Polyspecific intravenous immunoglobulin in clindamycin-treated patients with streptococcal toxic shock syndrome: a systematic review and meta-analysis

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Abstract

We evaluated the effect of adjunctive intravenous immunoglobulin (IVIG) on mortality in clindamycin-treated streptococcal toxic shock syndrome patients using a meta-analysis. In association with IVIG, mortality fell from 33.7% to 15.7% (risk ratio 0.46, 95% confidence intervals 0.26-0.83, p=0.010) with remarkable consistency across the single randomised and four non-randomised studies.

Brief report

Streptococcal toxic shock syndrome (STSS) is a complication of invasive *Streptococcus pyogenes* infection (IGAS) characterised by hypotension and end-organ failure often with immunological manifestations such as rash [1]. Notwithstanding the formal case definition, it should be noted that shock in a patient with IGAS will almost always represent STSS [2]. Complicating IGAS in approximately 10% of cases, STSS is thought to be triggered in part by superantigens and other bacterial virulence factors. Mortality associated with STSS is substantial exceeding 25% within the first twenty-four hours in some studies [3]. In addition, STSS is associated with substantial morbidity with most cases requiring intensive care.

Polyspecific intravenous immunoglobulin (IVIG) is recommended by some experts as an adjunctive treatment for STSS, not least because of laboratory data indicating potentially beneficial effects including neutralisation of superantigens and enhanced bacterial clearance [4]. However, the use of IVIG for STSS has been difficult to evaluate clinically; the only randomised controlled trial (RCT) was stopped early due to slow recruitment [5]. Although a small number of non-randomised studies have been reported, the interpretation of these data is complicated by the inherent risk of bias, the variable inclusion criteria and the inconsistent use of clindamycin, which is widely advocated as an adjunct to penicillin. We undertook a systematic review of randomised and non-randomised studies that evaluated the use of adjunctive IVIG in STSS. We then did a meta-analysis of the effect of

IVIG on mortality in the subgroup of patients with STSS whose antibiotic therapy included clindamycin.

We searched English language entries in MEDLINE and EMBASE since 1980 using the terms “streptococcus” OR “streptococcal” and “intravenous immunoglobulin” OR “ivig” (Supplementary Figure 1). We also searched reference lists of shortlisted articles. We included studies that evaluated the relationship between IVIG and mortality in patients with STSS prospectively identified using the consensus criteria [2]. We excluded studies that were retrospective and did not detail the use of clindamycin or did not define STSS. Eligibility assessment and data extraction were done unblinded by the first and second authors. We also assessed risk of bias using tools published by the Cochrane Collaboration. In addition, we contacted the authors of eligible studies including unpublished abstracts to request a breakdown of all results by use of clindamycin. Our primary measure of treatment effect was the risk ratio (RR) of death at 30 days calculated with its standard error for the subgroup of patients with STSS who received clindamycin. We then did a meta-analysis using a random effects model and assessed heterogeneity using the I^2 statistic. All analyses were done using Stata 12.1 (StataCorp, Texas).

The search, which was last updated on 31st December 2017, revealed 412 articles after removal of duplicates (Supplementary Figure 2). Fourteen articles were shortlisted of which one randomised [5] and four non-randomised studies [6-9] met the inclusion criteria (Supplementary Table 1 and Supplementary Table 2). The included studies were undertaken between 1992 and 2009 in Northern Europe, Canada and Australia. The randomised study compared IVIG to placebo and the non-randomised studies compared IVIG to standard care. One of the non-randomised studies used historical controls [6] while the other three used concurrent patients who did not receive IVIG as controls [7-9]. Across all five studies, IVIG was administered to 70 and not administered to 95 of the STSS patients treated with clindamycin (Supplementary Table 3). Overall mortality was 26.1%, ranging between 14.3 and 40.5% in the individual studies.

We found risk of bias across several domains in the non-randomised studies (Supplementary Table 4). In particular, we noted at least moderate risk of bias due to baseline differences between IVIG-treated cases and controls. Although adjusted analyses were reported, it is likely that some baseline confounding persisted, not least because the small sample sizes limited the utility of multivariate regression. Despite limiting our analyses to the subgroups treated with clindamycin, we expect some of this bias remained in our analyses. In addition, two of these studies collected some information retrospectively, using questionnaires, with the potential for selection bias. Furthermore, three of these studies provided no details of IVIG dosing, potentially introducing classification bias. Separately, a funnel plot of the four non-randomised studies – using all reported data rather than the subset analysed here – suggests the possibility of reporting bias, although interpreting the plot with so few studies is difficult (Supplementary Figure 3). In contrast, we found limited risk of bias in the randomised study (Supplementary Table 5).

In all five studies, administration of IVIG in the clindamycin-treated subgroup was associated with lower mortality, although none reached statistical significance in isolation (Figure 1; Supplementary Table 6). However, in the pooled analysis, administration of IVIG was associated with a reduction in mortality from 33.7% to 15.7% (RR 0.46, 95% confidence intervals, CI, 0.26-0.83, p=0.010) with negligible heterogeneity (I^2=0%). The pooled result of the non-randomised studies (RR 0.47, 95% CI 0.25-0.86) was remarkably consistent with the effect size estimate of the RCT (RR 0.42, 95% 0.05-3.28).

This systematic review and meta-analysis provides evidence that administration of adjunctive IVIG to clindamycin-treated patients with STSS is associated with a statistically significant reduction in mortality. Crucially, our analysis disentangles the effects of clindamycin from those of IVIG, which has sometimes been problematic [6,7]. Our results therefore corroborate the findings of the Linnér *et al.* study [8], the largest of the three more recent non-randomised studies, which suggested both clindamycin and IVIG were beneficial. Moreover, by limiting the analysis to clindamycin-treated subgroups, we provide a more informative effect size estimate than those derived from the individual datasets. Overall our results imply that as many as one additional death could be prevented for every six clindamycin-treated patients with STSS administered IVIG.

Three of the studies we excluded are worthy of further discussion not least because their main results appear to contradict our findings. The first prospectively assessed the efficacy of IVIG in patients with IGAS with or without STSS admitted to the ICU at four tertiary hospitals in Canada [10]. Unfortunately, the authors of this report were unable to provide us with the results for the subset of patients with STSS treated with clindamycin. Thus, while IVIG had no effect on mortality from IGAS overall, the impact of IVIG in the subset of patients with STSS remains unknown. The second retrospectively identified STSS patients admitted to tertiary paediatric hospitals in the USA using ICD-9 coded discharge diagnoses [11]. Accordingly, this study is highly likely to have included patients with diagnoses other than STSS, a group that would have been both less likely to receive IVIG and less likely to die than those with STSS. The third respectively identified patients with necrotising fasciitis and vasopressor-dependent shock from 121 hospitals in the USA [12]. In a propensity-matched analysis based on 322 patients, the authors found that IVIG had no effect on mortality. However, addition of data from 49 patients with coding for *S. pyogenes* and clindamycin (Supplementary Table 7) to our meta-analysis had a negligible effect on our results (Supplementary Figure 4).

Our study has three main limitations. First, despite pooling five studies, our analysis remains small and consequently our effect size estimate lacks precision. Second, despite limiting the meta-analysis to the clindamycin-treated subgroup, there is a sizeable risk the baseline characteristics differed between those administered and not administered IVIG. For example, in the Linnér *et al.* study [8], there were differences at baseline in terms of age, co-morbidities and presence of necrotising fasciitis, all of which were associated with increased risk of death. Nonetheless, we predict IVIG would be administered more frequently to the most unwell patients, thereby introducing any bias towards a null effect. That said, while the similarity of the signal in the single RCT and four non-randomised studies is reassuring, it remains plausible that the reduction in mortality associated with IVIG in this analysis is due to confounding. Third, relatively limited information was available regarding the use antibiotics other than clindamycin. This issue could theoretically bias our results in favour of IVIG if certain potentially beneficial antibiotics including penicillin were used more often with IVIG. It is noteworthy, however, that the antibiotic regimen in the RCT was pre-specified [5] and all but one patient in the Linnér et al. study received a β-lactam agent [8]. Fourth, we were unable to address a number of outstanding questions including the optimum dosing and timing of IVIG. Ultimately, therefore, in the absence of sufficiently sized RCTs, a meta-analysis of observational studies may be the best means available to evaluate such an intervention. Looking forward, establishment of an international registry of STSS cases may provide more robust data to inform management of this devastating condition.

In conclusion, our study helps address doubt surrounding the use of IVIG in STSS. It also highlights the utility of synthesising findings from small non-randomised studies in the

absence of large-scale trials. Overall, given the high morbidity and mortality associated with STSS, we support the use of IVIG as an adjunctive treatment for STSS, a recommendation that applies to the vast majority of patients with IGAS complicated by shock.

Funding

This work was supported by the Medical Research Council [G1100449 to T.P.]; the National Institute for Health Research [ACF-2016-20-001 to T.P.]; the National Institute for Health Research in partnership with Public Health England [HPRU-2012-10047]; and the National Institute for Health Research Imperial Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, the Department of Health or Public Health England.

Conflict of Interest

We declare no potential conflicts of interest.

Acknowledgements

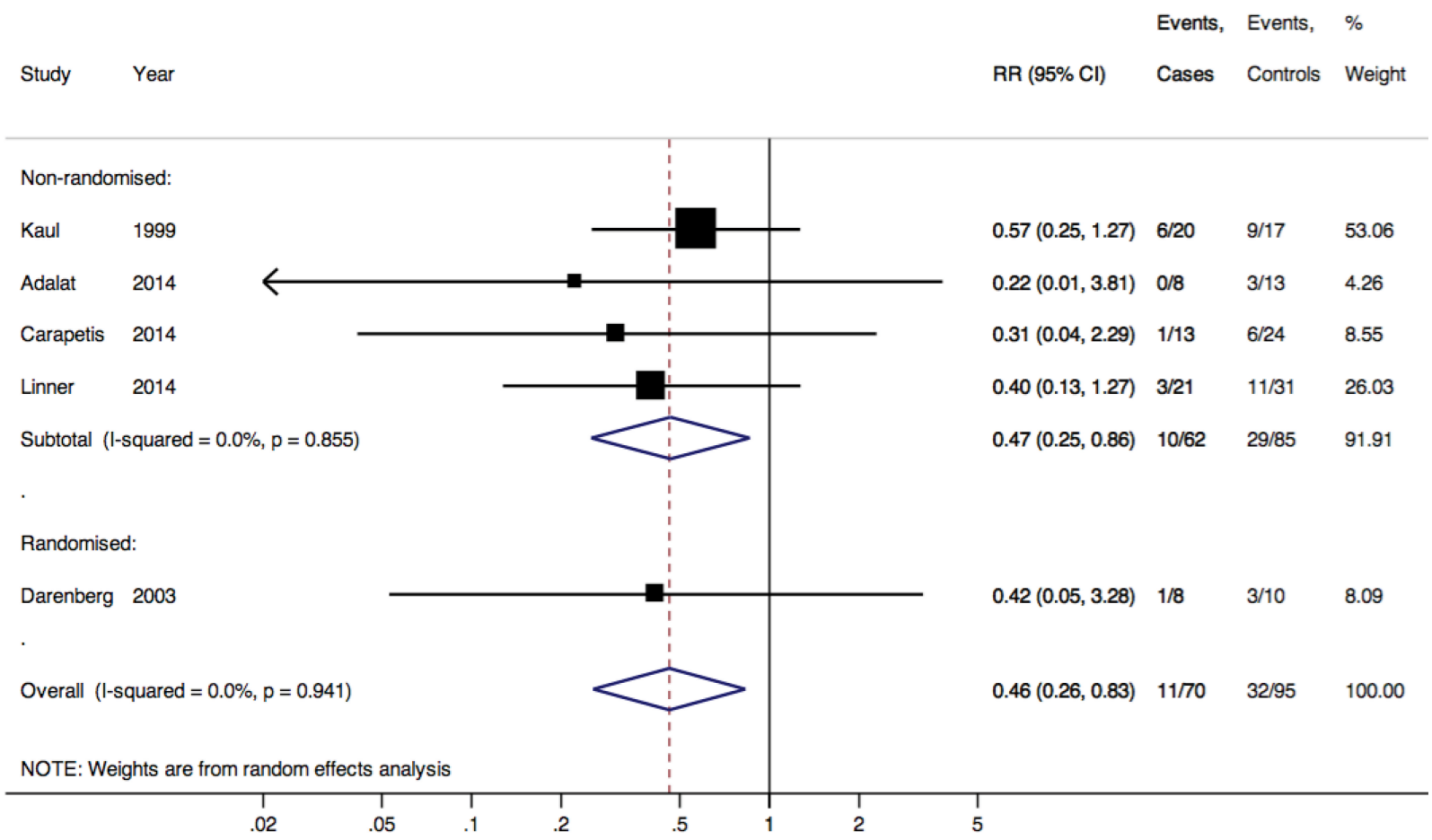
We thank the authors of the underlying studies who responded to our requests for a breakdown of their results by use of clindamycin.

References

1. Stevens DL. Streptococcal toxic-shock syndrome: spectrum of disease, pathogenesis, and new concepts in treatment. Emerging Infect Dis **1995**; 1:69–78.
2. The Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. JAMA **1993**; 269:390–391.
3. Lamagni TL, Neal S, Keshishian C, et al. Predictors of death after severe Streptococcus pyogenes infection. Emerging Infect Dis **2009**; 15:1304–1307.
4. Sriskandan S, Ferguson M, Elliot V, Faulkner L, Cohen J. Human intravenous immunoglobulin for experimental streptococcal toxic shock: bacterial clearance and modulation of inflammation. J Antimicrob Chemother **2006**; 58:117–124.
5. Darenberg J, Ihendyane N, Sjölin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis **2003**; 37:333–340.
6. Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study. The Canadian Streptococcal Study Group. Clin Infect Dis **1999**; 28:800–807.
7. Carapetis JR, Jacoby P, Carville K, Ang S-JJ, Curtis N, Andrews R. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. Clin Infect Dis **2014**; 59:358–365.
8. Linnér A, Darenberg J, Sjölin J, Henriques-Normark B, Norrby-Teglund A. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis **2014**; 59:851–857.
9. Adalat S, Dawson T, Hackett SJ, Clark JE, In association with the British Paediatric Surveillance Unit. Toxic shock syndrome surveillance in UK children. Arch Dis Child **2014**; 99:1078–1082.
10. Mehta S, McGeer A, Low DE, et al. Morbidity and mortality of patients with invasive group A streptococcal infections admitted to the ICU. Chest **2006**; 130:1679–1686.
11. Shah SS, Hall M, Srivastava R, Subramony A, Levin JE. Intravenous immunoglobulin in children with streptococcal toxic shock syndrome. Clin Infect Dis **2009**; 49:1369–1376.

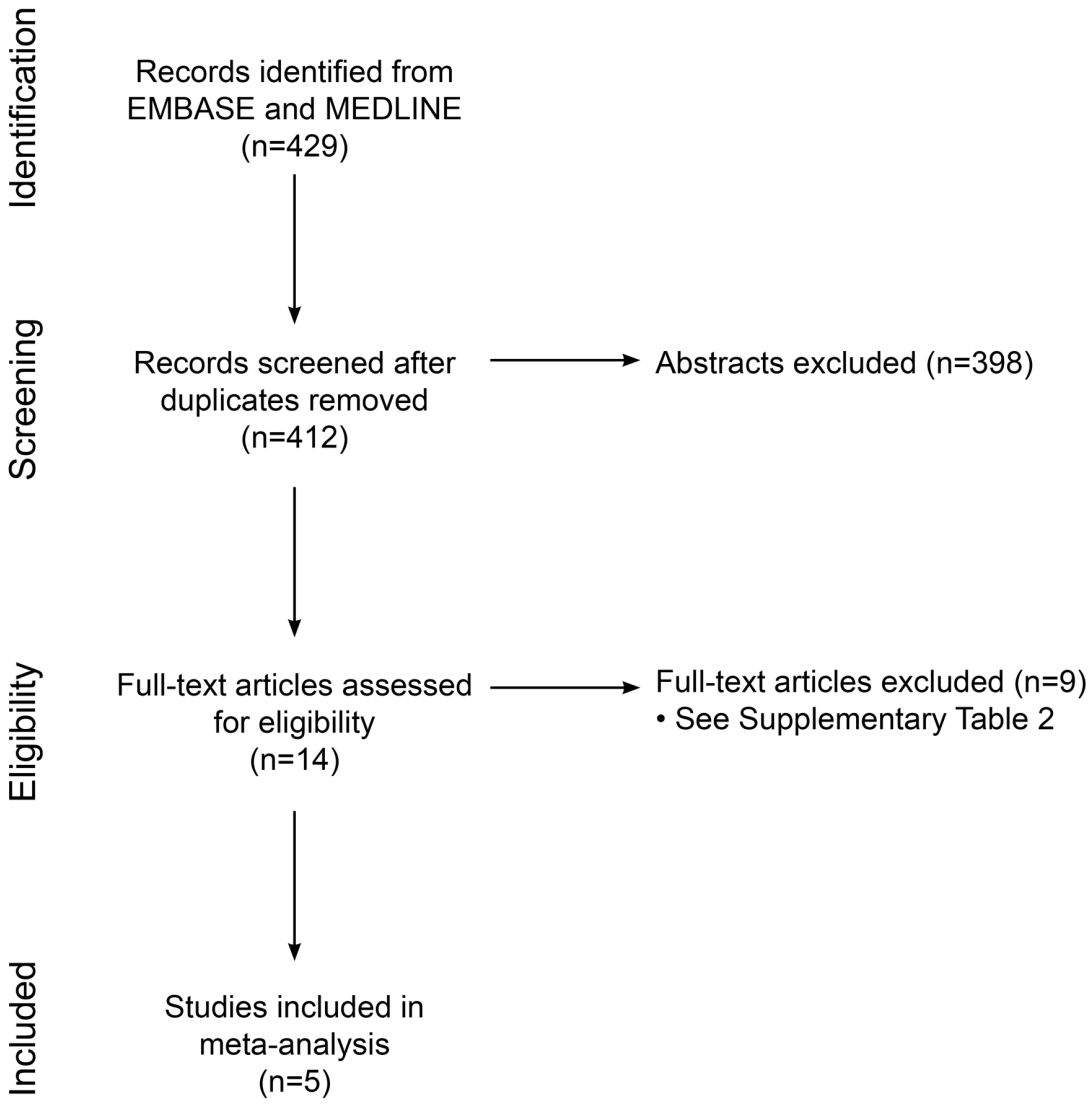
12. Kadri SS, Swihart BJ, Bonne SL, et al. Impact of Intravenous Immunoglobulin on Survival in Necrotizing Fasciitis with Vasopressor-dependent Shock: A Propensity-Score Matched Analysis from 130 US Hospitals. Clin Infect Dis **2016**;64:877-885.

Figure 1. Forest plot showing the estimated risk ratio for mortality with and without IVIG in clindamycin-treated STSS

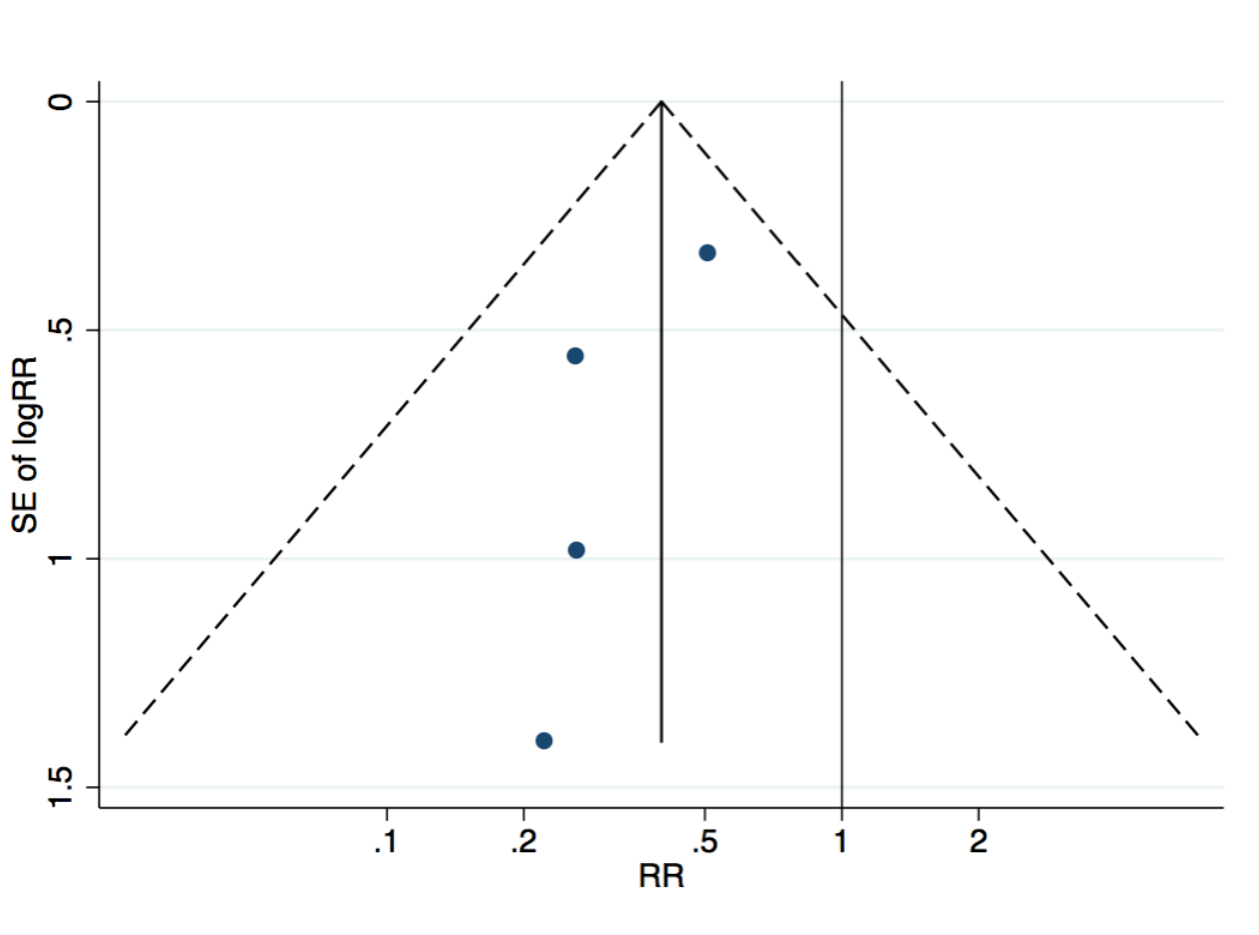

Study
Year
RR (95% CI)
Events, Cases
Events, Controls
% Weight
Non-randomised:
Kaul 1999 0.57 (0.25, 1.27) 6/20 9/17 53.06
Adalat 2014 0.22 (0.01, 3.81) 0/8 3/13 4.26
Carapetis 2014 0.31 (0.04, 2.29) 1/13 6/24 8.55
Linner 2014 0.40 (0.13, 1.27) 3/21 11/31 26.03
Subtotal (I-squared = 0.0%, p = 0.855) 0.47 (0.25, 0.86) 10/62 29/85 91.91
.
Randomised:
Darenberg 2003 0.42 (0.05, 3.28) 1/8 3/10 8.09
.
Overall (I-squared = 0.0%, p = 0.941) 0.46 (0.26, 0.83) 11/70 32/95 100.00
NOTE: Weights are from random effects analysis
.02
.05
.1
.2
.5
1
2
5

Search strategy: MEDLINE/EMBASE (OVID)
1. (streptococcus or streptococcal).af.
2. limit 1 to english language
3. limit 2 to yr="1980 - 2017"
4. (intravenous immunoglobulin or ivig).af.
5. 3 and 4

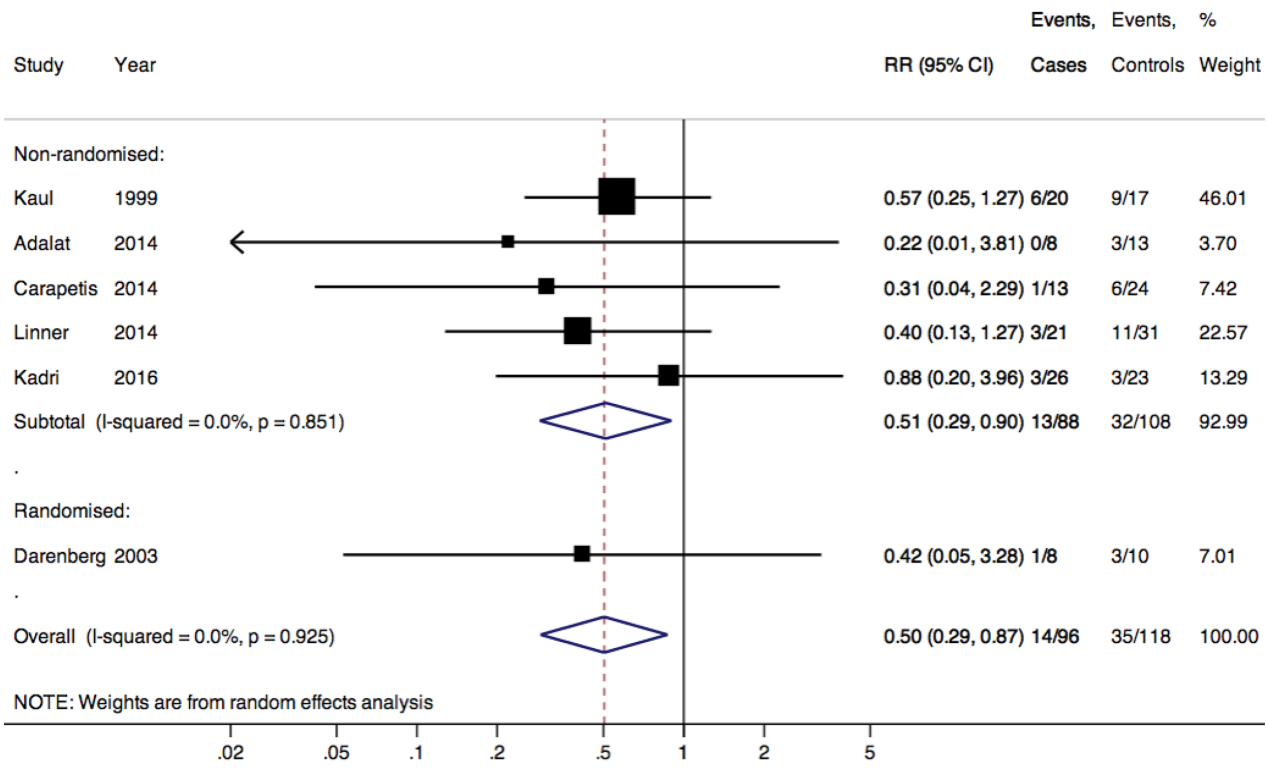
Supplementary Figure 1. Search strategy



Supplementary Figure 2. Flow diagram showing study selection



Supplementary Figure 3. Funnel plot for the non-randomised studies showing the unadjusted risk ratio for mortality with and without IVIG calculated from the full reported dataset (i.e. irrespective of clindamycin, GAS or STSS)



Supplementary Figure 4. Forest plot showing the estimated risk ratio for mortality with and without IVIG in clindamycin-treated STSS with the addition of data from the propensity-matched case-control analysis by Kadri *et al.* [12].

Supplementary Table 1. Summary of the included studies

Study	Location	Year	Design	Age range	Outcome	Intervention	Cases	Controls	Ref.
Kaul *et al.* 1999	Canada	1992-1995	Non-randomised with historical controls	Adults (mean 56.8 years; range not reported)	Mortality at 30 days	IVIG vs standard care	GAS-associated STSS patients identified prospectively through surveillance treated with IVIG	GAS-associated STSS patients identified prospectively through earlier surveillance not treated with IVIG	[6]
Darenberg *et al.* 2003	Sweden, Norway, Finland, Netherlands	1999-2001	Randomised double-blind, placebo-controlled trial	Adults (28-83 years)	Mortality at 28 days	IVIG vs placebo (equal vol. 1% albumin)	STSS patients enrolled on the basis of suspicion of GAS infection randomised to IVIG	STSS patients enrolled on the basis of suspicion of GAS infection randomised to placebo	[5]
Carapetis *et al.* 2014	Australia	2002-2004	Non-randomised with concurrent controls	Adults and children (3-88 years)	Mortality at 30 days	IVIG vs standard care	Severe IGAS patients identified prospectively through surveillance treated with IVIG	Severe IGAS patients identified prospectively through surveillance not treated with IVIG	[7]
Linnér *et al.* 2014	Sweden	2002-2004	Non-randomised with concurrent controls	Adults (31-92 years)	Mortality at 28 days	IVIG vs standard care	GAS-associated STSS patients identified prospectively through surveillance treated with IVIG	GAS-associated STSS patients identified prospectively through surveillance not treated with IVIG	[8]
Adalat *et al.* 2014	UK	2008-2009	Non-randomised with concurrent controls	Children (0-15 years)	Mortality at 28 days	IVIG vs standard care	GAS-associated STSS patients identified prospectively through surveillance treated with IVIG	GAS-associated STSS patients identified prospectively through surveillance not treated with IVIG	[9]

Supplementary Table 2. Summary of the excluded studies

Study	Location	Year	Principal Reason(s) for Exclusion	Total IGAS	Proportion STSS	Ref.
Haywood *et al.* 1999	Canada	1995-1997	Less than 10 STSS cases	20	5/20 (25%)	[13]
Huang *et al.* 2001	Taiwan	1995-2000	Retrospective study	76	12/76 (16%)	[14]
Norrby-Teglund *et al.* 2005	Canada	1996-2002	Less than 10 STSS cases	7	6/7 (86%)	[15]
Mehta *et al.* 2006	Canada	1992-2002	Subset data unavailable	62	34/62 (55%)	[10]
Aronoff & Mulla 2008	USA	1996-2001	Retrospective study Less than 10 STSS cases	7	1/7 (14%)	[16]
Shah *et al.* 2009	USA	2003-2007	Retrospective study Consensus criteria not used	192	192/192 (100%)	[11]
McViety *et al.* 2014	UK	2008-2013	Retrospective study No deaths in clindamycin treated cases	23	17/23 (74%)	[17]
Chen *et al.* 2016	Australia	2003-2014	Retrospective study No deaths in clindamycin treated cases	19	19/19 (100%)	[18]
Kadri *et al.* 2016*	USA	2010-2014	Retrospective study Consensus criteria not used	228	228/228(100%)	[12]

*In total 50 of 228 (21.9%) patients with coding for GAS in the entire study were included in the propensity-matched analysis.

Supplementary Table 3. Derivation of subgroup of interest from included studies

Study	Total IGAS	Proportion STSS	Proportion treated with clindamycin	Proportion treated with clindamycin & IVIG (i.e. cases)	Proportion treated with clindamycin & not IVIG (i.e. controls)	Ref.
Kaul *et al.* 1999*	53	53/53 (100%)	37/53 (37%)	20/37 (54%)	17/37 (46%)	[6]
Darenberg *et al.* 2003	18	18/18 (100%)	18/18 (100%)	8/18 (44%)	10/18 (56%)	[5]
Carapetis *et al.* 2014†	84	49/84 (58%)	37/49 (76%)	13/37 (35%)	24/37 (65%)	[7]
Linnér *et al.* 2014	746	67/746 (9%)	52/67 (78%)	21/52 (40%)	31/52 (60%)	[8]
Adalat *et al.* 2014	29	29/29 (100%)	21/29 (72%)	8/21 (38%)	13/21 (62%)	[9]

*Data on clindamycin not available for one control who died.
†Includes severe IGAS patients with and without STSS; 49 classified as having STSS.

Supplementary Table 4. Risk of bias in the non-randomised studies [19]

Study	Confounding at baseline*	Bias in selection	Bias in classification	Bias in deviations	Bias in missingness	Bias in measurement	Bias in reporting	Ref.
Kaul *et al.* 1999	Moderate	Low	Low	Low	Low	Low	Low	[6]
Carapetis *et al.* 2014	Moderate	Low	Moderate	Low	Low	Low	Moderate	[7]
Linnér *et al.* 2014	Moderate	Low	Moderate	Low	Low	Low	Low	[8]
Adalat *et al.* 2014	Serious	Low	Moderate	Low	Low	Low	Low	[9]

*Data included in the meta-analysis was corrected for confounding only by limiting the analysis to patients treated with clindamycin.

Supplementary Table 5. Risk of bias in the randomized control trial [20]

Study	Bias in selection	Bias in performance	Bias in detection	Bias in attrition	Bias in reporting	Other bias	Ref.
Darenberg *et al.* 2003	Unclear*	Low	Low	Low	Low	Stopped early	[5]

*Neither random sequence nor allocation concealment reported.

Supplementary Table 6. Summary results of included studies

Study	Mortality in full dataset (i.e. irrespective of clindamycin, GAS or STSS)		Mortality in subgroup of interest (i.e. clindamycin-treated STSS)		Ref.
	Cases	Controls	Cases	Controls	
Kaul *et al.* 1999	7/21 (33%)	21/32 (66%)	6/20 (30%)	9/17 (53%)	[6]
Darenberg *et al.* 2003	1/10 (10%)	4/11 (36%)	1/8 (13%)	3/10 (30%)	[5]
Carapetis *et al.* 2014†	1/14 (7%)	19/70 (27%)	1/13 (8%)	6/24 (25%)	[7]
Linnér *et al.* 2014	3/23 (13%)	22/44 (50%)	3/21 (14%)	11/31 (35%)	[8]
Adalat *et al.* 2014	0/8 (0%)	10/41 (24%)	0/8 (0%)	3/13 (23%)	[9]

Supplementary Table 7. Derivation of subgroup of interest from the propensity-matched case-control analysis in Kadri *et al.* [12]

Study	Total IGAS	Proportion STSS	Proportion treated with clindamycin	Proportion treated with clindamycin & IVIG (i.e. cases)	Proportion treated with clindamycin & not IVIG (i.e. controls)	Ref.
Kadri *et al.* 2016	50*	50/50 (100%)†	49/50 (100%)	26/49 (53%)	23/49 (47%)	[12]

*In total 50 of 228 (21.9%) patients with coding for GAS in the entire study were included in the propensity-matched analysis.
†Only 25 of the 49 patients with coding for GAS and clindamycin in the propensity-matched analysis also had coding for toxic shock syndrome. For the purposes of this analysis, however, we presumed all 49 would have met diagnostic criteria for STSS based on the combination of GAS, vasopressor-dependent shock and necrotising infection.

Supplementary References

13. Haywood CT, McGeer A, Low DE. Clinical experience with 20 cases of group A Streptococcus necrotizing fasciitis and myonecrosis: 1995 to 1997. Plast. Reconstr. Surg. **1999**; 103:1567–1573.
14. Huang YC, Chiu CH, Chang LY, Leu HS, Lin TY. Characteristics of group A streptococcal bacteremia with comparison between children and adults. J Microbiol Immunol Infect **2001**; 34:195–200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/?term=11605811.
15. Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. Scand. J. Infect. Dis. **2005**; 37:166–172.
16. Aronoff DM, Mulla ZD. Postpartum invasive group A streptococcal disease in the modern era. Infect Dis Obstet Gynecol **2008**; 2008:796892–6.
17. McViety J, Horan M, Timmis A, Parkins K. Don't forget IGAS: Lessons learnt from review of 2 peak seasons in the North West and North Wales, UK [Abstract 665]. Paediatric Critical Care Medicine **2014**; 15:115.
18. Chen KYH, Cheung M, Burgner DP, Curtis N. Toxic shock syndrome in Australian children. Arch Dis Child **2016**; 101:736–740.
19. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ **2016**; 355:i4919.
20. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ **2011**; 343:d5928–d5928.