 0.15							Favors Single Dose	Favours Multiple Dose	
		iffied 5-r	ng/kg Sta	andard inducti	on		Odds Ratio		Odds Ra	itio	
	Events 23	Total 28	ng/kg Sta Eve	andard inducti nts 7 15		Veight M 8.5%	Odds Ratio -H, Random, 95% Cl 0.31 (0.03 to 2.89)		Odds Ra M-H, Random		
Al Khoury 2017	Events	Total	ng/kg St Eve	nts T	Total V		-H, Random, 95% CI				
Al Khoury 2017 An 2017	Events 23	Total 28	ng/kg Sta Eve	nts 1 15	Total V 16	8.5%	-H, Random, 95% CI 0.31 (0.03 to 2.89)				
Al Khoury 2017 An 2017 Gibson 2015	Events 23 33	Total 28 40	ng/kg Sta Eve	nts 7 15 36	Total V 16 37	8.5% 9.0%	-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12)				
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018	Events 23 33 14	Total 28 40 15	Eve	nts 1 15 36 22	Total V 16 37 35	8.5% 9.0% 9.0%	-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42)				
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Nalagatla 2018 Seah 2017	Events 23 33 14 53 74 9	Total 28 40 15 58 81 10	Eve	nts 1 15 36 22 71 121 28	Total V 16 37 35 87 132 30	8.5% 9.0% 9.0% 17.7% 18.4% 7.2%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95)				
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Nalagatla 2018 Seah 2017 Shah 2018	Events 23 33 14 53 74 9 28	Total 28 40 15 58 81 10 37	Eve	nts 7 15 36 22 71 121 28 78	Total V 16 37 35 87 132 30 89	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.66 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17)				
Study or Subgroup AI Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Nalagatla 2018 Seeh 2017 Shah 2018 Sly 2017	Events 23 33 14 53 74 9	Total 28 40 15 58 81 10	Eve	nts 1 15 36 22 71 121 28	Total V 16 37 35 87 132 30 89	8.5% 9.0% 9.0% 17.7% 18.4% 7.2%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95)				
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Nalagatla 2018 Seah 2017 Shah 2018 Sly 2017	Events 23 33 14 53 74 9 28	Total 28 40 15 58 81 10 37 23	Eve	nts 7 15 36 22 71 121 28 78	Total V 16 37 35 87 132 30 89 18	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7%	-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59)				
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Nalagatla 2018 Seah 2017 Shah 2018 Sly 2017 Total (95% CI)	Events 23 33 14 53 74 9 28 16	Total 28 40 15 58 81 10 37	Eve	nts 1 15 36 22 71 121 28 78 16	Total V 16 37 35 87 132 30 89	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.66 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17)				
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Nalagatla 2018 Seah 2017 Shah 2018 Sly 2017 Total (95% Cl) Total events	Events 23 33 14 53 74 9 28 16 250	Total 28 40 15 58 81 10 37 23 292	Eve	nts 7 15 36 22 71 121 28 78 16 387	Total V 16 37 35 87 132 30 89 18	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68)				
Al Khoury 2017 An 2017 Cibson 2015 Cibson 2015 Cibson 2018 Sulagata 2018 Seah 2017 Shah 2018 Sily 2017 Total (95% CI) Fotal events Heterogenetty: Tau ² =	23 33 14 53 74 9 28 16 250 0.64; Chi ² =	Total 28 40 15 58 81 10 37 23 292 15.08, df	Eve	nts 7 15 36 22 71 121 28 78 16 387	Total V 16 37 35 87 132 30 89 18	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68)		M-H, Random	n, 95% Cl	100
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Gibson 2018 Saha 2018 Saha 2018 Sily 2017 Total (95% CI) Total events Heterogeneity: Tau ² =	23 33 14 53 74 9 28 16 250 0.64; Chi ² =	Total 28 40 15 58 81 10 37 23 292 15.08, df	Eve	nts 7 15 36 22 71 121 28 78 16 387	Total V 16 37 35 87 132 30 89 18	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68)		M-H, Random	- -	100
Al Khoury 2017 An 2017 Jibson 2015 Jibson 2015 Jibson 2018 Jibson 2018 Jibson 2018 Jibson 2017 Fotal (95% CI) Fotal events Jeterogenetity: Tau ² =	Events 23 33 14 53 74 9 28 16 250 0.64; Chi ² = Z = 0.68 (P =	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49)	Eve	nts 7 15 36 22 71 121 28 78 16 387 0.04); $l^2 = 54\%$	Total V 16 37 35 87 132 30 89 18 444 1	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68)		M-H, Random	n, 95% CI	100
Al Khoury 2017 An 2017 Libson 2015 Libson 2015 Sibson 2018 Seah 2017 Jalagatla 2018 Seah 2017 Jishah 2018 Siy 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = Test for overall effect:	Events 23 33 14 53 74 9 28 16 250 0.64; Chi ² = Z = 0.68 (P =	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49)	Eve = 7 (P = 1 mg/kg St	nts 7 15 36 22 71 121 28 28 78 16 387 0.004); f² = 54% andard induct	Total V 16 37 35 87 132 30 89 18 444 1	8.5% 9.0% 9.0% 17.7% 18.4% 18.5% 11.7% 00.0%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68)		M-H, Random	n, 95% CI	
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Valagata 2018 Siban 2018 Siban 2018 Siban 2017 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017	Events 23 33 14 53 74 9 28 0.64; Chi² = Z = 0.68 (P = Dose intens Events 22	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) sified 5-1 Total 28	Eve = 7 (P = 1 mg/kg St	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct ints 13	Total V 16 37 37 35 87 132 30 89 18 444 444 1 Fotal V 16 16	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% Cl 0.85 (0.18 to 3.97)		M-H, Random	n, 95% CI	100
Al Khoury 2017 An 2017 Libson 2015 Libson 2015 Libson 2018 Valagatla 2018 Johan 2017 Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017	$\begin{tabular}{ c c c c } \hline Events & 23 \\ \hline & 23 \\ \hline & 33 \\ \hline & 33 \\ \hline & 33 \\ \hline & 14 \\ \hline & 53 \\ \hline & 74 \\ \hline & 9 \\ \hline & 26 \\ \hline & 250 \\ \hline & 0.68 (P=$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) sified 5-1 Total 28 40	Eve = 7 (P = 1 mg/kg St	nts T 15 36 22 71 121 28 28 78 16 387 0.04); $f^2 = 54\%$ andard induct 13 35	Total V 16 37 37 37 132 30 89 18 444 1 fon Fotal 16 37	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% Veight N 9.8% 9.2%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.15 to 7.95) 0.44 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16)		M-H, Random	n, 95% CI	100
Al Khoury 2017 An 2017 Libson 2015 Libson 2018 Valagatla 2018 Valagatla 2018 Sily 2017 Fotal (95% CI) Total events Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2015	Events 23 33 14 53 74 9 28 16 250 0.64; Chi ² = Z = 0.68 (P = Dose intens Events 22 12	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) sified 5-1 Total 28	Eve = 7 (P = 1 mg/kg St	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct ints 13	Total V 16 37 37 35 87 132 30 89 18 444 444 1 Fotal V 16 16	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0%	I-H, Random, 95% Cl 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) I-H, Random, 95% Cl 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55)		M-H, Random	n, 95% CI	100
Al Khoury 2017 An 2017 Libson 2015 Libson 2018 Valagatla 2018 Valagatla 2018 Sily 2017 Fotal (95% CI) Total events Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2015	$\begin{tabular}{ c c c c } \hline Events & 23 \\ \hline & 23 \\ \hline & 33 \\ \hline & 33 \\ \hline & 33 \\ \hline & 14 \\ \hline & 53 \\ \hline & 74 \\ \hline & 9 \\ \hline & 26 \\ \hline & 250 \\ \hline & 0.68 (P=$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) sified 5-1 Total 28 40	Eve = 7 (P = 1 mg/kg St	nts T 15 36 22 71 121 28 28 78 16 387 0.04); $f^2 = 54\%$ andard induct 13 35	Total V 16 37 37 37 132 30 89 18 444 1 fon Fotal 16 37	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% Veight N 9.8% 9.2%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.15 to 7.95) 0.44 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16)		M-H, Random	n, 95% CI	100
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Al Khoury 2017 An 2017 Jibson 2015 Jibson 2015 Jibson 2018 Valagatla 2018 Jibah 2018 Jiy 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Sulagatla 2018	Events 23 33 14 53 74 9 28 16 250 0.64; Chi² = Z 0.64; Chi² = Z 0.64; Chi² = Z 32 12 49	Total 28 40 15 58 10 37 23 292 15.08, df = 0.49) sified 5-1 Total 28 40 15 58	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 0.004); $l^2 = 54\%$ andard induct 13 35 20 66	Total V 16 37 35 87 132 30 89 18 444 1 ion 16 37 35 87 35	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% Veight N 9.8% 9.2% 10.8% 10.8%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11)		M-H, Random	n, 95% CI	100
Al Khoury 2017 An 2017 Jibson 2015 Jibson 2015 Jibson 2018 Valagatla 2018 Jibah 2018 Jibah 2017 Fotal (95% CI) Fotal (95% CI) Fotal (95% CI) Fotal (95% CI) Fotal (95% CI) Fotal (95% CI) Fotal events Hetrogeneity: Tau ² = Exet for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2015 Gibson 2015 Gibson 2018 Nalagatla 2018 Seah 2017	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) sified 5-4 28 40 15 58 81	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct nts 13 20 66 113 28	Total V 16 37 35 87 132 30 89 18 444 1 ion 1 Fotal V 132 37 35 87 132 30	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 11.7% 00.0% Veight N 9.8% 9.2% 10.8% 17.8%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.30 to 1.23)		M-H, Random	n, 95% CI	10
Al Khoury 2017 An 2017 Jibson 2015 Jibson 2015 Jibson 2018 Valagatla 2018 Valagatla 2018 Vig 2017 Fotal (95% CI) Fotal events feterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Valagatla 2018 Seah 2017 Shah 2018	$\begin{tabular}{ c c c c } \hline Events & & & & \\ \hline & & & & & \\ \hline & & & & & \\ \hline & & & &$	Total 28 40 15 58 10 37 23 292 15.08, dff = 0.49) siffied 5-1 28 40 15 88 81 10 28 40 15 88 81 10 37	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 128 78 16 387 0.004); $f^2 = 54\%$ andard induct 13 35 20 66 113 28 28 72	rotal V 16 37 35 87 132 30 89 18 444 1 ion 1 16 37 35 87 132 36 87 132 36 87 132 30 89 9	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 11.7% 00.0% Veight M 9.8% 9.2% 10.8% 9.2% 10.8% 19.9% 6.2%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17)		M-H, Random	n, 95% CI	10
Al Khoury 2017 An 2017 Jibson 2015 Jibson 2015 Jibson 2018 Seah 2017 Jibah 2018 Jiy 2017 Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Nalagata 2018 Seah 2017 Shah 2018 Shah 2018 Shah 2018 Shah 2018	$\begin{tabular}{ c c c c } \hline Events & $$23$ \\ 23 \\ 33 \\ 14 \\ 53 \\ 74 \\ 9 \\ 28 \\ 16 \\ \hline 250 \\ $0.64; Chi^2 = $$20$ \\ $0.64; Chi^2 = $$20$ \\ $0.64; Chi^2 = $$20$ \\ 25 \\ \hline 20 \\ 25 \\ $	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) sified 5-1 70tal 28 40 15 58 81 10 37 23	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct nts 13 20 66 113 28	Total V 16 37 37 35 87 132 30 89 18 444 1 1 rotal N 16 37 35 87 132 30 89 18	8.5% 9.0% 9.0% 17.7% 18.4% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 9.2% 10.8% 17.8% 19.9% 6.2% 17.7% 8.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.33 to 1.25) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06)		M-H, Random	n, 95% CI	
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2015 Gibson 2018 Seah 2017 Shah 2018 Sly 2017 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Seah 2018 Seah 2018 Shah 2018 Shah 2018 Shah 2018	$\begin{tabular}{ c c c c } \hline Events & & & & \\ \hline & & & & & \\ \hline & & & & & \\ \hline & & & &$	Total 28 40 15 58 10 37 23 292 15.08, dff = 0.49) siffied 5-1 28 40 15 88 81 10 28 40 15 88 81 10 37	= 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 121 28 16 387 0.004); $f' = 54\%$ andard induct 13 35 20 66 113 28 72 16	Total V 16 37 37 35 87 132 30 89 18 444 1 1 rotal N 16 37 35 87 132 30 89 18	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 11.7% 00.0% Veight M 9.8% 9.2% 10.8% 9.2% 10.8% 19.9% 6.2%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17)		M-H, Random	n, 95% CI	
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2015 Gibson 2018 Nalagatla 2018 Seah 2017 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Gibson 2018 Nalagatla 2018 Seah 2017 Shah 2018 Siy 2017 Total (95% CI) Total events	$\begin{tabular}{ c c c c } \hline Events & & & \\ \hline & & & & \\ \hline & & & & \\ \hline & & & &$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) sified 58 40 15 58 81 10 37 23 292 sified 58 81 10 37 23 292	Eve = 7 (P = 4 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct nts 1 35 20 66 72 16 28 72 16 363 363	Total V 16 37 37 35 87 132 30 89 18 444 11 10 11 10 11 10 11 10 11 10 11 11 12	8.5% 9.0% 9.0% 17.7% 18.4% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 9.2% 10.8% 17.8% 19.9% 6.2% 17.7% 8.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 7.95) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.33 to 1.25) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06)		M-H, Random	n, 95% CI	100
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2015 Gibson 2018 Seah 2017 Shah 2018 Sly 2017 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Nalagatla 2018 Seah 2017 Shah 2018 Sly 2017 Total (95% CI) Total (95% CI)	$\begin{tabular}{ c c c c } \hline Events & $$23$ \\ 23 \\ 33 \\ 14 \\ 4 \\ 53 \\ 74 \\ 9 \\ 28 \\ 16 \\ 250 \\ $0.64; Chi^2 = $$0.68$ (P = $$$20$ \\ 20 \\ 20 \\ 16 \\ 20 \\ 21 \\ 22 \\ 12 \\ 49 \\ 65 \\ 8 \\ 25 \\ 14 \\ 227 \\ $0.33; Chi^2 = $$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	Total 28 40 15 58 10 37 23 292 15.08, df = 0.49) sified 5i 70tal 28 40 15 58 81 10 58 81 10 37 23 292 13.51, df	Eve = 7 (P = 4 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct nts 1 35 20 66 72 16 28 72 16 363 363	Total V 16 37 37 35 87 132 30 89 18 444 11 10 11 10 11 10 11 10 11 10 11 11 12	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 9.2% 10.8% 17.8% 19.9% 6.2% 17.7% 8.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 1.25) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27)	Favors ! 	M-H, Random	n, 95% CI	
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2018 Nalagatla 2018 Seeah 2017 Shah 2018 Sly 2017 Total (95% CI)	$\begin{tabular}{ c c c c } \hline Events & $$23$ \\ 23 \\ 33 \\ 14 \\ 4 \\ 53 \\ 74 \\ 9 \\ 28 \\ 16 \\ 250 \\ $0.64; Chi^2 = $$0.68$ (P = $$$20$ \\ 20 \\ 20 \\ 16 \\ 20 \\ 21 \\ 22 \\ 12 \\ 49 \\ 65 \\ 8 \\ 25 \\ 14 \\ 227 \\ $0.33; Chi^2 = $$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	Total 28 40 15 58 10 37 23 292 15.08, df = 0.49) sified 5i 70tal 28 40 15 58 81 10 58 81 10 37 23 292 13.51, df	Eve = 7 (P = 4 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct nts 1 35 20 66 72 16 28 72 16 363 363	Total V 16 37 37 35 87 132 30 89 18 444 11 10 11 10 11 10 11 10 11 10 11 11 12	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 9.2% 10.8% 17.8% 19.9% 6.2% 17.7% 8.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 1.25) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27)	Favors ! 	M-H, Random	n, 95% CI	
Al Khoury 2017 An 2017 Sibson 2015 Sibson 2015 Sibson 2015 Sibson 2018 Valagatla 2018 Siy 2017 Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Nalagatla 2018 Seah 2017 Stal (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	$\begin{tabular}{ c c c c } \hline Events & $$23$ \\ 23 \\ 33 \\ 14 \\ 53 \\ 74 \\ 9 \\ 28 \\ 16 \\ \hline 250 \\ 0.64; Chi^2 = $$0.68$ (P-$$$$2$ \\ \hline 20 \\ 20 \\ 16 \\ \hline 20 \\ 20 \\ 12 \\ 49 \\ 65 \\ 8 \\ 8 \\ 25 \\ 14 \\ \hline 227 \\ 0.33; Chi^2 = $$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 58 81 10 28 40 15 88 81 10 37 23 292 13.51, df = 0.24)	Eve = 7 (P = 0) mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 387 0.004); $l^2 = 54\%$ andard induct 13 35 20 66 113 28 72 16 363 30.06); $l^2 = 48\%$	otal V 16 37 37 35 87 132 30 89 18 444 1 ion 30 89 1 ib 444 ion 1	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 9.2% 10.8% 17.8% 19.9% 6.2% 17.7% 8.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27)	Favors ! 	M-H, Random	n, 95% CI	
Al Khoury 2017 An 2017 Sibson 2015 Sibson 2015 Sibson 2015 Sibson 2018 Valagatla 2018 Sight 2017 Fotal (95% CI) Total events Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Stah 2018 Stah 2018 Stah 2018 Stah 2018 Stah 2017 Total events Heterogeneity: Tau ² = Test for overall effect:	$\begin{tabular}{ c c c c } \hline Events & $$23$ \\ 23 \\ 33 \\ 14 \\ 53 \\ 74 \\ 9 \\ 28 \\ 16 \\ \hline 250 \\ 0.64; Chi^2 = $$0.68$ (P-$$$$2$ \\ \hline 20 \\ 20 \\ 16 \\ \hline 20 \\ 20 \\ 12 \\ 49 \\ 65 \\ 8 \\ 8 \\ 25 \\ 14 \\ \hline 227 \\ 0.33; Chi^2 = $$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 58 81 10 28 40 15 88 81 10 37 23 292 13.51, df = 0.24)	Eve = 7 (P = 0) mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 0.04); $f^2 = 54\%$ andard induct 13 5 20 66 72 16 363 0.06); $f^2 = 48\%$ andard inducti 113 28 72 16 363 0.060); $f^2 = 48\%$	votal V 16 37 37 35 87 132 30 89 18 444 1 16 16 77 37 30 37 312 30 16 37 37 32 30 89 18 4444 1	8.5% 9.0% 9.0% 9.0% 17.7% 18.4% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 17.8% 9.2% 10.8% 17.8% 6.2% 17.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 1.25) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27)	Favors ! 	M-H, Random	h, 95% CI	
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2015 Gibson 2018 Seah 2017 Shah 2018 Siy 2017 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Nalagatla 2018 Seah 2017 Total events Heterogeneity: Tau ² = Test for overall effect:	Events 23 33 14 33 14 9 8 16 250 0.64; Chi ² = 2 2 0.64; Chi ² = 2 0.64; Chi ² = 22 32 12 49 65 8 25 12 49 65 2 2.5 12 2.7 0.33; Chi ² = Z Z 1.17 (P; Dose intense 2.5	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 5-1 Total 28 40 15 58 81 10 37 23 292 13.51, df 13.51, df ified 5-n	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 0.04); $f^2 = 54\%$ andard induct 13 5 20 66 72 16 363 0.06); $f^2 = 48\%$ andard inducti 113 28 72 16 363 0.060); $f^2 = 48\%$	votal V 16 37 37 35 87 132 30 89 18 444 1 16 16 77 37 30 37 312 30 16 37 37 32 30 89 18 4444 1	8.5% 9.0% 9.0% 9.0% 17.7% 18.4% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 17.8% 9.2% 10.8% 17.8% 6.2% 17.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27)	Favors ! 	M-H, Random	h, 95% CI	
Al Khoury 2017 An 2017 Gibson 2015 Gibson 2015 Gibson 2018 Seah 2017 Shah 2018 Sly 2017 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2018 Nalagatla 2018 Seah 2017 Stal (95% CI) Total (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017	$\begin{tabular}{ c c c c } \hline Events & 23 \\ 33 \\ 33 \\ 14 \\ 4 \\ 53 \\ 74 \\ 9 \\ 28 \\ 16 \\ \hline 250 \\ 0.64; Chi^2 = 2 \\ 20.68 (P^2 \\ \hline 22 \\ 22 \\ 12 \\ 49 \\ 65 \\ 8 \\ 25 \\ 14 \\ \hline 227 \\ 0.33; Chi^2 = 2 \\ 21 \\ \hline 227 \\ 0.33; Chi^2 = 2 \\ 21 \\ \hline 23 \\ \hline 23 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 21 \\ \hline 21 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 21 \\ \hline 23 \\ \hline 21 \hline 21 \\ \hline 21 \\ \hline 21 \\ \hline 21 \hline$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 5-n 23 292 13.51, df = 0.24) ified 5-n Total 28	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $l^2 = 54\%$ andard induct 13 35 20 66 113 28 72 16 363 0.06); $l^2 = 48\%$ andard inducti nts T 13	rotal V 16 37 37 35 87 132 30 89 18 444 1 16 37 37 32 30 89 18 444 1 444 1 1 16 37 30 30 89 18 4444 1 1 00 16 1 01 16 1 02 16 1	8.5% 9.0% 9.0% 17.7% 18.4% 11.7% 11.7% 00.0% 9.8% 9.2% 10.8% 19.9% 6.2% 19.9% 6.2% 17.7% 19.9% 6.2% 8.7%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) Odds Ratio I-H, Random, 95% CI 0.69 (0.15 to 3.16)	Favors ! 	M-H, Random	h, 95% CI	100
Al Khoury 2017 An 2017 Sibson 2015 Sibson 2015 Sibson 2015 Sibson 2018 Valagatla 2018 Siy 2017 Fotal (95% CI) Total events Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Total 2018 Seah 2017 Shah 2018 Sig 2017 Total 2018 Seah 2017 Shah 2017 Total 2017 Total 2017 Study or Subgroup Al Khoury 2017 An 2017	$\begin{tabular}{ c c c c } \hline Events & & & & & & \\ \hline & & & & & & & \\ \hline & & & &$	Total 28 40 15 881 10 37 23 292 15.08, df = 0.49) sified 5-n 76 10 37 28 40 15 58 81 10 37 292 13.51, df = 0.24) ified 5-n Total 28 40	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 0.04); $l^2 = 54\%$ andard induct 13 35 20 66 663 0.06); $l^2 = 48\%$ 363 0.06); $l^2 = 48\%$ andard inducti 11 13 33	oracial V 16 37 37 35 87 132 30 89 18 444 1 444 1 1 16 37 35 30 89 18 444 1 1 16 37 30 89 18 444 1 0 89 18 444 1 0 16 37 36 18 0 18 18 14 1 0 10 37 37 37	8.5% 9.0% 9.0% 17.7% 18.4% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 17.8% 9.2% 10.8% 17.8% 6.2% 17.7% 00.0%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) Odds Ratio I-H, Random, 95% CI 0.69 (0.15 to 3.16) 0.42 (0.12 to 1.50)	Favors ! 	M-H, Random	h, 95% CI	
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Al Khoury 2017 An 2017 Jaho 2017 Jibson 2015 Jibson 2015 Jibson 2018 Jiban 2018 Jiban 2018 Jiy 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Gibson 2015 Sibah 2018 Seah 2017 Total (95% CI) Total (95% CI)	$\begin{tabular}{ c c c c } \hline Events & & & & \\ \hline & & & & \\ \hline & & & & \\ \hline & & & &$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 58 81 10 37 23 292 13.51, dff 13.51, dff 16 3.51, dff 40 23 292 13.51, dff 40 58 81 10 37 23 292 13.51, dff 16ied 58 40 58	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 30.04); $f^2 = 54\%$ andard inducti 13 35 20 66 363 20 66 363 30.06); $l^2 = 48\%$ andard inducti nts T 13 33 18 60	ortal V 16 37 37 35 87 132 30 89 18 444 1 444 1 1 16 37 35 89 18 444 1 444 1 1 1 00 89 18 1 4444 1 1 1 01 18 1 1 01 18 1 1 01 10 1 1 01 10 1 1 01 10 1 1 01 10 1 1 02 10 1 1 03 10 1 1 03 10 1 1 04 10 1 1 13 10 1 1 14 10	8.5% 9.0% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.8% 9.2% 9.2% 10.8% 17.8% 9.2% 17.8% 19.9% 6.2% 8.7% 00.0%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.05 to 1.75) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) Odds Ratio I-H, Random, 95% CI 0.69 (0.15 to 3.16) 0.42 (0.12 to 1.50) 2.60 (0.69 to 9.75) 1.41 (0.67 to 3.01)	Favors ! 	M-H, Random	h, 95% CI	
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Al Khoury 2017 An 2017 Sibson 2015 Sibson 2015 Sibson 2015 Sibson 2018 Valagatla 2018 Sig 2017 Fotal (95% CI) Total events Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Total 2018 Sig 2017 Total 2017 Sinha 2018 Study or Subgroup Al Khoury 2017 An 2017 Sibson 2015 Situdy or Subgroup Al Khoury 2017 An 2017 Sibson 2018 Valagatla 2018 Sig 2017 Study Of Subgroup Al Khoury 2017 Sibson 2018 Valagatla 2018 Sig 2017 Sibson 2018 Sibson 2018 Sig 2017 Sibson 2018 Sibson 2018 Sibson	$\begin{tabular}{ c c c c } \hline Events & & & & & \\ \hline & & & & & & \\ \hline & & & & &$	Total 28 40 15 81 10 37 23 292 15.08, df = 0.49) sified 5-n 723 28 40 15 58 81 10 37 23 292 13.51, df = 0.24) ified 5-n 7 28 0 15 58 81 10 37	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 0.04); $l^2 = 54\%$ andard induct 13 5 20 66 113 28 22 16 363 0.06); $l^2 = 48\%$ andard inducti 13 363 0.06); $l^2 = 48\%$ andard inducti 13 18 60 96 24 65 65	oracial V 16 37 37 35 87 132 30 89 18 444 1 444 1 1 00 16 37 35 87 132 30 89 18 444 1 1 0 16 37 30 89 18 4444 1 1 0 7 35 87 132 30 89 37 35 30 37 35 89 89 89	8.5% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.8% 9.2% 10.8% 9.2% 10.8% 17.8% 9.2% 10.8% 17.7% 6.2% 17.7% 00.0%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 1.25) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) Codds Ratio I-H, Random, 95% CI 0.69 (0.15 to 3.16) 0.42 (0.12 to 1.50) 2.60 (0.69 to 9.75) 1.41 (0.67 to 3.01) 0.95 (0.51 to 1.77) 0.68 (0.30 to 1.55) 0.68 (0.30 to 1.55)	Favors ! 	M-H, Random	h, 95% CI	
Al Khoury 2017 An 2017 Jibson 2015 Jibson 2015 Jibson 2018 Jiban 2018 Jiban 2018 Jiban 2018 Jiy 2017 Fotal events feterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Cibson 2018 Nalagatla 2018 Seah 2017 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Al Khoury 2017 Total (95% CI) Total (95% CI) Total for overall effect: Study or Subgroup Al Khoury 2017 An 2017 Jibson 2015 Jibson 2015 Jibson 2018 Valagatla 2018 Valagatla 2018 Valagatla 2018 Valagatla 2018	$\begin{tabular}{ c c c c } \hline Events & & & & & \\ \hline & & & & & & \\ \hline & & & & &$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 5-n 723 28 40 15 81 10 37 23 292 13.51, df = 0.24) ified 5-n 28 40 15 58 81 10	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 387 0.004); $l^2 = 54\%$ andard induct 13 35 20 66 113 28 72 16 363 30.06); $l^2 = 48\%$ andard inducti T 13 33 18 60 96 24	otal V 16 37 37 35 87 132 30 89 18 444 1 444 1 1 16 37 30 89 18 444 1 444 1 1 60 7 30 89 18 4 444 1 1 0 89 18 444 1 1 0 70 16 37 30 30	8.5% 9.0% 9.0% 17.7% 18.4% 11.7% 00.0% 9.8% 9.2% 10.8% 19.9% 6.2% 19.9% 6.2% 10.8% 17.7% 8.7% 19.9% 6.2%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) Odds Ratio I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) Odds Ratio I-H, Random, 95% CI 0.69 (0.15 to 3.16) 0.42 (0.12 to 1.50) 2.60 (0.69 to 9.75) 1.41 (0.67 to 3.01) 0.95 (0.51 to 1.75) 0.38 (0.08 to 1.77)	Favors ! 	M-H, Random	h, 95% CI	
N Khoury 2017 In 2017 Ibson 2015 Ibson 2015 Ibson 2015 Ibson 2018 Ialagatla 2018 Ialagatla 2018 Ialagatla 2017 fotal (95% CI) Total events Ieterogeneity: Tau ² = Test for overall effect: Ibson 2017 Ibson 2018 Ibson 2	$\begin{tabular}{ c c c c } \hline Events & & & & & \\ \hline & & & & & & \\ \hline & & & & &$	Total 28 40 15 81 10 37 23 292 15.08, df = 0.49) sified 5-n 723 28 40 15 58 81 10 37 23 292 13.51, df = 0.24) ified 5-n 7 28 0 15 58 81 10 37	Eve = 7 (P = 1 mg/kg St Eve	nts T 15 36 22 71 121 28 28 78 16 387 0.04); $l^2 = 54\%$ andard induct 13 5 20 66 113 28 22 16 363 0.06); $l^2 = 48\%$ andard inducti 13 363 0.06); $l^2 = 48\%$ andard inducti 13 18 60 96 24 65 65	oracial V 16 37 37 35 87 132 30 89 18 444 1 444 1 1 00 16 37 35 87 132 30 89 18 444 1 1 0 16 37 30 89 18 4444 1 1 0 7 35 87 132 30 89 37 35 30 37 35 89 89 89	8.5% 9.0% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.2% 9.2% 9.2% 10.8% 9.2% 17.8% 9.2% 17.8% 8.7% 00.0% 00.0%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 1.25) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) Codds Ratio I-H, Random, 95% CI 0.69 (0.15 to 3.16) 0.42 (0.12 to 1.50) 2.60 (0.69 to 9.75) 1.41 (0.67 to 3.01) 0.95 (0.51 to 1.77) 0.68 (0.30 to 1.55) 0.68 (0.30 to 1.55)	Favors ! 	M-H, Random	h, 95% CI	
I Khoury 2017 in 2017 ibson 2015 ibson 2015 ibson 2018 alagatla 2018 eah 2017 iotal quents leterogeneity: Tau ² = est for overall effect: istudy or Subgroup N Khoury 2017 ibson 2015 ibson 2018 sidagatla 2018 istah 2018 istah 2017 Fotal (95% CI) Total events lagatla 2018 ibson 2017 ibson 2017 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2015 ibson 2018 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2015 ibson 2018 ibson 2018 ibson 2017 ibson 2018 ibson 2017 ibson 2018 ibson 2018 ibson 2017 ibson 2018 ibson 2018 ibson 2017 ibson 2018 ibson 2018 ibson 2017 ibson 2018 ibson 2018 ib	$\begin{tabular}{ c c c c } \hline Events & & & & & \\ \hline & & & & & & \\ \hline & & & & &$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 51 723 292 13.51, df = 0.24) ified 5n 70tal 28 40 15 58 81 10 23 292 13.51, df = 0.24) ified 5n 28 40 15 58 81 10 37 23 28 40 58 81 10 37 23 292	Eve $= 7 (P = 1)$ $mg/kg St$ Eve $mg/kg St$ Eve	nts T 15 36 22 71 121 28 28 78 16 387 387 0.004); $l^2 = 54\%$ andard induct 13 35 20 66 113 363 0.006); $l^2 = 48\%$ andard inducti T 13 33 363 0.006); $l^2 = 48\%$ andard inducti T 13 33 18 60 96 24 65 13 322 322	oracial V 16 37 37 35 89 18 444 1 16 37 35 89 18 444 1 16 37 35 80 18 444 1 0 17 35 87 18 37 35 87 132 30 18 89 18 89 18 89 18 89 132 30 35 87 132 30 132 30 132 30 132 30 132 30 132 30 132 30 132 30 133 13 134 14	8.5% 9.0% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.2% 9.2% 9.2% 10.8% 9.2% 17.8% 9.2% 17.8% 8.7% 00.0% 00.0%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.44 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) I-H, Random, 95% CI 0.85 (0.18 to 3.97) 0.23 (0.05 to 1.61) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.68 (0.33 to 1.42) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) Codds Ratio I-H, Random, 95% CI 0.69 (0.15 to 3.16) 0.42 (0.12 to 1.50) 2.60 (0.69 to 9.75) 1.41 (0.67 to 3.01) 0.55 (0.31 to 1.75) 0.38 (0.08 to 1.77) 0.68 (0.30 to 1.55) 0.35 (0.09 to 1.32)	Favors ! 	M-H, Random	h, 95% CI	
I Khoury 2017 an 2017 ibson 2015 ibson 2015 ibson 2018 lalagatla 2018 eah 2017 otal 2018 iy 2017 otal events leterogeneity: Tau ² = est for overall effect: itudy or Subgroup Vi Khoury 2017 ibson 2018 ibson 2018 ibson 2018 ibson 2018 idalagatla 2018 leterogeneity: Tau ² = est for overall effect: Itudy or Subgroup ibson 2017 ibson 2018 ibson 2018 ieterogeneity: Tau ² = est for overall effect: Itudy or Subgroup I Khoury 2017 ibson 2018 ibson 2018 ibson 2015 ibson 2015 ibson 2018 ibson 2018 ibso	$\begin{tabular}{ c c c c } \hline Events & & & & & \\ \hline & & & & & & \\ \hline & & & & &$	Total 28 40 15 58 81 10 37 23 292 15.08, df = 0.49) siffied 51 723 292 13.51, df = 0.24) ified 5n 70tal 28 40 15 58 81 10 23 292 13.51, df = 0.24) ified 5n 28 40 15 58 81 10 37 23 28 40 58 81 10 37 23 292	Eve $= 7 (P = 1)$ $mg/kg St$ Eve $mg/kg St$ Eve	nts T 15 36 22 71 121 28 28 78 16 387 387 0.004); $l^2 = 54\%$ andard induct 13 35 20 66 113 363 0.006); $l^2 = 48\%$ andard inducti T 13 33 363 0.006); $l^2 = 48\%$ andard inducti T 13 33 18 60 96 24 65 13 322 322	on V 16 37 37 35 89 18 444 1 16 37 35 89 18 444 1 16 37 35 80 18 444 1 0 17 35 87 132 30 18 444 10 10 0 137 35 87 132 30 18 89 18 89 18 89	8.5% 9.0% 9.0% 9.0% 17.7% 18.4% 7.2% 18.5% 11.7% 00.0% 9.2% 9.2% 9.2% 10.8% 9.2% 17.8% 9.2% 17.8% 8.7% 00.0% 00.0%	I-H, Random, 95% CI 0.31 (0.03 to 2.89) 0.13 (0.02 to 1.12) 8.27 (0.97 to 70.42) 2.39 (0.82 to 6.93) 0.96 (0.36 to 2.59) 0.64 (0.16 to 1.17) 0.29 (0.05 to 1.59) 0.76 (0.34 to 1.68) 0.76 (0.34 to 1.68) 0.76 (0.34 to 1.68) 0.73 (0.51 to 3.97) 0.23 (0.05 to 1.16) 3.00 (0.72 to 12.55) 1.73 (0.73 to 4.11) 0.85 (0.18 to 3.97) 0.29 (0.03 to 2.36) 0.49 (0.21 to 1.17) 0.19 (0.04 1.06) 0.70 (0.39 to 1.27) 0.40 (0.15 to 3.16) 0.42 (0.12 to 1.50) 2.60 (0.69 to 9.75) 1.41 (0.67 to 3.01) 0.95 (0.51 to 1.75) 0.38 (0.08 to 1.77) 0.68 (0.30 to 1.35) 0.35 (0.09 to 1.32) 0.83 (0.55 to 1.25)	Favors !	M-H, Random	h, 95% CI	

FIGURE 3. Forest plot using random-effects models assessing CFS at month 1, 3, and 12 for (A) 5-mg/kg multiple-dose vs 5-mg/kg single-dose induction and (B) dose-intensified vs 5-mg/kg standard-schedule induction.

tudy or Subgroup	Dose Mean [mg/L]	Intensified SD [mg/L]	Total	Sta Mean [mg/L]	andard SD [mg/L]	Total	Weight	Mean Difference IV, Random, 95% CI [mg/L]	Mean Difference] IV, Random, 95% CI [mg/L]
l Khoury 2017	82.425	62.042	40	59.1	56.4	37	6.7%	23.32 (-3.13 to 49.78)	
n 2017	49.5	36.71	28	26.47667	37.44669	16	9.1%	23.02 (0.19 to 45.86))
iibson 2015	58.46667	49.319	15	36.6	49.47	35	5.3%	21.87 (-7.99 to 51.73))
iibson 2018	40.666667	42.5724697	58	31.7241379	38.8739227	87	25.3%	8.94 (-4.72 to 22.61))
lalagatla 2018	35.5	54.9	81	29.6	51.9	132	21.3%	5.90 (-8.98 to 20.78)	
eah 2017	39.87	18.92	10	19.82	26.12		21.0%	20.05 (5.05 to 35.05))
hah 2018	74.29	64.65	37	57.5	61.3		7.9%	16.79 (-7.63 to 41.21)	
ly 2017	76	71	23	49	52	18	3.3%	27.00 (-10.67 to 64.67))
otal (95% CI)			292			444	100.0%	14.78 (7.91 to 21.65)	
eterogeneity: Tau ² =	-0.00 Chi ² - 4	00 df = 7 (p)		$l^2 = 0\%$			100.070	14.70 (7.51 to 21.05)	
est for overall effect			- 0.77),	1 - 0/0					-50 -25 Ó 25 50 Favors Standard Favours Dose Intensified
Albumin									
	Dose	Intensified		Sta	ndard			Mean Difference	Mean Difference
tudy or Subgroup	Mean [g/L]	SD [g/L]	Total	Mean [g/L]	SD [g/L] 1	Fotal \	Weight I	V, Random, 95% CI [g/L]	IV, Random, 95% CI [g/L]
l Khoury 2017	29.8375	5.694737	40	31.9	2.64167	37	19.3%	-2.06 (-4.02 to -0.10)	
n 2017	26.66667	7.811586	28	27.41667	7.2	16	3.6%	-0.75 (-5.31 to 3.81)	
ibson 2015	23	2.453682	15	24.33333	7.729794	35	9.1%	-1.33 (-4.18 to 1.51)	
iibson 2018	26	6.08178138	58	26.685824	6.6168757	87	16.9%	-0.69 (-2.78 to 1.41)	
lalagatla 2018	31	7	81	32	7	132	19.7%	-1.00 (-2.94 to 0.94)	
eah 2017	21	5.160021	10	25.66667	7.005782	30	4.5%	-4.67 (-8.73 to -0.60)	
hah 2018	24.7027	4	37	28	6	89	23.0%	-3.30 (-5.09 to -1.50)	_ _
ly 2017	33	8	23	36	6	18	4.0%	-3.00 (-7.29 to 1.29)	
									•
otal (95% CI)	-		292			444 :	100.0%	–1.95 (–2.81 to –1.09)	
leterogeneity: Tau ²			P = 0.4	4); $I^2 = 0\%$				H	-10 -5 0 5
est for overall effec	t: $Z = 4.44 (P < $	0.00001)							Favors Standard Favours Dose Intensified
IV steroid	duration								
		Intensified	_		andard			Mean Difference	Mean Difference
tudy or Subgroup	Mean) Tota					IV, Random, 95% CI	IV, Random, 95% Cl
I Khoury 2017	4.44125	3.284211			3.7	37	7.5%	-1.53 (-3.10 to 0.04)	
n 2017	4	1.1717			2.2991	16	12.4%	0.50 (–0.71 to 1.71)	
Jibson 2015	7	1.63578							
					1.545959	35	18.6%	, ,	
ibson 2018	5.6666667	3.80111337	7 58	5.6130268	3.3496463	87	12.4%	0.05 (-1.15 to 1.26)	
iibson 2018 eah 2017	5.6666667 4.666667	3.80111337 0.86	7 58 5 10	5.6130268 5	3.3496463 1.55684	87 30	12.4% 28.5%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44)	
iibson 2018 eah 2017	5.6666667	3.80111337	7 58 5 10	5.6130268 5	3.3496463	87	12.4%	0.05 (-1.15 to 1.26)	
Gibson 2018 Jeah 2017 Jhah 2018	5.6666667 4.666667	3.80111337 0.86	7 58 5 10 7 37	5.6130268 5 4	3.3496463 1.55684	87 30 89	12.4% 28.5% 20.6%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22)	
ibson 2018 eah 2017 hah 2018 F otal (95% CI)	5.6666667 4.6666667 4.3	3.80111337 0.86 2.2647	7 58 5 10 7 37 188	5.6130268 5 4	3.3496463 1.55684	87 30 89	12.4% 28.5% 20.6%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44)	
iibson 2018 eah 2017 hah 2018 F otal (95% CI) leterogeneity: Tau ²	5.66666667 4.6666667 4.3 = 0.02; Chi ² =	3.80111337 0.86 2.2647 5.31, df = 5	7 58 5 10 7 37 188	5.6130268 5 4	3.3496463 1.55684	87 30 89	12.4% 28.5% 20.6%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22)	
iibson 2018 eah 2017 hah 2018 F otal (95% CI) leterogeneity: Tau ²	5.66666667 4.6666667 4.3 = 0.02; Chi ² =	3.80111337 0.86 2.2647 5.31, df = 5	7 58 5 10 7 37 188	5.6130268 5 4	3.3496463 1.55684	87 30 89	12.4% 28.5% 20.6%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22)	-4 -2 0 2 4 Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ²	5.6666667 4.666667 4.3 = 0.02; Chi ² = ct: Z = 0.36 (P	3.80111337 0.86 2.2647 5.31, df = 5	7 58 5 10 7 37 188	5.6130268 5 4	3.3496463 1.55684	87 30 89	12.4% 28.5% 20.6%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22)	
iibson 2018 eah 2017 ihah 2018 Total (95% CI) leterogeneity: Tau ² rest for overall effect Disease du	5.6666667 4.666667 4.3 = 0.02; Chi ² = tt: Z = 0.36 (P ration Dose	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72)	7 58 5 10 7 37 188 6 (P = 0.5)	5.6130268 5 7 4 38); / ² = 6% Stanc	3.3496463 1.55684 2.7	87 30 89 294	12.4% 28.5% 20.6% 100.0%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.90 (-0.51 to 0.36)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 "otal (95% CI) leterogeneity: Tau ² est for overall effec <u>Disease dun</u> itudy or Subgroup	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose Mean	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72)	7 58 5 10 7 37 188 5 (P = 0.	5.6130268 5 38); / ² = 6% Stanc Mean	3.3496463 1.55684 2.7 lard <u>SD Tot</u>	87 30 89 294	12.4% 28.5% 20.6% 100.0% M eight IV,	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 ihah 2018 'otal (95% CI) leterogeneity: Tau ² 'est for overall effec Disease dun itudy or Subgroup VI Khoury 2017	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose Mean 5.9	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72)	7 58 5 10 7 37 188 1 (P = 0. Total 40	5.6130268 5 $38); l^2 = 6\%$ Stanc Mean 6.375 9.4	3.3496463 1.55684 2.7 Iard <u>SD Tot</u> 131579	87 30 89 294 37	12.4% 28.5% 20.6% 100.0% Meight IV, 7.7% -	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.03 (-0.51 to 0.36)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease dun</u> i tudy or Subgroup I Khoury 2017 n 2017	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P cation Dose i 5.9 2.5	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811	$\frac{7}{5} = 58$ $\frac{5}{5} = 10$ $\frac{188}{5}$ $\frac{7}{6} (P = 0.0)$ $\frac{100}{28}$	5.6130268 5 $38); l^2 = 6\%$ Stanc <u>Mean</u> 6.375 9.2 2.33333 2.8	3.3496463 1.55684 2.7 Iard <u>SD Tot</u> 331579 3 344876 1	87 30 89 294 294 37 16 1	12.4% 28.5% 20.6% 100.0% <u>eight IV,</u> 7.7% – 5.6%	ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease dun</u> i tudy or Subgroup I Khoury 2017 n 2017	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P cation Dose i 5.9 2.5	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72)	$\frac{7}{5} = 58$ $\frac{5}{5} = 10$ $\frac{188}{5}$ $\frac{7}{6} (P = 0.0)$ $\frac{100}{28}$	5.6130268 5 $38); l^2 = 6\%$ Stanc Mean 6.375 9.4	3.3496463 1.55684 2.7 Iard <u>SD Tot</u> 331579 3 344876 1	87 30 89 294 37 16 1 35 1	12.4% 28.5% 20.6% 100.0% <u>eight IV,</u> 7.7% – 5.6% 2.6%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.07 (-2.21 to 3.62)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease duu</u> tudy or Subgroup Il Khoury 2017 n 2017 Sibson 2015	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P cation Dose i 5.9 2.5	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811	$\frac{7}{5} = 58$ $\frac{5}{5} = 10$ $\frac{188}{5}$ $\frac{7}{6} (P = 0.0)$ $\frac{100}{28}$	5.6130268 5 $38); l^2 = 6\%$ Stanc <u>Mean</u> 6.375 9.2 2.33333 2.8	3.3496463 1.55684 2.7 Iard <u>SD Tot</u> 331579 3 344876 1	87 30 89 294 37 16 1 35 1	12.4% 28.5% 20.6% 100.0% <u>eight IV,</u> 7.7% – 5.6% 2.6%	ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² 'est for overall effec Disease dun tudy or Subgroup Il Khoury 2017 ni 2017 jibson 2015 lalagatla 2018	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose b Mean 5.9 2.5 2.76	3.8011133 0.86 2.2647 5.5.31, df = 5 = 0.72) Intensified <u>50</u> 5.46811 5.079121 2.8	$ \begin{array}{r} 7 & 58 \\ 5 & 10 \\ 7 & 37 \\ 188 \\ 6 (P = 0. \\ \hline 15 & 10 \\ 7 & 10 \\ $	5.6130268 5.6130268 5 $38); l^2 = 6\%$ Stanc Mean 6.375 9.4 2.33333 2.1 2.006667 3.1	3.3496463 1.55684 2.7 431579 344876 3.1 1 303059 3.1 1 3 3.1 1	87 30 89 294 37 16 1 35 1 32 3	12.4% 28.5% 20.6% 100.0% Meight IV, 7.7% – 5.6% 8.9%	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.07 (-2.21 to 3.62)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect Disease dun tudy or Subgroup N Khoury 2017 vn 2017 ilbson 2015 ialagatla 2018 eah 2017	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration bose bose bose bose cose	3.8011133 0.86 2.2647 5.5.31, df = 5 = 0.72) Intensified <u>50</u> 5.46811 5.079121 2.8	$ \begin{array}{r} 7 & 58 \\ 5 & 10 \\ 7 & 37 \\ 188 \\ 6 (P = 0. \\ \hline 188 \\ 40 \\ 28 \\ 15 \\ 81 \\ \end{array} $	5.6130268 5 $38); l^2 = 6\%$ Stand Mean 6.375 9.2 2.33333 2.8 2.006667 3.8 4	3.3496463 1.55684 2.7 4ard 5D Tot 431579 = 344876 = 303059 = 3.1 = 24433 = 2024433 =	87 30 89 294 37 16 1 35 1 32 3 30	12.4% 28.5% 20.6% 100.0% Meight IV, 7.7% – 5.6% 2.6% 8.9% 2.3% 3	ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.07 (-2.29 to 2.63) 0.07 (-2.29 to 2.63) 0.07 (-2.29 to 2.63) 0.75 (-2.11 to 3.62)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect Disease dun tudy or Subgroup N Khoury 2017 vn 2017 ilbson 2015 ialagatla 2018 eah 2017	5.6666667 4.666667 4.3 = 0.02; Chi2 = ct: Z = 0.36 (P	3.80111337 0.86 2.2647 5.5.31, df = 5 = 0.72) intensified 5.0 7.9 5.46811 5.079121 2.8 12.17765		5.6130268 5 $38); l^2 = 6\%$ Stanc Mean $6.375 9.4$ $2.33333 2.8$ $2.00667 3.3$ 4 $3.33 4.0$	3.3496463 1.55684 2.7 4ard 5D Tot 431579 = 344876 = 303059 = 3.1 = 24433 = 2024433 =	87 30 89 294 37 16 1 35 1 32 3 30	12.4% 28.5% 20.6% 100.0% M sight IV, 7.7% – 5.6% 8.9% 2.3% 3 2.8% –2	ean Difference Random, 95% Cl 0.47 (-4.38 to 3.43) 0.77 (-4.38 to 3.43) 0.75 (-2.21 to 1.62) 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) 0.77 (-3.86 to -0.28)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 ihah 2018 Total (95% CI) deterogeneity: Tau ² est for overall effect Disease dun tudy or Subgroup N Khoury 2017 Nn 2017 Sibson 2015 sialagatta 2018 ieah 2017 ihah 2018	5.6666667 4.666667 4.3 = 0.02; Chi2 = ct: Z = 0.36 (P	3.80111337 0.86 2.2647 5.5.31, df = 5 = 0.72) intensified 5.0 7.9 5.46811 5.079121 2.8 12.17765		5.6130268 5 $38); l^2 = 6\%$ Stanc Mean $6.375 9.4$ $2.33333 2.8$ $2.00667 3.3$ 4 $3.33 4.0$	3.3496463 1.55684 2.7 431579 3 344876 3 303059 3 3.1 1 303059 3 3.1 1 3.1 1 3.	87 30 89 294 37 16 1 35 1 32 3 30	12.4% 28.5% 20.6% 100.0% M sight IV, 7.7% – 5.6% 8.9% 2.3% 3 2.8% –2	ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.77 (-2.29 to 2.63) 0.77 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) 1.84 (-3.85 to 11.52)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect Disease dun tudy or Subgroup I Khoury 2017 vn 2017 iibson 2015 lalagatla 2018 eah 2017 hah 2018 'otal (95% CI)	5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose Mean 5.9 2.5 2.76 4.6 7.166667 3.3297	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) intensified <u>5.46811</u> 5.46811 5.079121 2.8 12.17765 3.5735	7 58 6 10 7 37 188 6 (P = 0. 7 7 7 18 8 1 1 9 11 1 111 1	5.6130268 5 $38); l^2 = 6\%$ Stanc Mean $6.375 \ 9.4$ $2.33333 \ 2.8$ $2.006667 \ 3.8$ 4 $3.33 \ 4.6$ 5.4	3.3496463 1.55684 2.7 4ard 5D Tot 334876 3.1 13 303059 3.1 13 3024433 6.6 8 33	87 30 89 294 37 16 1 35 1 35 1 32 3 30 89 2	12.4% 28.5% 20.6% 100.0% M sight IV, 7.7% – 5.6% 8.9% 2.3% 3 2.8% –2	ean Difference Random, 95% Cl 0.47 (-4.38 to 3.43) 0.77 (-4.38 to 3.43) 0.75 (-2.21 to 1.62) 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) 0.77 (-3.86 to -0.28)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% Cl) leterogeneity: Tau ² est for overall effect Disease duu tudy or Subgroup I Khoury 2017 iibson 2015 lalagatla 2018 eah 2017 hah 2018 'otal (95% Cl) leterogeneity: Tau ¹	$5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose (P 2.5 2.76 4.6 7.166667 3.3297 ^{2} = 0.77; Chi2$	3.8011133 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df =	7 58 6 10 7 37 188 6 (P = 0. 7 7 7 18 8 7 7 18 8 1 9 9 11 1	5.6130268 5 $38); l^2 = 6\%$ Stanc Mean $6.375 \ 9.4$ $2.33333 \ 2.8$ $2.006667 \ 3.8$ 4 $3.33 \ 4.6$ 5.4	3.3496463 1.55684 2.7 4ard 5D Tot 334876 3.1 13 303059 3.1 13 3024433 6.6 8 33	87 30 89 294 37 16 1 35 1 35 1 32 3 30 89 2	12.4% 28.5% 20.6% 100.0% M sight IV, 7.7% – 5.6% 8.9% 2.3% 3 2.8% –2	ean Difference Random, 95% Cl 0.47 (-4.38 to 3.43) 0.77 (-4.38 to 3.43) 0.75 (-2.21 to 1.62) 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) 0.77 (-3.86 to -0.28)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% Cl) leterogeneity: Tau ² est for overall effect Disease duu tudy or Subgroup I Khoury 2017 iibson 2015 lalagatla 2018 eah 2017 hah 2018 'otal (95% Cl) leterogeneity: Tau ¹	$5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose (P 2.5 2.76 4.6 7.166667 3.3297 ^{2} = 0.77; Chi2$	3.8011133 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df =	7 58 6 10 7 37 188 6 (P = 0. 7 7 7 18 8 7 7 18 8 1 9 9 11 1	5.6130268 5 $38); l^2 = 6\%$ Stanc Mean $6.375 \ 9.4$ $2.33333 \ 2.8$ $2.006667 \ 3.8$ 4 $3.33 \ 4.6$ 5.4	3.3496463 1.55684 2.7 4ard 5D Tot 334876 3.1 13 303059 3.1 13 3024433 6.6 8 33	87 30 89 294 37 16 1 35 1 35 1 32 3 30 89 2	12.4% 28.5% 20.6% 100.0% M sight IV, 7.7% – 5.6% 8.9% 2.3% 3 2.8% –2	ean Difference Random, 95% Cl 0.47 (-4.38 to 3.43) 0.77 (-4.38 to 3.43) 0.75 (-2.21 to 1.62) 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) 0.77 (-3.86 to -0.28)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease dun</u> <u>tudy or Subgroup</u> I Khoury 2017 vn 2017 jibson 2015 lalagatla 2018 eah 2018 'otal (95% CI) leterogeneity: Tau' est for overall effe	$5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose (P 2.5 2.76 4.6 7.166667 3.3297 ^{2} = 0.77; Chi2$	3.8011133 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df =	7 58 6 10 7 37 188 6 (P = 0. 7 7 7 18 8 7 7 18 8 1 9 9 11 1	5.6130268 5 $38); l^2 = 6\%$ Stanc Mean $6.375 \ 9.4$ $2.33333 \ 2.8$ $2.006667 \ 3.8$ 4 $3.33 \ 4.6$ 5.4	3.3496463 1.55684 2.7 4ard 5D Tot 334876 3.1 13 303059 3.1 13 3024433 6.6 8 33	87 30 89 294 37 16 1 35 1 35 1 32 3 30 89 2	12.4% 28.5% 20.6% 100.0% M sight IV, 7.7% – 5.6% 8.9% 2.3% 3 2.8% –2	ean Difference Random, 95% Cl 0.47 (-4.38 to 3.43) 0.77 (-4.38 to 3.43) 0.75 (-2.21 to 1.62) 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) 0.77 (-3.86 to -0.28)	Favors Standard Favours Dose intensified
iibson 2018 eah 2017 hah 2018 'otal (95% Cl) leterogeneity: Tau ² rest for overall effect <u>Disease dun</u> <u>tudy or Subgroup</u> I Khoury 2017 un 2017 bibson 2015 lalagatla 2018 eah 2017 hah 2018 'otal (95% Cl) leterogeneity: Tau ¹	$5.6666667 \\ 4.666667 \\ 4.3 \\ = 0.02; Chi2 = 0.36 (P \\ critical Z = 0.36 (P \\ critical Z$	3.8011133 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df = P = 0.91)	7 58 6 10 7 37 188 6 (P = 0. 7 7 7 18 8 7 7 18 8 1 9 9 11 1	$5.6130268 \\ 5 \\ 4 \\ 38); l^2 = 6\% $ $6.375 9.4 \\ 2.33333 2.6 \\ 2.00667 3.4 \\ 3.33 4.6 \\ 5.4 \\ 0.114); l^2 = 39$	3.3496463 1.55684 2.7 SD Tot 344876 3311 12 224433 6.6 8 33 33 33 33 34 33 33 33 33 33	87 30 89 294 37 16 1 35 1 35 1 32 3 30 89 2	12.4% 28.5% 20.6% 100.0% M sight IV, 7.7% – 5.6% 8.9% 2.3% 3 2.8% –2	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) ean Difference Random, 95% Cl 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) .07 (-1.25 to 1.12) 	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified
iibson 2018 eah 2017 ihah 2018 Total (95% CI) deterogeneity: Tau ² est for overall effect <u>Disease dun</u> <u>Study or Subgroup</u> N Khoury 2017 Nn 2017 Sibson 2015 Valagatla 2018 ieah 2017 ihah 2018 Total (95% CI) deterogeneity: Tau ² rest for overall effect	$5.6666667 \\ 4.66667 \\ 4.3 \\ = 0.02; Chi2 = \\ t: Z = 0.36 (P \\ cation \\ b \\ cation \\ catio$	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df = P = 0.91)	7 58 5 10 7 37 188 ((P = 0.) Total 40 28 15 1 81 10 37 211 5 (P =	$5.6130268 \\ 5 \\ 4 \\ 38); l^2 = 6\%$ $\frac{5}{38}; l^2 = 6\%$ $\frac{6.375 \ 9.2}{2.33333} \ 2.6 \\ 2.33333 \ 2.6 \\ 2.33333 \ 2.6 \\ 3.33 \ 4.0 \\ 5.4 \\ 0.14); l^2 = 39$	3.3496463 1.55684 2.7 4.31579 3.44876 3.1 3.31579 3.44876 3.1 3.31579 3.44876 3.31 3.31 3.3 3.3 3.3 3.3 3.3 3	87 30 89 294 37 16 1 35 1 32 3 39 2 39 10	12.4% 28.5% 20.6% 100.0% M eight IV, 7.7% - 5.6% 2.6% 2.3% 3 2.8% -2 0.0% -4	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) .07 (-3.86 to -0.28) 0.07 (-1.25 to 1.12) Mean Difference	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease dun</u> tudy or Subgroup I Khoury 2017 in 2017 ibson 2015 lalagatla 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau' 'est for overall effect <u>Age</u> tudy or Subgroup	$5.6666667 \\ 4.666667 \\ 4.3 \\ = 0.02; Chi2 = 0.36 (P \\ critical Z = 0.36 (P \\ critical Z$	3.80111337 0.86 2.2647 5.5.31, df = 5 = 0.72) Intensified 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df = P = 0.91) Intensified SD	7 58 5 10 7 37 188 ((P = 0.) Total 40 28 15 1 81 10 37 211 5 (P =	$5.6130268 \\ 5 \\ 4 \\ 38); l^2 = 6\% $ $6.375 9.4 \\ 2.33333 2.6 \\ 2.00667 3.4 \\ 3.33 4.6 \\ 5.4 \\ 0.114); l^2 = 39$	3.3496463 1.55684 2.7 4ard 31579 344876 334876 3.1 224433 6.6 8 33 % 33 33 33 34 33 33 33 33 33 33	87 30 89 294 37 35 135 135 30 30 39 2 39 10 39 10 7 7 0 7 7 0 7 7 7 7 7 7 7 7 7 7 7 7	12.4% 28.5% 20.6% 100.0% [±] ight IV, 7.7% - 5.6% 2.6% - 2.6% 2.3% 3 2.8% -2 0.0% -4	0.05 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) 1.84 (-3.85 to 11.52) .07 (-3.86 to -0.28) 0.07 (-1.25 to 1.12) Mean Difference t IV, Random, 95% CI	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease dun</u> tudy or Subgroup I Khoury 2017 in 2017 ibson 2015 lalagatla 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau' 'est for overall effect <u>Age</u> tudy or Subgroup	$5.6666667 \\ 4.66667 \\ 4.3 \\ = 0.02; Chi2 = \\ t: Z = 0.36 (P \\ cation \\ b \\ cation \\ catio$	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>SD</u> 7.9 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df = P = 0.91)	7 58 5 10 7 37 188 ((P = 0.) Total 40 28 15 1 81 10 37 211 5 (P =	$5.6130268 \\ 5 \\ 4 \\ 38); l^2 = 6\%$ $\frac{5}{38}; l^2 = 6\%$ $\frac{6.375 \ 9.2}{2.33333} \ 2.6 \\ 2.33333 \ 2.6 \\ 2.33333 \ 2.6 \\ 3.33 \ 4.0 \\ 5.4 \\ 0.14); l^2 = 39$	3.3496463 1.55684 2.7 4.31579 3.44876 3.1 3.31579 3.44876 3.1 3.31579 3.44876 3.31 3.31 3.3 3.3 3.3 3.3 3.3 3	87 30 89 294 37 35 135 135 30 30 39 2 39 10 39 10 7 7 0 7 7 0 7 7 7 7 7 7 7 7 7 7 7 7	12.4% 28.5% 20.6% 100.0% ^{kight} IV, 7.7% - 5.6% 2.6% 2.6% 2.3% 3 2.8% -2 0.0% -4 1 Weigh	0.05 (-1.15 to 1.26) -0.33 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) ean Difference Random, 95% CI -0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) .07 (-3.86 to -0.28) 0.07 (-1.25 to 1.12) Mean Difference t IV, Random, 95% CI 6 -1.16 (-8.58 to 6.25)	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference
iibson 2018 eah 2017 hah 2018 fotal (95% CI) leterogeneity: Tau ² est for overall effect Disease duu M Khoury 2017 An 2017 Jibson 2015 Jalagatla 2018 iceah 2017 Jibson 2015 Idalagatla 2018 Fotal (95% CI) leterogeneity: Tau ² est for overall effect	$5.6666667 4.666667 4.3 = 0.02; Chi2 = t: Z = 0.36 (P ration Dose Mean 5.9 2.5 2.76 4.6 7.166667 3.3297 ^{2} = 0.77; Chi2ct: Z = 0.11 (PDose MeanCt: Z = 0.11 (PCt: Z = 0.11 (P$	3.80111337 0.86 2.2647 5.5.31, df = 5 = 0.72) Intensified 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df = P = 0.91) Intensified SD	 5 10 37 188 40 28 15 211 5 (P = Total 	5.6130268 5 $38); l^2 = 6\%$ $Mean$ $6.375 9.4$ $2.33333 2.8$ $2.006667 3.8$ 4 $3.33 4.6$ $0.14); l^2 = 39$ $Steady = 39$	3.3496463 1.55684 2.7 4ard 31579 3 344876 1 303059 3 3.1 13 024433 3 6.6 8 33 % 33 %	87 30 30 89 294 30 30 30 31 33 32 33 39 2 30 30 39 2 39 10 39 10 30 30 30 <t< td=""><td>12.4% 28.5% 20.6% 100.0% M eight 1V, 7.7% − 5.6% 2.3% 3 2.8% −2 0.0% −4 100.0%</td><td>0.05 (-1.15 to 1.26) -0.33 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) .07 (-1.25 to 1.12) Mean Difference t IV, Random, 95% CI 6 -1.16 (-8.58 to 6.25)</td><td>Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference</td></t<>	12.4% 28.5% 20.6% 100.0% M eight 1V, 7.7% − 5.6% 2.3% 3 2.8% −2 0.0% −4 100.0%	0.05 (-1.15 to 1.26) -0.33 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) ean Difference Random, 95% CI 0.47 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) .07 (-1.25 to 1.12) Mean Difference t IV, Random, 95% CI 6 -1.16 (-8.58 to 6.25)	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference
iibson 2018 eah 2017 ihah 2018 Total (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease duu</u> <u>itudy or Subgroup</u> N Khoury 2017 ibson 2015 Jalagatla 2018 icah 2018 Total (95% CI) leterogeneity: Tau ² est for overall effect <u>Age</u> <u>itudy or Subgroup</u> N Khoury 2017	$5.6666667 \\ 4.666667 \\ 4.3 \\ = 0.02; Chi2 = 0.36 (P \\ ration \\ \hline max \\ ration \\ \hline max \\ ration \\ ration \\ ration \\ ratio \\$	3.8011133 0.86 2.2647 5.31, df = 5 = 0.72) Intensified 5.079121 2.8 12.17765 3.5735 = 8.24, df = P = 0.91) Intensified SD 15.9 15.9	$\begin{array}{c} & 58\\ 5 & 10\\ 7 & 37\\ \hline & 188\\ (P = 0. \\ \hline & 10\\ 28\\ 15\\ 10\\ 37\\ \hline & 81\\ 10\\ 37\\ \hline & 81\\ 10\\ 37\\ \hline & 81\\ 5 (P = \\ \hline & 10\\ \hline & 10\\ 37\\ \hline & 211\\ \hline & 10\\ \hline & 37\\ \hline & 211\\ \hline & 10\\ \hline & 37\\ \hline & 211\\ \hline & 10\\ \hline & 37\\ \hline & 211\\ \hline & 10\\ \hline & 37\\ \hline & 211\\ \hline & 10\\ \hline & 37\\ \hline & 211\\ \hline & 10\\ \hline & 37\\ \hline & 211\\ \hline & 10\\ \hline & 37\\ \hline & 211\\ \hline & 10\\ \hline & 28\\ \hline & 20\\ \hline$	$5.6130268 \\ 5 \\ 4 \\ 38); l^2 = 6\% $ $\frac{Mean}{6.375 9.4} \\ 2.33333 2.6 \\ 4 \\ 3.33 4.6 \\ 5.4 \\ 0.14); l^2 = 39 $ $\frac{St}{Mean} $ 41.2	3.3496463 1.55684 2.7 1.55684 2.7 1.55684 2.7 1.55684 1.55684 3.1 1.55684 3.1 1.5 3.44876 3.3 3.1 1.5 3.44833 3.3 3.1 1.5 3.44833 3.3 3.3 3.3 3.3 3.3 3.3 3.3	87 30 89 294 201 201 37 1 37 1 37 1 37 1 37 30 37 1 38 2 39 2 39 2 39 10 2 36 2 10	12.4% 28.5% 20.6% 100.0% M eight IV, 7.7% - 5.6% 2.6% 2.6% 3.2% 2.3% 3 2.8% -2 0.0% -4 M 1.0000 1.0000 1.0000 1.0000 1.0000 1.000 1.000 1.000 1.00	0.05 (-1.15 to 1.26) -0.33 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.07 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) .84 (-3.85 to 11.52) .07 (-3.86 to -0.28) 0.07 (-1.25 to 1.12) 	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference
iibson 2018 eah 2017 ihah 2018 Total (95% CI) deterogeneity: Tau ² est for overall effect <u>Disease dun</u> itudy or Subgroup N Khoury 2017 ibson 2015 idalagatla 2018 ieah 2017 ihah 2018 Total (95% CI) deterogeneity: Tau ² rest for overall effect <u>Age</u> itudy or Subgroup N Khoury 2017	$5.6666667 \\ 4.666667 \\ 4.3$ = 0.02; Chi ² = t: Z = 0.36 (P ration Dose 1 Mean 5.9 2.5 2.76 4.6 7.166667 3.3297 2 = 0.77; Chi ² ct: Z = 0.11 (P <u>Mean</u> 40.0375 35.08333 41	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>50</u> 7.9 5.46811 2.8 12.17765 3.5735 = 8.24, df = $^{2} = 0.91)$ Intensified <u>50</u> 15.9 15.9962	$\begin{array}{c} & 58\\ 5 & 10\\ 7 & 37\\ \hline & 188\\ (P = 0.\\ \hline & 10\\ 28\\ 10\\ 37\\ \hline & 81\\ 10\\ 37\\ \hline & 81\\ 10\\ 37\\ \hline & 81\\ 5 (P = \\ \hline & 10\\ \hline & 10\\ 37\\ \hline & 211\\ \hline $	5.6130268 $5 - 4$ $38); l^2 = 6\%$ $Mean$ $6.375 9.4$ $2.33333 2.8$ $2.006667 3.8$ 4 $3.33 4.0$ 5.4 $0.14); l^2 = 39$ 51 $Mean$ 41.2 33 35	3.3496463 1.55684 2.7 4.31579 3.44876 3.31579 3.44876 3.3.1 3.31579 3.44876 3.3.1 3.31579 3.44876 3.31 3.315797 3.3157977777777777777777777777777777777777	87 30 89 294 294 294 37 36 37 33 33 33 33 33 33 33 33 33 39 10 37 33 39 10 32 33 33 33 33 30 2 33 33 39 10 32 33 30 2 3	12.4% 28.5% 20.6% 100.0% ^m ^m ^m ^m ^m ^m ^m ^m	0.05 (-1.15 to 1.26) -0.33 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.07 (-0.51 to 0.36) -0.07 (-0.51 to 0.36) -0.07 (-0.21 to 1.41) -0.06 (-0.21 to 1.41) -0.06 (-0.21 to 1.41) -0.07 (-1.25 to 1.12) 	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference
iibson 2018 eah 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ² est for overall effect <u>Disease duu</u> <u>itudy or Subgroup</u> Il Khoury 2017 hah 2018 'otal (95% CI) leterogeneity: Tau ¹ est for overall effect <u>Age</u> <u>tudy or Subgroup</u> Il Khoury 2017 in 2017 iibson 2015 iibson 2015	$5.6666667 \\ 4.666667 \\ 4.3 \\ = 0.02; Chi2 = 0.36 (P \\ ct: Z = 0.75; Chi2 \\ 4.6 \\ 7.166667 \\ 3.3297 \\ ct: Z = 0.77; Chi2 \\ ct: Z = 0.77; Chi2 \\ ct: Z = 0.11 (P \\ ct:$	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) Intensified 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df = 2 = 0.91) Intensified <u>SD</u> 15.9 16.59962 18.81156	$\begin{array}{c} & 58\\ 5 & 10\\ 5 & 10\\ 7 & 37\\ \hline & 188\\ (P=0.\\ \hline & 188\\ (P=0.\\ \hline & 188\\ (P=0.\\ \hline & 188\\ 15\\ 10\\ 37\\ 211\\ 5 & (P=\\ \hline & 10\\ 28\\ 15\\ 5 & 8\\ 15\\ 5 & 8\\ 15\\ 5 & 8\\ 15\\ 5 & 8\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10$	5.6130268 5 $38); l^2 = 6\%$ Stanc Mean 6.375 9.4 2.33333 2.6 4 3.33 4.0 5.4 $0.14); l^2 = 39$ St Mean 41.2 33 35 38.5095787	3.3496463 1.55684 2.7 1.55684 2.7 1.55684 1.55684 1.55684 1.55684 1.55684 3.1 1.59463 3.1 1.585002 1.585002 1.59466 1.52179566	87 30 89 294 294 30 30 30 31 31 35 11 32 33 30 33 30 33 30 33 30 33 30 33 30 33 30 33 30 33 30 33 30 30 33 30 33 30 30 33 30 33 30 33 30	12.4% 28.5% 20.6% 100.0% ⁴ ⁴ ⁴ ⁴ ⁴ ⁴ ⁴ ⁴	0.05 (-1.15 to 1.26) -0.33 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.07 (-0.51 to 0.36) -0.07 (-0.51 to 0.36) -0.07 (-1.25 to 1.2) -0.07 (-1.25 to 1.12) -0.07 (-1.25 to 1.12) -0.07 (-1.16 (-8.58 to 6.25) % -0.08 (-7.82 to 1.99) % -0.01 (-4.27 to 16.27)	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference
iibson 2018 eah 2017 ihah 2018 Total (95% CI) teterogeneity: Tau ² test for overall effect <u>Disease dun</u> itudy or Subgroup V Khoury 2017 vn 2017 Gibson 2015 Valagatla 2018 ieah 2017 ihah 2018 Total (95% CI) teterogeneity: Tau ² test for overall effect <u>Age</u> itudy or Subgroup V Khoury 2017 vn 2017 ibson 2015	$5.6666667 \\ 4.66667 \\ 4.3 \\ = 0.02; Chi2 = ct: Z = 0.36 (P) \\ ctime = $	3.80111337 0.86 2.2647 5.31, df = 5 = 0.72) Intensified <u>50</u> 7.9 5.46811 5.079121 2.8 12.17765 3.5735 = 8.24, df = $^{2} = 0.91$) Intensified <u>50</u> 15.9962 18.81156 15.99642761 13.84606	$\begin{array}{c} 7 & 58 \\ 5 & 10 \\ 7 & 37 \\ 188 \\ (P = 0. \\ 7 \\ 10 \\ 28 \\ 10 \\ 37 \\ 211 \\ 5 & (P = \\ 7 \\ 7 \\ 10 \\ 37 \\ 211 \\ 5 \\ 5 \\ 8 \\ 10 \\ 28 \\ 15 \\ 5 \\ 5 \\ 8 \\ 10 \\ $	5.6130268 $5 - 4$ $38); l^2 = 6\%$ $Mean$ $6.375 9.4$ $2.33333 2.8$ $2.006667 3.8$ 4 $3.33 4.0$ 5.4 $0.14); l^2 = 39$ 51 $Mean$ 41.2 33 35	3.3496463 1.55684 2.7 4.31579 3.44876 3.3 3.1 2.24433 6.6 8 3.3 % 5.85002 11.59456 13.85588	87 30 89 294 294 30 30 37 16 1 32 3 30 2 33 30 2 33 30 2 33 30 2 33 30 2 33 30 2 33 30 2 33 30 2 31 32 31 31 32 31	12.4% 28.5% 20.6% 100.0% M eight IV, 7.7% - 5.6% 8.9% 2.3% 3 2.8% -2 0.0% -4 1 0.0% -4	0.05 (-1.15 to 1.26) -0.33 (-1.15 to 1.26) -0.33 (-1.10 to 0.44) 0.30 (-0.62 to 1.22) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.08 (-0.51 to 0.36) -0.07 (-4.38 to 3.43) 0.17 (-2.29 to 2.63) 0.75 (-2.11 to 3.62) 0.60 (-0.21 to 1.41) 84 (-3.85 to 11.52) .07 (-3.86 to -0.28) 0.07 (-1.25 to 1.12) 	Favors Standard Favours Dose intensified Mean Difference IV, Random, 95% CI -10 -5 Favors Standard Favours Dose Intensified Mean Difference Mean Difference
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FIGURE 4. Forest plot using random-effects model to assess mean differences in covariates between dose-intensified and 5-mg/kg standard-schedule cohorts.

failure. Among all pooled studies, the I^2 test was 67.0%–77.0%, indicating a high proportion of variation across studies due to heterogeneity rather than chance. This was subsequently

investigated with subgroup analyses of different IFX strategies. There was no significant publication bias (3 month outcomes: Egger's intercept = 0.26; P = 0.74). In the comparative cohort

meta-analysis: 5-mg/kg single-dose vs 5-mg/kg multiple-dose induction comparisons; there was a low level of heterogeneity between the 5 studies at 3 months ($I^2 = 0.0\%$). Among dose-intensified vs standard induction comparisons, the I^2 test was 48%, indicating a moderate amount of heterogeneity.

DISCUSSION

In this systematic review and meta-analysis, we summarize the published experience of IFX induction and CFS in ASUC under different induction strategies. Despite being used for more than 15 years, the optimal IFX dose strategy in ASUC is unknown, due to the infrequency of this life-threatening condition and the difficulty of performing well-constructed RCTs. IFX salvage in ASUC has evolved from 5-mg/kg single-dose induction to high-dose and short-interval therapy based on studies with vastly different clinical settings and clinician experiences. Apart from a single RCT by Sands and colleagues exploring different IFX doses in ASUC that was terminated due to slow recruitment,48 no published RCTs have investigated dose induction strategies in ASUC. The lack of strong evidence guiding the optimal use of IFX in ASUC has consequently led to marked variability in clinical management.

In this study, 5-mg/kg multiple-dose IFX induction was superior to 5-mg/kg single-dose rescue therapy for CFS at 3 months. This supports current consensus statements on multiple IFX 5-mg/kg salvage therapy dosing in ASUC⁶³ and provides evidence to avoid the use of 5-mg/kg single-dose induction, which was proposed in older guidelines⁶⁴. 5-mg/kg multiple-dose induction CFS was favored at 1 and 12 months; however, efficacy at these time points did not reach statistical significance, likely due to the small number of studies that have compared these strategies over time.

Contrary to current trends in clinical practice, dose intensification to 10 mg/kg or dose acceleration with 5 mg/kg was not associated with improved outcomes over 5-mg/kg standard-dose induction. However, we found that dose-intensified strategies were used in patient groups with an overall higher CRP and lower albumin, biochemical profiles indicating greater disease severity and associated with an increased likelihood of colectomy. Although these biochemical differences should be interpreted with caution due to the risk of aggregation bias of mean data, this may mask the true benefit of dose intensification and its potential effect of attenuating the rate of colectomy in high-risk patients. This indicates the need for clinical trials to control for these parameters of disease severity in the future.

Although a recent meta-analysis by Nalagatla and colleagues⁵⁸ also concluded no difference between dose-intensified and standard induction, our systematic review has, for the first time, quantified the differences in existing cohort severity with respect to CRP and albumin, includes a larger cohort, and demonstrates the poor quality of current source data. Although we recognize that performing a meta-analysis with these available studies of variable quality may be controversial, our paper draws together the currently available evidence and highlights that the optimal dosing regimen for infliximab salvage therapy for ASUC remains unclear. It is also important to note that these findings may be confounded by patient selection and provider bias with respect to how dose intensification strategies were adopted in the included observational cohorts.

The basis on which to apply IFX dose intensification is unknown. Elevated CRP,65 low albumin, antidrug antibodies, and increased body mass index⁶⁶ are factors that have been associated with increased IFX drug clearance. Although increased IFX drug clearance and a reduced serum half-life have recently been shown to be associated with therapeutic failure in ASUC, it is unclear if dose intensification in this circumstance will improve therapeutic success.⁶⁷ Higher IFX drug exposure in the ASUC induction phase has not presently been shown to be associated with treatment success,^{67, 68} with 1 study in fact finding that lower IFX drug exposure within the first week in ASUC was associated with clinical response.⁶⁹ Although this counterintuitive finding may be explained by responders needing less drug overall, there are likely to be differences in the pharmacodynamic and immunological effects of IFX in individuals that may not be explained by pharmacokinetics alone. Hence, as clinicians increasingly turn to dose escalation, timely clinical assessment of response to rescue therapy is imperative. Although signals exist and algorithms have been proposed regarding dose escalation of IFX based on baseline biochemical profiles^{70, 71} or CRP and albumin response after induction,^{13, 72} they have either not been validated or not been shown to improve outcomes.14

Emergent colectomy is associated with a significantly higher mortality rate in comparison with elective surgical management.⁷³ Although perioperative IFX therapy was not shown to increase UC surgical complications in a recent meta-analysis,⁷⁴ the impact of high-dose therapy is unknown. Decisions regarding dose-escalated salvage therapy vs colectomy in ASUC require careful consideration, particularly with regard to adverse events associated with intensive immunosuppression vs the risk of postoperative complications. Failure to make appropriate decisions on treatment futility and delayed surgical intervention can lead to increased morbidity, mortality, and health care costs.⁷⁵ Although the overall pooled mortality rate of 1% in our present study is in line with published data,³ the studies examined in this analysis did not provide sufficient information to robustly ascertain complication or mortality rates of dose intensification vs standard induction. Although dose intensification in outpatient UC has not been associated with increased complications,⁵ it is important that future studies assess adverse events and postoperative complications carefully in ASUC.

There were several limitations of our meta-analysis. Of all the eligible studies, only 11 assessed outcomes prospectively. Infliximab levels were not reported in these cohorts, which represents an important potential confounder of the analysis. Although 2 cohorts^{11, 58} were analyzed by propensity scoring methodology to adjust for increased biochemical severity in the dose-intensified cohort compared with standard-dose patients, no differences in colectomy rate were observed between dose-intensified and standard-dose induction with matched and unmatched cohorts; hence, unadjusted data were utilized for the analysis. Accelerated induction and high-dose induction were grouped as a single category, owing to the limited number of studies. Additionally, 2 studies by Gibson and colleagues^{10, 56} may have included patients who overlapped between the cohorts; however, we were unable to obtain this information from the authors. As this likely affected <10% of the Gibson cohort, the studies were included; exclusion of either study did not affect the meta-analysis findings. A high degree of heterogeneity, as measured by the I^2 test, also relates to how the use of IFX has evolved over time. Although we assessed for baseline covariates, we were unable to control for all potential confounding factors due to variable study quality and data.

Though this analysis only included hospitalized, steroid-refractory UC, the definition of UC severity and steroid failure was variable and may have resulted in clinical heterogeneity between studies. Clinical response and remission were not examined in this study, given the variable definition of these clinical entities and lack of reporting. Although we attempted to address potential outcome bias for those treated with a single dose of IFX by applying an ITT analysis, the outcomes of single-dose induction may have been adversely impacted, as those who proceeded to colectomy may not have had an opportunity to receive more than 1 dose. Maintenance therapy was also variable between the cohorts and may have affected long-term colectomy rates. Despite these limitations, these data provide confident estimates of CFS with IFX salvage therapy under different strategies in real-world practice.

This meta-analysis highlights the challenges associated with performing controlled trials in ASUC. In particular, the variance in clinical practice and IFX induction permutations presented here underscore the complexity of interpreting data in this setting. Given that placebo-controlled trials of IFX are no longer ethically feasible when exploring optimal IFX dose induction, it is likely that future trials of IFX will require an active control. Although standard-schedule arms may be utilized as comparators to dose-intensified strategies, current practice in patients who are not responding to a first dose is generally to dose-escalate, rather than proceed directly to colectomy. This calls into question whether trials in ASUC should use colectomy as a primary end point, or instead, utilize clinical response or need for further rescue dosing as a pragmatic outcome. Estimates of colectomy rate in this study with standard-schedule dose induction may therefore serve as a useful historical comparator for future studies.

In conclusion, IFX 5-mg/kg multiple-dose induction is effective as medical salvage therapy for ASUC. Although our data do not presently demonstrate the superiority of dose intensification over standard induction, it remains to be seen whether a dose-intensified strategy can further reduce the risk of colectomy when applied uniformly to all patients. However, this approach risks overtreating patients who are destined for a favorable outcome at the expense of increased costs and potential morbidity. Prospective RCTs comparing dose-intensified with standard-dose therapy in ASUC are both planned⁷¹ and underway (PREDICT UC; Clinicaltrials.gov: NCT02770040), which may provide more clarity, allow the generation of precise risk profiles, and facilitate prediction of outcome for patients who present with this highly challenging clinical condition.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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