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Risk related therapy in meta-analyses of critical care interventions: Bayesian meta-regression analysis

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ABSTRACT

Purpose: The relationship between treatment efficacy and patient risk is explored in a series of meta-analyses from the critical care domain, focusing on mortality outcome.
Methods: Systematic reviews of randomized controlled trials were identified by electronic search over the period 2002 to July 2018. A Bayesian meta-regression model was employed, using the risk difference metric to estimate the relationship between mortality difference and control arm risk, and estimate the mortality difference with and without adjusting for control arm risk.
Results: Of 780 initially identified published systematic reviews, 113 had appropriate mortality data comprising 123 analysable groups. The 123 meta-analyses were pharmaceutical therapeutic (59.3%), non-pharmaceutical therapeutic (24.4%) and nutritional (16.3%), with a 25% overall average control arm mortality. In 25/123 (20%) analyses, meta-regression indicated significant baseline risk (Bayesian 95% credible intervals excluding zero). In all analyses, the relationship between risk-difference and control arm risk was negative indicating a positive treatment effect with increasing control arm risk. Adjusted estimates identified six studies with significant positive treatment effects, not evident until after adjustment for control arm risk.
Conclusion: Underlying risk-related therapy is apparent in meta-analyses of the critically-ill and identification is of importance to both the conduct and interpretation of these meta-analyses.

1. Introduction

In the meta-analytic literature, the relationship between treatment efficacy and underlying patient risk has been a lively topic for >20 years [1-3]; that is, the attempt to define patient groups benefiting most and least (according to an estimate of underlying risk) from proposed therapy [4]. Heterogeneity of treatment effect is common and can be explored through meta-regression of predictors such as underlying (control arm) "risk" [5,6]. Use of control arm risk as a surrogate for say, patient severity of illness, has been undertaken in both the general medical [2,7,8] and critical care literature [3,9-11].

The aim of this paper was to explore the relationship between treatment efficacy and control arm risk in a series of critical care binary-outcome meta-analyses where risk dependent treatment effects may be expected to be obtained [12]. We utilised the risk difference metric as it is considered to best communicate the clinical treatment effects [13,14] allowing more informed medical and policy decisions [15].

Previous discussions of risk related therapy in critical care have been dominated by the sepsis paradigm [1,9,10,16,17], but with the withdrawal of the paradigmatic sepsis-active pharmacotherapeutic agent drotecogin alpha activated [18] by Eli Lilly and Company in 2011 [19], debate upon risk-related therapy appeared to have waned until recently, when such issues have been revived, but with a similar refrain [20,21]. Our purpose was to re-invigorate this debate, using methods similar in spirit to previous surveys [22-24].

2. Methods

Systematic reviews of randomized controlled trials (RCT) with binary-outcomes were identified by electronic search over the period January 2002 to July 2018. The search strategy comprised an electronic search with key-words "meta-analysis", "critically-ill" using Web of Science™ and a focused electronic search, using the same key words, of major critical care (Annals of Intensive Care, American Journal of Respiratory and Critical Care Medicine, Annals of the American Thoracic Society, Chest, Critical Care Medicine, European Respiratory Journal, Intensive Care Medicine, Critical Care, Journal of Critical Care, American Journal of Critical Care, and Thorax), specialist and general high impact-factor medical journals (New England Journal of Medicine,

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We reviewed abstracts of systematic reviews identified by the electronic search and the full-text of the systematic reviews was retrieved for detailed evaluation. The mortality outcome of included meta-analyses was extracted, entered, reviewed and verified by both investigators (JLM, PLG). Where distinct clinical subgroups were identified within a published systematic review these were analysed and considered as "separate" meta-analyses. When multiple meta-analyses addressed the same question, the most recent publication was preferred.

2.1. Statistical analysis

The Bayesian meta-regression model of Warn et al. [25] was employed to estimate the mortality risk difference (RD) for treatment versus control with 95% credible interval, CrI, with and without adjusting for control arm risk. In this formulation the risk difference is obtained by directly modelling treatment and control group outcomes using binomial distributions. Underlying or control arm risk is added to the model as a trial level covariate obtained from the control group proportion of deaths. The R (version 3.5.1 [26]) package R2jags [27] was used for all analyses with summaries presented based on three chains each using 50,000 iterates after discarding burn-in. Similar to Warn et al. [25], we used a Uniform prior on the interval 0 to 1 for the proportion of deaths in the control arm and a Uniform distribution on the interval 0 to 5 as a prior for the between studies standard deviation (τ). Values of τ close to 0 indicate little heterogeneity, τ between 0.1 and 0.5 indicates small to moderate heterogeneity and $\tau > 0.5$ reflects substantial heterogeneity [28]. For those meta-analyses exhibiting a significant relationship between estimated risk difference and control arm risk (i.e. the CrI interval for the slope of the regression line did not include 0), random effects meta-analysis of the risk difference was undertaken using frequentist methods for comparison. Frequentist random effects meta-analyses were undertaken using the "metafor" R package with the REML option [29].

3. Results

Of 780 initially identified published systematic reviews,113 had appropriate mortality data; 8 of these contained distinct subgroups (see Methods, above), for a total of 123 individual meta-analyses; the final data-set of the current study. The 123 meta-analyses were pharmaceutical therapeutic in 59.3% (average control arm mortality 24%), non-pharmaceutical therapeutic in 24.4% (control arm mortality 29%) and nutritional in 16.3% of studies (control arm mortality 23%), for an overall control arm mortality of 25%. Active control arm therapies were used in 30% and placebo or "usual care" in 70%. Four of these meta-analyses assessed the effect of control arm risk on mortality using conventional frequentist meta-regression: Annane et al. [9], $p = .06$; Kumar et al. [16], $p < .0001$; Rochwerg et al. [30], $p = .26$; and Roquilly et al. [31], $p = .07$; and one used Bayesian meta-regression: Peter et al. [32], mean slope parameter (log OR) -0.448, 95% credible interval − 1.28 to 0.741.

Twenty-five meta-analyses [33-57] demonstrated a significant relationship between estimated risk difference and control arm risk (that is, the CrI for the estimated coefficient for control arm risk excluded the null). These meta-analyses are summarised in Table 1 together with conventional frequentist risk difference estimates (with 95% confidence interval, CI) and estimates of τ. Nine meta-analyses [37,42,43,45,47,48,50,51,55] had significant treatment effects (95% CI excluding zero). A list of those meta-analyses in which risk-related therapeutic effect was not demonstrated appears in Appendix 1.

Unadjusted pooled (Bayesian) estimates (with 95% CrI) for the studies with a significant risk-related effect are seen in the second column of Table 2. For all but three of these [39,42,43] the 95% CrI were wider than the frequentist random-effect counterparts. Unadjusted and frequentist RD conclusions (regarding presence or absence of significance) were consistent for all but three meta-analyses [43,52,53]. All twenty-five studies in Table 2 showed a significant negative slope for control arm risk, indicating a positive effect of treatment with increasing control arm risk. Sixteen meta-analyses demonstrated significant adjusted estimates of risk difference [35-39,42,45,47,48,50-53,55,56,58], six of which showed no significant risk difference in the unadjusted model [35,36,38,39,43,56]. The adjusted estimates preserved null treatment efficacy in nine meta-analyses [33,34,40,41,44,46,49,54,57]. Heterogeneity (τ) was small or very small (≤0.1) in all but one meta-analysis [57] and most analyses showed at least a 10% reduction in between studies variability in the adjusted model (τ_a). Two studies [35,54] had an 8% and 1% reduction, respectively, in between studies variability, while the between studies variability increased after adjustment in four studies [37,49,52,53] (Table 2).

The meta-analyses showing evidence of risk-related therapeutic effect had significantly more studies (median number of studies 15, range 9–80) compared with those meta-analyses not demonstrating a risk-related effect (median number of studies 8, range 3–45; Wilcoxon rank-sum test $p < .001$). Studies with significant risk-related effects had significantly smaller median heterogeneity post adjustment than studies without significant risk-related effects (median τ_a 0.029 vs 0.051, Wilcoxon rank-sum test p-value = .005). Use of a less informative prior for τ had very little impact on results (not presented).

4. Discussion

Previous reviews of the control arm mortality rate as a predictor of treatment efficacy [22-24] have not systematically sourced the meta-analyses from a patient domain; the current study would appear to be one of the first to do so. Given that the average control arm event rate in the 123 meta-analyses under investigation was 25%, as opposed to much lower rates (10%) in large cardiovascular trials [59], the expectation was that in this particular group of meta-analyses, risk-related therapy would be evident. The former non-specific reviews had found risk related therapy in 6–15% of meta-analyses and in the current review this was 20% (i.e. 25/123). This being said, the estimated adjusted risk differences (Table 2) were quite modest, ranging from 0.3% to 13% (mean 5.0% (SD, 3.0%)), which estimates were consistent with recent opinion regarding the plausible magnitude (5%) of absolute risk reduction in randomized controlled critical care trials [60]. Our finding that meta-analyses showing evidence of risk-related therapeutic effects had significantly more studies than those not demonstrating risk-related effects was also consistent with recent analysis [61].

The twenty-five meta-analyses with significant control arm risk embraced a rather wide spectrum of interventions, although 32% had interventions directed specifically to sepsis (Table 1. [33,41,48,50,51,53-55]). Of recent therapeutic interest, none of the meta-analyses (Appendix 1) of steroid use in sepsis and septic shock, by Annane et al. (2009) [9] and more recently Rygard et al. (2018) [62] and Rochwerg et al. [30], nor the meta-analysis of Angus et al. [63] of early goal-directed therapy (EGDT) for septic shock, demonstrated evidence of risk-related therapeutic effects. Similarly, the patient level meta-analysis of three large and recent EGDT trials (2014–2015) by Rowan et al. [64] failed to demonstrate benefit of EGDT for patients with worse shock. Of note however, four specific antibiotic regimen meta-analyses [48,50,54,55] and one meta-analysis of intravenous immunoglobulin for sepsis [51] did demonstrate risk related therapeutic effects. A plausible explanation for these divergences is that risk related therapy in sepsis is not a generalised phenomenon; rather it is context specific. Thus, recent invocations of sepsis risk-related therapy [20,21] must be viewed cautiously. With respect to ventilatory strategies in the management of acute lung injury, the use of pressure- and volume-limited ventilation demonstrated both risk-related and significant adjusted effects [36], but conventional low tidal ventilation versus non–volume-limited strategies [65] and high versus low positive end expiratory pressure [66] did not display risk related effects. Although current renal replacement

Table 1
Details of the meta-analyses with evidence of a relationship between risk difference and control arm risk.

Author	N	Year published	Intervention	Trial Type	Calculated frequentist RD (95%CI)	τ
Avni [33]	11	2015	Norepinephrine versus dopamine for the Treatment of Septic Shock	AC	−0.031 (−0.128, 0.066)	0.114
Bagshaw [34]	9	2008	Continuous vs intermittent renal replacement therapy	AC	−0.005 (−0.062, 0.052)	0.037
Brar [35]	13	2009	Use of drug-eluting stents in Acute Myocardial Infarction	AC	−0.004 (−0.013, 0.005)	0.001
Burns [36]	10	2011	Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury	AC	−0.072 (−0.147, 0.003)	0.079
Chen [38]	12	2014	Omega-3 fatty acids enriched nutrition support for critically ill patients	AC	−0.051 (−0.119, 0.017)	0.083
Chen [37]	17	2017	Effect of levosimendan on prognosis in adult patients undergoing cardiac surgery	PC	−0.017 (−0.033, −0.001)[a]	0.000
Gonzalez [39]	18	2008	Combination endoscopic and drug therapy to prevent variceal re-bleeding in cirrhosis	AC	−0.026 (−0.062, 0.011)	0.016
Koster [40]	9	2016	Milrinone for cardiac dysfunction in critically ill adult patients	PC	0.008 (−0.034, 0.051)	0.001
Lu [41]	16	2017	Omega-3 supplementation in patients with sepsis	PC	−0.025 (−0.076, 0.027)	0.045
Manzanares [42]	21	2012	Antioxidant micronutrients in the critically ill	PC	−0.071 (−0.139, −0.003)[a]	0.123
Manzanares [43]	13	2016	High-dose intravenous selenium and clinical outcomes in the critically ill	PC	−0.124 (−0.230, −0.019)[a]	0.159
Marik [44]	13	2008	Immuno-nutrition in critically ill patients (ICU subgroup)	AC	−0.031 (−0.086, 0.025)	0.073
Osadnik [45]	12	2017	Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease	PC	−0.069 (−0.110, −0.027)[a]	0.000
Parikh [46]	16	2016	Calorie delivery and clinical outcomes in the critically ill	AC	−0.003 (−0.031, 0.025)	0.001
Piccini [47]	15	2009	Amiodarone for the prevention of sudden cardiac death	PC	−0.020 (−0.030, −0.010)[a]	0.003
Rhodes [48]	17	2018	Effect of prolonged Infusion Piperacillin-Tazobactam in Severely Ill Patients	AC	−0.033 (−0.053, −0.013)[a]	0.005
Siempos [49]	11	2007	Impact of passive humidification on clinical outcomes of mechanically ventilated patients	AC	−0.001 (−0.038, 0.036)	0.001
Silvestri [50]	31	2007	Selective decontamination of the digestive tract in critically ill patients	PC	−0.031 (−0.054, −0.009)[a]	0.019
Soares [51]	17	2014	Intravenous immunoglobulin for severe sepsis and septic shock	PC	−0.112 (−0.181, −0.044)[a]	0.098
Sung [53]	80	2007	Prophylactic hematopoietic colony-stimulating factors in infection	PC	−0.003 (−0.011, 0.004)	0.005
Sun [52]	34	2017	Effect of perioperative goal-directed hemodynamic therapy on postoperative recovery following major abdominal surgery	AC	−0.005 (−0.016, 0.005)	0.002
Teo [54]	13	2014	Prolonged infusion versus intermittent boluses of beta-lactam antibiotics for treatment of acute infections	AC	−0.021 (−0.053, 0.011)	0.016
Vardakas [55]	17	2018	Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis	AC	−0.027 (−0.049, −0.005)[a]	0.002
Whitlock [56]	16	2008	Steroids in cardio-pulmonary bypass	PC	−0.001 (−0.013, 0.010)	0.000
Yang [57]	9	2017	Early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients	AC	−0.079 (−0.232, 0.074)	0.217

ICU, intensive care unit. PC, placebo or standard care control. AC, active control. RD, risk difference.
[a] Significant RD.

strategies, continuous versus intermittent [34] and early versus late initiation [57], did demonstrate risk relation, no significant adjusted effect was evident. Somewhat surprisingly, six nutritional meta-analyses (Table 1, [38,41-44,46]) also demonstrated risk related effects and in three [38,42,43], the overall adjusted risk differences were significant. This was not the case for the meta-analysis of intensive insulin therapy in the critically ill by Griesdale et al. [67] (Appendix 1).

Within the critical care domain, the assessment of therapies for sepsis and septic shock has been a persistent focus, and the question of risk related therapy has been variously determined, with varying levels of complexity. Using weighted least squares regression in a L'Abbe plot, relating log odds of treatment to log odds of control mortality, Eichacker et al. [10] in 2002, in both human and animal studies, concluded that the efficacy of anti-inflammatory agents during sepsis was dependent upon the risk of death. Contrary to this conclusion, Macais et al. [17] in 2005, looked at a diverse selection of phase III randomized controlled trials in sepsis and septic shock, and concluded that the relative treatment effect was independent of the patient risk of death and future studies in severe sepsis should enrol patients with a wide degree of illness severity. An accompanying Editorial [68] to the latter paper drew attention to the disconcerting (biologically) disparate group of studies, and, on the basis of stratified analysis of several key therapeutic studies in sepsis and septic shock, suggested that heterogeneity was a recipe for "…mask(ing) a potential treatment effect..". Kalil et al. [1] in 2011, using a stratified analysis of phase II and significant phase III trials, concurred with Eichacker et al. and criticised Macais et al. for "lumping" anti-inflammatory agents and not undertaking an appropriately (stratified) analysis. A more recent non-stratified analysis of randomized trials in sepsis by de Grooth et al. has also proposed the determinacy of control arm risk [20].

However, such analyses, including the 4 frequentist meta-regressions [9,16,30,31] currently identified (see Results, above), were subject to certain methodological problems [69,70]: a failure to allow for regression to the mean, the difference between outcome and baseline being correlated with baseline [71], and the stochastic nature of the control rate (regression dilution bias [72]). That is, there was no inherent accounting for the random error in estimation of this control rate. Thus estimates from such methods may be both inconsistent and biased [69], and cannot be recommended; a position re-iterated in a relatively recent review from the critical care literature [12]. The recommended method for baseline risk adjustment is a fully Bayesian approach [73,74], such as that used here.

Absolute therapeutic risk reduction, that is, a constant proportional reduction in effect, may be expected to vary across patient risk [75]; nonetheless, we have utilised a method that appropriately incorporated the effect of control arm risk into final effect estimation. The risk difference metric is conventionally associated with increased heterogeneity, albeit explanation of this finding appears unsatisfactory [14]. Although scale dependent heterogeneity may be problematic in terms of the nexus between analysis and presentation of results [76], recent work has suggested that interactions, in this case risk-related therapy, may be more easily established on the additive (risk difference) rather than the multiplicative (odds ratio and relative risk) scale [77,78]. We find the sentiments of Jackson et al. [79], that a metric choice should be "…guided by empirical evidence and clinical debate" and Poole et al. [14], that "…meta-analytic results…do not support a policy of routinely shunning any of the three measures [odds ratio, relative risk, risk difference], including the risk difference" entirely consistent with our purpose. We were somewhat reassured by the low heterogeneity in the studies of interest (Tables 1 and 2), preferring to use the between study standard deviation, τ, as a measure of heterogeneity. This variability statistic is measured on the same scale as the outcome and does not systematically increase with either the number, or size, of studies in a meta-analysis, as opposed to I^2, and can be "… directly used to quantify variability" [80].

Table 2
Meta-analytic summaries for studies with a significant relationship with control arm risk.

Author	Bayesian Unadjusted RD (95%CrI)	τ	Bayesian Adjusted RD (95% CrI)	τ_a	Slope for control arm risk (95%CrI)
Avni [33] 2015	−0.034 (−0.135, 0.065)	0.102	−0.039 (−0.123, 0.039)	0.056	−0.572 (−0.978, −0.199)
Bagshaw [34] 2008	−0.004 (−0.073, 0.067)	0.049	−0.003 (−0.065, 0.065)	0.038	−0.619 (−1.195, −0.027)
Brar [35] 2009	−0.006 (−0.020, 0.006)	0.008	−0.016 (−0.033, −0.001)[a]	0.008	−0.542 (−0.937, −0.033)
Burns [36] 2011	−0.070 (−0.157, 0.015)	0.083	−0.091 (−0.167, −0.008)[a]	0.066	−0.856 (−1.499, −0.194)
Chen [38] 2014	−0.057 (−0.148, 0.024)	0.102	−0.073 (−0.145, −0.004)[a]	0.069	−0.542 (−0.929, −0.046)
Chen [37] 2017	−0.033 (−0.076, −0.008)[a]	0.025	−0.050 (−0.094, −0.016)[a]	0.031	−0.673 (−1.262, −0.080)
Gonzalez [39] 2008	−0.027 (−0.066, 0.012)	0.027	−0.048 (−0.091, −0.007)[a]	0.019	−0.507 (−0.833, −0.103)
Koster [40] 2016	−0.005 (−0.123, 0.068)	0.056	−0.067 (−0.136, 0.010)	0.027	−0.779 (−1.099, −0.284)
Lu [41] 2017	−0.032 (−0.090, 0.024)	0.050	−0.049 (−0.105, 0.010)	0.037	−0.417 (−0.718, −0.033)
Manzanares [42] 2012	−0.055 (−0.123, −0.005)[a]	0.074	−0.072 (−0.120, −0.029)[a]	0.043	−0.332 (−0.552, −0.155)
Manzanares [43] 2016	−0.068 (−0.175, 0.003)	0.076	−0.100 (−0.183, −0.029)[a]	0.040	−0.631 (−1.144, −0.211)
Marik [44] 2008	−0.028 (−0.099, 0.031)	0.076	−0.038 (−0.099, 0.019)	0.067	−0.426 (−0.818, −0.064)
Osadnik [45] 2017	−0.082 (−0.149, −0.024)[a]	0.036	−0.098 (−0.156, −0.042)[a]	0.025	−0.574 (−1.002, −0.052)
Parikh [46] 2016	−0.004 (−0.044, 0.032)	0.028	−0.012 (−0.051, 0.027)	0.025	−0.477 (−0.840, −0.061)
Piccini [47] 2009	−0.022 (−0.040, −0.010)[a]	0.009	−0.035 (−0.053, −0.018)[a]	0.006	−0.273 (−0.471, −0.032)
Rhodes [48] 2018	−0.042 (−0.076, −0.017)[a]	0.017	−0.065 (−0.101, −0.034)[a]	0.013	−0.239 (−0.438, −0.041)
Siempos [49] 2007	−0.001 (−0.051, 0.045)	0.026	−0.014 (−0.060, 0.035)	0.029	−0.434 (−0.828, −0.000)
Silvestri [50] 2007	−0.032 (−0.058, −0.008)[a]	0.024	−0.050 (−0.077, −0.024)[a]	0.016	−0.261 (−0.419, −0.074)
Soares [51] 2014	−0.100 (−0.187, −0.027)[a]	0.095	−0.126 (−0.192, −0.064)[a]	0.063	−0.366 (−0.615, −0.147)
Sung [53] 2007	−0.009 (−0.018, −0.000)[a]	0.010	−0.017 (−0.030, −0.006)[a]	0.018	−0.238 (−0.427, −0.049)
Sun [52] 2017	−0.016 (−0.036, −0.002)[a]	0.016	−0.028 (−0.051, −0.009)[a]	0.027	−0.456 (−0.776, −0.116)
Teo [54] 2014	−0.036 (−0.134, 0.031)	0.072	−0.069 (−0.144, 0.009)	0.066	−0.479 (−0.959, −0.000)
Vardakas [55] 2018	−0.057 (−0.120, −0.019)[a]	0.031	−0.085 (−0.129, −0.042)[a]	0.020	−0.332 (−0.575, −0.082)
Whitlock [56] 2008	−0.003 (−0.020, 0.010)	0.008	−0.031 (−0.054, −0.008)[a]	0.005	−0.648 (−0.899, −0.303)
Yang [57] 2017	−0.055 (−0.220, 0.090)	0.178	−0.069 (−0.211, 0.066)	0.159	−0.816 (−1.745, −0.015)

RD, risk difference. Unadjusted, no adjustment made for control arm risk. Adjusted, estimate after adjustment for control arm risk.
τ, between study standard deviation, τ_a, adjusted between study standard deviation.. CrI, credible interval.
[a] Significant RD (95% CrI not including zero).

Some caveats apply to our study. As we did not source individual patient data (IPD), analytic inference was at the study, not patient, level [12,24]. Our search for risk related therapy within meta-analyses does not encompass either the paradox of the frequency of critical care meta-analyses and the dearth of IPD meta-analyses, nor the impact of such analyses upon individual patient outcome, by virtue of the ecological fallacy [12]. Ours is a meta-epidemiological study which relates to a specific but important aspect of meta-analytic methodology. Our electronic search strategy, with key-words "meta-analysis", "critically-ill", was applied generally to available data-bases in Web of Science™ and focused on key critical care and high impact journals. The aim was not to produce an exhaustive set of meta-analyses but a representative set from which to examine the effect of control arm risk.

5. Conclusions

Identification of underlying risk-related therapy is of importance to both the conduct of meta-analysis and the interpretation of the overall effect of therapeutic interventions, particularly in the critically-ill. This may be appropriately achieved via Bayesian meta-regression.

Declaration of interests

The authors declare that they have no conflict of interest.

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Contributions

JLM: study design, data collection, drafting of the manuscript, revising the manuscript, interpretation of results. PLG: study design, data collection, data analysis, drafting of the manuscript, revising the manuscript, interpretation of results.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.003.

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