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TITLE

Systematic Review and Meta-analysis: Optimal salvage therapy in Acute Severe Ulcerative Colitis

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ABBREVIATIONS

ASUC, Acute Severe Ulcerative Colitis; CFS, Colectomy Free Survival; CI, Confidence Interval; CRP, C-reactive protein; DI, Dose Intensified; IFX, Infliximab; ITT, Intention to treat; Medical Subject Headings (MeSH); OR, Odds Ratio; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RCT, Randomized Controlled Trial; SCCAI, Simple Clinical Colitis Activity Index); SD, standard deviation; SI, Standard induction; TLW, Truelove and Witt's.

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CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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ABSTRACT

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

41 cohorts (n=2158 cases) were included. Overall colectomy-free survival with infliximab salvage was 79.7% (95%CI 75.48-83.6%) at 3 months and 69.8% (95%CI 65.7-73.7%) at 12 months. Colectomy-free survival at 3 months was superior with 5mg/kg multiple (≥2) doses compared to single dose induction (OR 4.24 (95% CI 2.44-7.36, p<0.001)). However, dose-intensification with either high-dose or accelerated strategies was not significantly different to 5mg/kg standard induction at 3 months (OR 0.70 (95% CI 0.39-1.27, 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 5mg/kg infliximab doses are superior to single dose salvage. Dose-intensified induction outcomes were not significantly different to standard induction and were more often used in patients with increased disease severity which may have confounded the results. This meta-analysis highlights marked variability in the management of infliximab salvage therapy and need for further studies to determine the optimal dose strategy.

KEYWORDS

Acute severe ulcerative colitis, Infliximab, Colectomy

INTRODUCTION

Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition which has historically resulted in emergency colectomy in 30% of patients within 3 months of presentation.(1) Twenty-five per cent of patients with ulcerative colitis develop ASUC during their disease course and 15% have two or more episodes.(2) Corticosteroids represent first-line 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 ASUC in randomized controlled trials (RCT); however, non-randomized 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 three doses at 5mg/kg given at weeks 0, 2 and 6, has been derived from studies in Crohn's disease and moderate-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 loss(8), 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 schedules(9) 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 two investigators (MCC, DS) 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 keywords 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 in order to identify additional studies for inclusion. Relevant abstracts from BSG/DDW/ECCO/UEGW from the year 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: (i) observational or interventional design; (ii) patients were hospitalized or had acute severe flares of UC, refractory to oral or intravenous (IV) corticosteroids; and (iii) treatment with IFX as rescue therapy was given. Furthermore, in order 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 (e.g. 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 within the last four years (prior to 2014) were excluded.

Outcomes of interest

The primary outcome was CFS at 3 months following 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 (5mg/kg or 10mg/kg), dose number (single or multiple dose induction) and dose schedule. Dose schedule was defined as follows: a) standard schedule induction - three IFX doses at weeks 0, 2 and 6; b) accelerated schedule induction - three doses within 4 weeks; c) dose intensified induction - use of either multiple 10mg/kg doses or an accelerated schedule with 5mg/kg (incorporating (b)). 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 two reviewers independently (MCC, DS). 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 two reviewers (MCC, DS) and any discrepancies were resolved in consultation with senior authors. Quality of 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). Quality of non-randomized studies was assessed with the Newcastle Ottawa Scale.(16) 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 (CI) 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 (OR).

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 ± standard deviation (SD). Reported medians and interquartile ranges or ranges were converted to means and SD 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) to derive pooled proportions and RevMan 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to determine ORs in comparative studies and mean covariate differences. A two-tailed P value <0.05 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% as 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 (Figure 1), of which 105 met the criteria for full text review. A total of 62 studies were subsequently excluded (Figure 1) - 12 were in non-ASUC cohorts; five reported on already included cohorts; one examined primary non-responders to IFX; one investigated IFX maintenance therapy; and one investigated the post-operative setting. Three studies were excluded due to co-morbid CMV colitis. There was insufficient information regarding IFX dosing and/or timing of administration in ten 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 four studies were not available. One abstract was not published as full text within four years and one 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 similarly, 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 five RCTs, 30 retrospective and six prospective observational cohorts. Study characteristics and considerations for analysis are outlined in Table 1. Of the five RCT populations, three reported on IFX versus placebo (28, 33, 48) and two reported on IFX versus cyclosporine.(37, 38, 54) Only the IFX treated arms from these RCTs were extracted for this review. Additional data were obtained from twelve 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 eleven studies,(10-12, 14, 20, 22, 32, 49, 56-58) Of these, ten studies utilized an accelerated dosing schedule,(10-12, 20, 22, 32, 49, 56-58) four utilized 10mg/kg dose induction therapy(11, 12, 14, 32) and four 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 versus accelerated schedule induction.(14) However, as both arms contained patients who were treated with a combination of 5 and 10mg/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 75.5-83.6%, I2=77%, 36 studies, 1659/2129 cases) at 3 months. Pooled CFS at 1 month was 85.7% (95%CI 82.0-89.0%, I2=70.6%, 36 studies, 1550/1860 cases); and 69.8% (95%CI 65.7-73.7%, I2=67%, 33 studies, 1357/1943 cases), Figure 2) at 12 months.

Pooled CFS with 5mg/kg single dose induction was 67.3% (57.1-76.8%, I2=55.1%, 10 studies, 200/307 cases) at 3 months; 78.8% (95%CI 68.4-88.0%, I2=40.2%, 9 studies, 127/168 cases) at 1 months; and 57.0% (40.7-72.7%, I2=60.2, 6 studies, 75/127 cases) at 12 months.

Pooled CFS with 5mg/kg standard week 0, 2, and 6 induction was 84.0% (78.3-89.1%, I2=80.5%, 25 studies, 923/1152 cases) at 3 months; 89.4% (83.9-93.9%, I2=81.5%, 24 studies, 882/1038 cases) at 1 months; and 73.8% (67.9-79.4%, I2=74.6%, 24 studies, 772/1080 cases) at 12 months.

Pooled CFS with dose intensified induction was 78.5% (70.8-85.4%, I2=49.2%, 11 studies, 254/325 cases) at 3 months; 84.8% (78.0-90.6%, I^2=46.1%, 11 studies, 274/325 cases) at 1 months; and 70.1% (60.2-79.2%, I2=65.9%, 10 studies, 231/321 cases) at 12 months.

CFS proportions by IFX strategy are described in Table 2.

Comparative cohort meta-analysis

a) 5mg/kg multiple dose induction versus 5mg/kg single dose induction (Figure 3A)

Amongst comparative studies, 5mg/kg multiple dose induction was superior to 5mg/kg single dose induction with respect to CFS at 3 months (OR 4.24 (95% CI 2.44-7.36), p<0.001, I^2 = 0%, five studies).(22, 50, 51, 53, 59) Multiple dose induction was numerically superior at 1 and 12 months, but this did not reach statistical significance.

b) Dose intensified induction versus standard induction (Figure 3B)

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

c) Subanalyses

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

1. 5mg/kg standard vs 5mg/kg accelerated induction

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

2. 5mg/kg standard vs 10mg/kg standard induction dose

Two studies (169 patients)(12, 60) reported the outcomes of 5mg/kg standard vs 10mg/kg standard induction. CFS was not statistically different between the two groups at 1 month (OR 0.30 (95% CI 0.08-1.15), p=0.08, I^2 = 0%), 3 months (OR 0.37 (95% CI 0.12-1.16), p=0.09, I^2 = 0%) and 12 months (OR 0.53 (95% CI 0.19-1.45), p=0.21, I^2 = 0%), favouring 5mg/kg standard induction.

3. 5mg/kg standard induction vs 10mg/kg accelerated dose

Two studies (137 patients)(12, 60) reported the outcomes of 5mg/kg standard vs 10mg/kg accelerated induction. CFS was not statistically different between the two groups at 1 month (OR 0.27 (95% CI 0.01-13.07), p=0.51, I^2 = 74%), 3 months (OR 0.32 (95% CI 0.00-31.34), p=0.62, I^2 = 84%) and 12 months (OR 0.56 (95% CI 0.01-41.34), p=0.79, I^2 = 83%), favouring 5mg/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 versus standard induction. A meta-regression 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 CRP +14.78mg/L (7.91 to 21.65) p<0.001)) as well as lower serum albumin (mean difference -1.95g/L (-2.81 to -1.09), p<0.001)). There was no significant difference in age, disease duration or IV steroid duration between the two groups (Figure 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 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 >1,922.5 mcg/g associated with an 87% risk of colectomy in 1 year.(61) Endoscopic features were also prognostic, with presence of severe endoscopic lesions found to be associated with a higher risk of colectomy by Monterubbianesi et al. (RR = 7.0; 95%CI 1.09–44.7).(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 two studies(36, 53) with a relative risk of 5.76 (95% CI 1.54–21.62, 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 5mg/kg and 10mg/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 (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 had 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 four studies (12, 56, 57, 60). In the study by Nalagatla et al., an initial dose of 10mg/kg was selected in patients with more severe clinical, biochemical or endoscopic disease activity, and among the subgroup of patients who were dose accelerated, an upfront dose of 10mg/kg was associated with a lower risk of colectomy compared to those who first received 5mg/kg.(58)

In individual studies, the use of maintenance therapy either with IFX(43) and/or immunomodulators(28) following induction was associated with reduced colectomy compared with no maintenance (HR = 0.26; 95% CI 0.09 to 0.85; p = 0.02).(43) Subanalyses to assess the effect of maintenance therapy amongst our included cohorts was unable to be performed to due to highly variable combinations of aminosalicylates, thiopurines and infliximab (Supplementary appendix 3).

Adverse Events, Post-operative complications and Mortality

The pooled adverse drug event rate was 26.1% (344/1319) from 24 studies; the pooled post-operative 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 one study provided data on adverse drug event rates and post-operative complication rates between 5mg/kg and 10mg/kg patients.(11) The adverse drug event rate was 42.9% (48/112) in those treated with 5mg/kg induction vs 28.6% (4/14), p=0.394 in those treated with 10mg/kg. The post-operative complication rate was 78.8% (26/33) amongst those treated with 5mg/kg vs 0% (0/4) treated with 10mg/kg (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 utilising 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 definition of disease severity and definition of steroid failure. Amongst 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 (Egger's intercept = 0.26, p=0.74 at 3 months). In the comparative cohort meta-analysis: 5mg/kg single versus 5mg/kg multiple dose induction comparisons, there was a low level of heterogeneity between the five studies at 3 months (I^2 =0.0%). Amongst dose intensified versus 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 over 15

years, the optimal IFX dose strategy in ASUC is unknown, due to the infrequency of this life-threatening condition and difficulty in performing well constructed RCTs. IFX salvage in ASUC has evolved from single dose 5mg/kg induction, to high dose and short interval therapy, based on studies in vastly different clinical settings and clinician experience. Apart from a single RCT by Sands and colleagues exploring different IFX doses in ASUC which 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 5mg/kg single dose rescue therapy for CFS at 3 months. This supports current consensus statements on multiple IFX 5mg/kg salvage therapy dosing in ASUC(63) provides evidence to avoid the use of single dose 5mg/kg induction which has been proposed in older guidelines(64)**.** 5mg/kg multiple dose induction CFS was favoured 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 10mg/kg or dose acceleration with 5mg/kg was not associated with improved outcomes over 5mg/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 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.

Whilst a recent meta-analysis by Nalagatla and colleagues(58) 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 current available evidence and highlights 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, anti-drug antibodies and increased body mass index(66) are factors that have been associated with increased IFX drug clearance. Although increased IFX drug clearance and a reduced serum half-life has 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 one study in fact finding that lower IFX drug exposure within the first week in ASUC was associated with clinical response.(69) Whilst this counter-intuitive 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 following induction,(13, 72) they have either not been validated or not 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 has not been 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 versus colectomy in ASUC require careful consideration of adverse events associated with intensive immunosuppression versus the risk of postoperative complications. Failure to make appropriate decisions on treatment futility and delayed surgical intervention can lead to increased morbidity, mortality and healthcare 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 versus 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 eleven assessed outcomes prospectively. Infliximab levels were not reported in these cohorts which represents an important potential confounder of the analysis. Whilst two cohorts(11, 58) were analysed 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 and hence, unadjusted data was utilized for the analysis. Accelerated induction and high-dose induction were grouped as a single category, owing to the limited number of studies. Additionally, two studies by Gibson and colleagues(10, 56) may have included patients that 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. Whilst 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 one 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 endpoint, 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 5mg/kg multiple dose induction is effective as medical salvage therapy for ASUC. Although our data do not presently demonstrate 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 over-treating patients who are destined for a favorable outcome at the expense of increased costs and potential morbidity. Prospective RCTs comparing dose intensified to standard dose therapy in ASUC are both planned(71) 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.

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TABLES AND FIGURES

Figure legends:

1. Figure 1. PRISMA flowchart
2. Figure 2. Forest plot using random-effects model for overall pooled colectomy free survival (proportions)
3. Figure 3. Forest plot using random-effects models assessing CFS at month 1,3 and 12 for (A) 5mg/kg multiple dose vs 5mg/kg single dose induction and (B) dose intensified vs 5mg/kg standard schedule induction.
4. Figure 4. Forest plot using random-effects model to assess mean differences in covariates between dose intensified and 5mg/kg standard schedule cohorts

Table legends:

1. Table 1. Study characteristics and considerations for analysis

   Abbreviations: CFS (colectomy free survival), IFX (Infliximab), ITT (intention to treat), RCT (Randomized controlled trial), TLW (Truelove and Witt's), SCCAI (simple clinical colitis activity index)
2. Table 2. Pooled colectomy free survival (random effects model), expressed as N%(95%CI)

Supplementary Appendices:

1. PRISMA Checklist
2. PICO and search strategy
3. Supplementary data extracted for analysis
4. Quality assessment

Table 1. Study characteristics and considerations for analysis

												CFS (N)			
Author	**Year**	**Country**	**Type of Study**	**Abstract or full-text**	**Definition of severity**	**Eligibility for rescue therapy**	**Sample Size**	**Subgroups**	**IFX dose**	**IFX dose number (ITT)**	**IFX dose strategy (ITT)**	**Month 1**	**Month 3**	**Month 12**	**Considerations for the meta-analysis**
Al Khoury	2017	Canada	Retrospective	Abstract	Mayo severity score 6-12 with Mayo endoscopic score ≥2	IV steroid-refractory (Oxford criteria)	72					69	67	64	
								37	5mg/kg	3	Standard	36	35	33	
								35	10mg/kg	3	Standard	30	30	29	
								5	10mg/kg	3	Accelerated	3	2	2	
An	2017	Australia	Retrospective	Abstract	TLW criteria	IV steroid-refractory	44		5mg/kg			38	35	34	
								16		3	standard	15	13	13	
								28		3	Accelerated	23	22	21	
Aratari	2008	Italy	Retrospective	Full-text	TLW criteria and Powell Tuck	IV steroid-refractory	11		5mg/kg	3	Standard	11	11	10	
Beswick	2016	Australia	Prospective observational	Abstract	TLW criteria	IV steroid-refractory	24		5mg/kg			22	22	19	
								3	5mg/kg	1	Single dose	3	3	3	
								9	5mg/kg	≥2	Standard	9	9	9	
								12	5mg/kg	≥2	Accelerated	10	10	7	
Bressler	2008	Canada	Retrospective	Full-text	Hospitalised UC	IV steroid-refractory	21		5mg/kg	1	Single dose	16	13	NS	
Croft	2013	Australia	Prospective observational	Full-text	TLW criteria	IV steroid-refractory	38		5mg/kg	1	Single dose	31	28	24	
Dean	2011	New Zealand	Retrospective	Full-text	Hospitalized UC	IV steroid-refractory	19		5mg/kg	1-5	Single or multiple dose	NS	15	12	

Duijvis	2016	Netherlands	Retrospective	Full-text	Hospitalized UC	IV or oral steroid-refractory	22		5mg/kg	3	Standard	21	16	12	Mixture of moderate-severe and severe patients
Fernandes	2016	Portugal	Retrospective	Full-text	TLW criteria	IV steroid-refractory (Oxford criteria)	25		5mg/kg	3	Standard	20	20	19	
Florhomen	2011	Norway	RCT	Full-text	TLW criteria	IV steroid-refractory	13		5mg/kg	3	Standard	13	13	NS	
Gibson	2015	Ireland	Retrospective	Full-text	Hospitalized UC	IV steroid-refractory	50					36	32	29	
								35	5mg/kg	3	Standard	22	20	18	
								15	5mg/kg	3	Accelerated	14	12	11	
Gibson	2018	Ireland	Retrospective	Abstract	Hospitalized UC	IV steroid-refractory	145								
								87	5mg/kg	3	Standard	71	66	60	
								58	5mg/kg	3	Accelerated	53	49	44	
Govani	2016	USA	Retrospective	Abstract	Hospitalized UC	IV steroid-refractory	55					44	42	33	Mixture of 5mg/kg and 10mg/kg given to patients in both accelerated and high dose cohorts, unable to include into the meta-analysis
								17	10mg/kg starting dose	3	NA	10	9	9	
								38	5mg/kg starting dose	3	NA	34	33	24	
Jarnerot/ Gustavsson	2005/2010	Sweden	RCT/Retrospective	Full-text	Seo index	IV steroid-refractory (failure to improve according to Seo index)	24		4-5mg/kg	1	Single dose	17	17	14	Jarnerot and Gustavsson cohorts merged; mixture of moderate-severe and severe patients

Halpin	2013	UK	Retrospective	Full-text	TLW criteria	IV steroid-refractory	44		5mg/kg	3	Standard	34	34	31	IV steroid-refractory
Ho	2009	UK / Scotland	Prospective observational	Full-text	TLW criteria	IV steroid-refractory (Oxford criteria or Ho index)	21		5mg/kg	1	Single dose	10	NS	NS	
Hulkower	2016	United States	Prospective observational	Abstract	Hospitalized UC / Mayo score >9	IV steroid-refractory	4		10mg/kg	2-3	accelerated	4	4	NS	
Kaser	2001	Austria	Prospective observational	Full-text	Hospitalized UC	IV steroid-refractory	6		5mg/kg	1	Single dose	6	6	NS	
Kim	2015	South Korea	Retrospective	Full-text	Hospitalized UC	IV steroid-refractory	33		5mg/kg	3	Standard	33	33	32	
Kohn	2007	Italy	Retrospective	Full-text	TLW criteria	IV steroid-refractory	83		5mg/kg			NS	71	NS	2 month analysed as 3 month outcomes; mixture of moderate-severe and severe patients
								26		1	Single dose	NS	17	NS	
								57		≥2	Week 0,2,4, or 0,2,6	NS	54	NS	
Laharie	2012/2017	France	RCT	Full-text	Lichtiger score >10	IV steroid-refractory	55		5mg/kg	3	Standard	NS	45	38	Laharie 2012/2017 cohorts merged; 2 patients excluded as received CyA; 12 month outcome derived % estimate
Lees	2007	UK	Retrospective	Full-text	TLW criteria	IV steroid-refractory	39		5mg/kg	1-3	Single or multiple dose	26	26	24	
Llao	2016	Spain	Retrospective	Full-text	Montreal classification / TLW	IV steroid-refractory	14		5mg/kg	3	Standard	14	14	11	
Lowenberg	2014	Netherlands	Retrospective	Full-text	TLW criteria	IV steroid-refractory (Oxford criteria)	16		5mg/kg	3	Standard	15	12	10	

Mocciaro	2012	Italy	Retrospective	Full-text	TLW criteria	IV steroid-refractory	30		5mg/kg	3	Standard	25	25	25	
Monterubbianesi	2014	Italy	Retrospective	Full-text	TLW criteria (modified by Chapman)	IV steroid-refractory	113		5mg/kg	3	Standard	96	91	83	
Mortensen	2011	Denmark	Retrospective	Full-text	Hospitalized UC / SCCAI	IV or oral steroid-refractory	56		5mg/kg	1-9	Single or Standard	46	39	NS	
Nalagatla	2018	USA	Retrospective	Full-text	Hospitalized UC	IV steroid-refractory	213								
								132	5mg/kg	>2	Standard	121	113	96	
								81	5-10mg/kg	>2	Accelerated/Intensified	74	65	58	
Ordas	2017	Spain	Retrospective	Full-text	Hospitalized UC	IV steroid-refractory	131		5mg/kg	1 or 3	Single or Standard	NS	112	100	
Regueiro	2006	United States	Retrospective	Full-text	Partial Mayo score >=9	IV steroid-refractory	11		5mg/kg	3	Standard	7	4	2	
Ribaldone	2017	Italy	Retrospective	Full-text	TLW criteria	IV steroid-refractory	20		5mg/kg	3	Standard	19	19	15	
Sands	2001	United States	RCT	Full-text	TLW criteria / Lichtiger score	IV steroid-refractory	11					7	4	NS	
								3	5mg/kg	1	Single dose	3	1	NS	
								3	10mg/kg	1	Single dose	2	1	NS	
								2	20mg/kg	1	Single dose	2	2	NS	
Seah	2017	Australia	Retrospective	Full-text	TLW criteria	IV steroid-refractory	41		5mg/kg	3		37	36	30	
								30			Standard	28	28	24	
								10			Accelerated	9	8	6	
Shah	2018	United States	Retrospective	Full-text	Hospitalized UC	IV or oral steroid-refractory	126			3		106	97	89	
								89	5mg/kg		Standard	78	72	65	
								23	5mg/kg		Accelerated	16	14	14	
								8	10mg/kg		Standard	6	5	4	

								6	10mg/kg		Accelerated	6	6	6	
Shepherd	2014	Australia	Retrospective	Abstract	TLW criteria	IV steroid-refractory	15		5mg/kg	1-3		12	10	6	
								11		1	Single dose	8	6	4	
								4		≥2	Multiple dose	4	4	2	
Sjoberg	2013	Sweden	Retrospective	Full-text	TLW criteria	IV steroid-refractory (fulminant colitis index - Lindgren 1998 or Seo index)	211		5mg/kg			153	149	133	
								124		1	Single dose	NS	76	NS	
								87		2-3	Standard	NS	73	NS	
Sly	2017	USA	Retrospective	Abstract	Hospitalized UC	IV steroid-refractory	41								
								18	5mg/kg	3	Standard	16	16	13	
								23	5-10mg/kg	3	Accelerated	16	14	11	
Sood	2014	India	Retrospective	Full-text	Lichtiger score	IV steroid-refractory	28		5mg/kg	3	Standard	25		19	
Van Langenberg	2015	Australia	Retrospective	Abstract	TLW criteria	IV steroid-refractory	88		5mg/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 judgement	IV steroid-refractory	135		5mg/kg	3	Standard	106	96	88	Moderate severity TLW in 27%
Yamamoto-Furusho	2008	Mexico	Prospective observational	Full-text	TLW criteria	IV steroid-refractory	10		5mg/kg	1	single dose	NS	2	2	

Abbreviations: CFS (colectomy free survival), IFX (Infliximab), ITT (intention to treat), RCT (Randomized controlled trial), TLW (Truelove and Witt's), SCCAI (simple clinical colitis activity index), NS (not stated)

Table 2. Pooled colectomy free survival (random effects model), expressed as N%(95%CI)

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

Figure 1

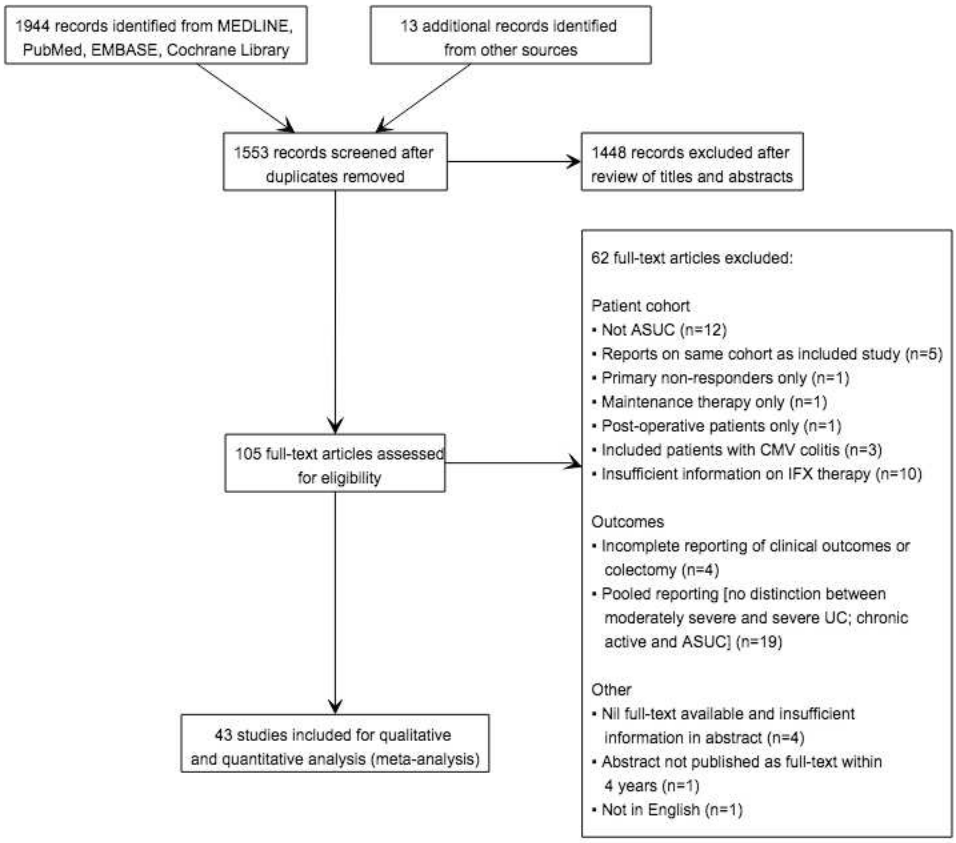

1944 records identified from MEDLINE, PubMed, EMBASE, Cochrane Library
13 additional records identified from other sources
1553 records screened after duplicates removed
1448 records excluded after review of titles and abstracts
105 full-text articles assessed for eligibility
62 full-text articles excluded:
Patient cohort
• Not ASUC (n=12)
• Reports on same cohort as included study (n=5)
• Primary non-responders only (n=1)
• Maintenance therapy only (n=1)
• Post-operative patients only (n=1)
• Included patients with CMV colitis (n=3)
• Insufficient information on IFX therapy (n=10)
Outcomes
• Incomplete reporting of clinical outcomes or colectomy (n=4)
• Pooled reporting [no distinction between moderately severe and severe UC; chronic active and ASUC] (n=19)
Other
• Nil full-text available and insufficient information in abstract (n=4)
• Abstract not published as full-text within 4 years (n=1)
• Not in English (n=1)
43 studies included for qualitative and quantitative analysis (meta-analysis)

Figure 2

Figure 3

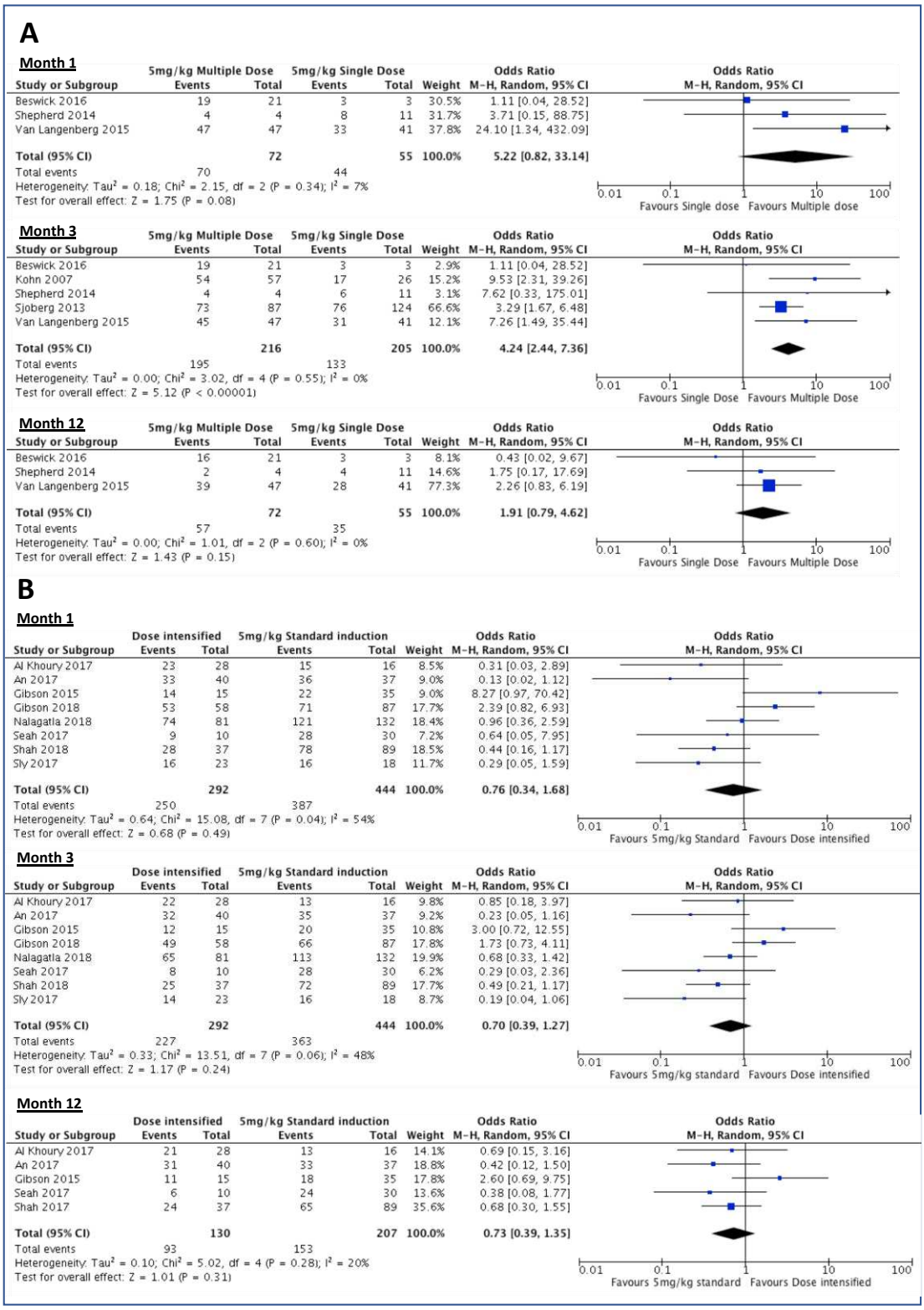
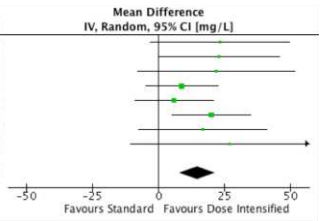

A
Month 1
5mg/kg Multiple Dose
5mg/kg Single Dose
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Beswick 2016 19 21 3 3 30.5% 1.11 [0.04, 28.52]
Shepherd 2014 4 4 8 11 31.7% 3.71 [0.15, 88.75]
Van Langenberg 2015 47 47 33 41 37.8% 24.10 [1.34, 432.09]
Total (95% CI) 72 55 100.0% 5.22 [0.82, 33.14]
Total events 70 44
Heterogeneity: Tau² = 0.18; Chi² = 2.15, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 1.75 (P = 0.08)
0.01 0.1 1 10 100
Favours Single dose Favours Multiple dose
Month 3
5mg/kg Multiple Dose
5mg/kg Single Dose
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Beswick 2016 19 21 3 3 2.9% 1.11 [0.04, 28.52]
Kohn 2007 54 57 17 26 15.2% 9.53 [2.31, 39.26]
Shepherd 2014 4 4 6 11 3.1% 7.62 [0.33, 175.01]
Sjoberg 2013 73 87 76 124 66.6% 3.29 [1.67, 6.48]
Van Langenberg 2015 45 47 31 41 12.1% 7.26 [1.49, 35.44]
Total (95% CI) 216 205 100.0% 4.24 [2.44, 7.36]
Total events 195 133
Heterogeneity: Tau² = 0.00; Chi² = 3.02, df = 4 (P = 0.55); I² = 0%
Test for overall effect: Z = 5.12 (P < 0.00001)
0.01 0.1 1 10 100
Favours Single Dose Favours Multiple Dose
Month 12
5mg/kg Multiple Dose
5mg/kg Single Dose
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Beswick 2016 16 21 3 3 8.1% 0.43 [0.02, 9.67]
Shepherd 2014 2 4 4 11 14.6% 1.75 [0.17, 17.69]
Van Langenberg 2015 39 47 28 41 77.3% 2.26 [0.83, 6.19]
Total (95% CI) 72 55 100.0% 1.91 [0.79, 4.62]
Total events 57 35
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.43 (P = 0.15)
0.01 0.1 1 10 100
Favours Single Dose Favours Multiple Dose
B
Month 1
Dose intensified
5mg/kg Standard induction
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Al Khoury 2017 23 28 15 16 8.5% 0.31 [0.03, 2.89]
An 2017 33 40 36 37 9.0% 0.13 [0.02, 1.12]
Gibson 2015 14 15 22 35 9.0% 8.27 [0.97, 70.42]
Gibson 2018 53 58 71 87 17.7% 2.39 [0.82, 6.93]
Nalagatla 2018 74 81 121 132 18.4% 0.96 [0.36, 2.59]
Seah 2017 9 10 28 30 7.2% 0.64 [0.05, 7.95]
Shah 2018 28 37 78 89 18.5% 0.44 [0.16, 1.17]
Sly 2017 16 23 16 18 11.7% 0.29 [0.05, 1.59]
Total (95% CI) 292 444 100.0% 0.76 [0.34, 1.68]
Total events 250 387
Heterogeneity: Tau² = 0.64; Chi² = 15.08, df = 7 (P = 0.04); I² = 54%
Test for overall effect: Z = 0.68 (P = 0.49)
0.01 0.1 1 10 100
Favours 5mg/kg Standard Favours Dose intensified
Month 3
Dose intensified
5mg/kg Standard induction
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Al Khoury 2017 22 28 13 16 9.8% 0.85 [0.18, 3.97]
An 2017 32 40 35 37 9.2% 0.23 [0.05, 1.16]
Gibson 2015 12 15 20 35 10.8% 3.00 [0.72, 12.55]
Gibson 2018 49 58 66 87 17.8% 1.73 [0.73, 4.11]
Nalagatla 2018 65 81 113 132 19.9% 0.68 [0.33, 1.42]
Seah 2017 8 10 28 30 6.2% 0.29 [0.03, 2.36]
Shah 2018 25 37 72 89 17.7% 0.49 [0.21, 1.17]
Sly 2017 14 23 16 18 8.7% 0.19 [0.04, 1.06]
Total (95% CI) 292 444 100.0% 0.70 [0.39, 1.27]
Total events 227 363
Heterogeneity: Tau² = 0.33; Chi² = 13.51, df = 7 (P = 0.06); I² = 48%
Test for overall effect: Z = 1.17 (P = 0.24)
0.01 0.1 1 10 100
Favours 5mg/kg standard Favours Dose intensified
Month 12
Dose intensified
5mg/kg Standard induction
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Al Khoury 2017 21 28 13 16 14.1% 0.69 [0.15, 3.16]
An 2017 31 40 33 37 18.8% 0.42 [0.12, 1.50]
Gibson 2015 11 15 18 35 17.8% 2.60 [0.69, 9.75]
Seah 2017 6 10 24 30 13.6% 0.38 [0.08, 1.77]
Shah 2017 24 37 65 89 35.6% 0.68 [0.30, 1.55]
Total (95% CI) 130 207 100.0% 0.73 [0.39, 1.35]
Total events 93 153
Heterogeneity: Tau² = 0.10; Chi² = 5.02, df = 4 (P = 0.28); I² = 20%
Test for overall effect: Z = 1.01 (P = 0.31)
0.01 0.1 1 10 100
Favours 5mg/kg standard Favours Dose intensified

Figure 4

CRP

Study or Subgroup	Dose intensified Mean [mg/L]	Dose intensified SD [mg/L]	Dose intensified Total	Standard Mean [mg/L]	Standard SD [mg/L]	Standard Total	Weight	Mean Difference IV, Random, 95% CI [mg/L]
Al Khoury 2017	82.425	62.042	40	59.1	56.4	37	6.7%	23.32 [-3.13, 49.78]
An 2017	49.5	36.71	28	26.47667	37.44669	16	9.1%	23.02 [0.19, 45.86]
Gibson 2015	58.46667	49.319	15	36.6	49.47	35	5.3%	21.87 [-7.99, 51.73]
Gibson 2018	40.666667	42.5724697	58	31.7241379	38.8739227	87	25.3%	8.94 [-4.72, 22.61]
Nalagatla 2018	35.5	54.9	81	29.6	51.9	132	21.3%	5.90 [-8.98, 20.78]
Seah 2017	39.87	18.92	10	19.82	26.12	30	21.0%	20.05 [5.05, 35.05]
Shah 2018	74.29	64.65	37	57.5	61.3	89	7.9%	16.79 [-7.63, 41.21]
Sly 2017	76	71	23	49	52	18	3.3%	27.00 [-10.67, 64.67]
Total (95% CI)			**292**			**444**	**100.0%**	**14.78 [7.91, 21.65]**

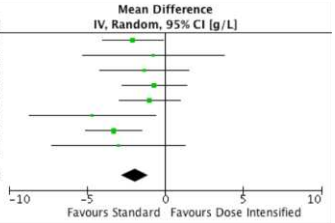
Heterogeneity: Tau² = 0.00; Chi² = 4.09, df = 7 (P = 0.77); I² = 0%
Test for overall effect: Z = 4.21 (P < 0.0001)



Albumin

Study or Subgroup	Dose intensified Mean [g/L]	Dose intensified SD [g/L]	Dose intensified Total	Standard Mean [g/L]	Standard SD [g/L]	Standard Total	Weight	Mean Difference IV, Random, 95% CI [g/L]
Al Khoury 2017	29.8375	5.694737	40	31.9	2.64167	37	19.3%	-2.06 [-4.02, -0.10]
An 2017	26.66667	7.811586	28	27.41667	7.2	16	3.6%	-0.75 [-5.31, 3.81]
Gibson 2015	23	2.453682	15	24.33333	7.729794	35	9.1%	-1.33 [-4.18, 1.51]
Gibson 2018	26	6.08178138	58	26.685824	6.6168757	87	16.9%	-0.69 [-2.78, 1.41]
Nalagatla 2018	31	7	81	32	7	132	19.7%	-1.00 [-2.94, 0.94]
Seah 2017	21	5.160021	10	25.66667	7.005782	30	4.5%	-4.67 [-8.73, -0.60]
Shah 2018	24.7027	4	37	28	6	89	23.0%	-3.30 [-5.09, -1.50]
Sly 2017	33	8	23	36	6	18	4.0%	-3.00 [-7.29, 1.29]
Total (95% CI)			**292**			**444**	**100.0%**	**-1.95 [-2.81, -1.09]**

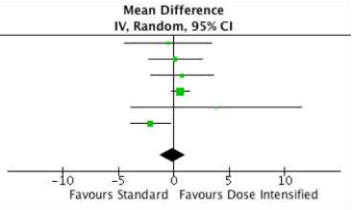
Heterogeneity: Tau² = 0.00; Chi² = 6.90, df = 7 (P = 0.44); I² = 0%
Test for overall effect: Z = 4.44 (P < 0.00001)



IV steroid duration

Study or Subgroup	Dose intensified Mean	Dose intensified SD	Dose intensified Total	Standard Mean	Standard SD	Standard Total	Weight	Mean Difference IV, Random, 95% CI
Al Khoury 2017	5.9	7.9	40	6.375	9.431579	37	7.7%	-0.47 [-4.38, 3.43]
An 2017	2.5	5.46811	28	2.33333	2.844876	16	15.6%	0.17 [-2.29, 2.63]
Gibson 2015	2.76	5.079121	15	2.006667	3.803059	35	12.6%	0.75 [-2.11, 3.62]
Nalagatla 2018	4.6	2.8	81	4	3.1	132	38.9%	0.60 [-0.21, 1.41]
Seah 2017	7.166667	12.17765	10	3.33	4.024433	30	2.3%	3.84 [-3.85, 11.52]
Shah 2018	3.3297	3.5735	37	5.4	6.6	89	22.8%	-2.07 [-3.86, -0.28]
Total (95% CI)			**211**			**339**	**100.0%**	**-0.07 [-1.25, 1.12]**

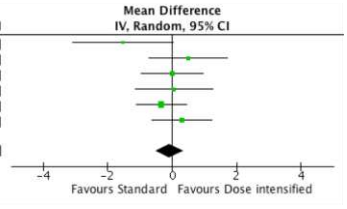
Heterogeneity: Tau² = 0.77; Chi² = 8.24, df = 5 (P = 0.14); I² = 39%
Test for overall effect: Z = 0.11 (P = 0.91)



Disease duration

Study or Subgroup	Dose intensified Mean	Dose intensified SD	Dose intensified Total	Standard Mean	Standard SD	Standard Total	Weight	Mean Difference IV, Random, 95% CI
Al Khoury 2017	4.44125	3.284211	40	5.97	3.7	37	7.5%	-1.53 [-3.10, 0.04]
An 2017	4	1.1717	28	3.5	2.2991	16	12.4%	0.50 [-0.71, 1.71]
Gibson 2015	7	1.63578	15	7	1.545959	35	18.6%	0.00 [-0.97, 0.97]
Gibson 2018	5.6666667	3.80111337	58	5.6130268	3.3496463	87	12.4%	0.05 [-1.15, 1.26]
Seah 2017	4.666667	0.86	10	5	1.55684	30	28.5%	-0.33 [-1.10, 0.44]
Shah 2018	4.3	2.2647	37	4	2.7	89	20.6%	0.30 [-0.62, 1.22]
Total (95% CI)			**188**			**294**	**100.0%**	**-0.08 [-0.51, 0.36]**

Heterogeneity: Tau² = 0.02; Chi² = 5.31, df = 5 (P = 0.38); I² = 6%
Test for overall effect: Z = 0.36 (P = 0.72)



Age

Study or Subgroup	Dose intensified Mean	Dose intensified SD	Dose intensified Total	Standard Mean	Standard SD	Standard Total	Weight	Mean Difference IV, Random, 95% CI
Al Khoury 2017	40.0375	15.9	40	41.2	17.2	37	15.7%	-1.16 [-8.58, 6.25]
An 2017	35.08333	16.59962	28	33	15.85002	16	8.8%	2.08 [-7.82, 11.99]
Gibson 2015	41	18.81156	15	35	11.59469	35	8.2%	6.00 [-4.27, 16.27]
Gibson 2018	35.666667	15.9646761	58	38.5095787	16.2179566	87	30.3%	-2.84 [-8.18, 2.50]
Seah 2017	37.26667	13.84606	10	35.57	13.85588	30	8.8%	1.70 [-8.21, 11.61]
Shah 2018	38.2459	18.3	37	38.5	15.1	89	19.4%	-0.25 [-6.93, 6.43]
Sly 2017	38.6	18.9	23	34.1	13.5	18	8.8%	4.50 [-5.43, 14.43]
Total (95% CI)			**211**			**312**	**100.0%**	**0.13 [-2.81, 3.07]**

Heterogeneity: Tau² = 0.00; Chi² = 3.57, df = 6 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.93)