

Risk of bias in pediatric critical care randomized controlled trials: A systematic review

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Background

Risk of bias is a critical consideration when interpreting and applying the results of randomized controlled trials (RCTs).

Objectives

To describe the risk of bias in RCTs in pediatric critical care, changes over time and the characteristics of trials at high risk of bias.

Methods

Searching: We identified trials by searching the Evidence in Pediatric Intensive Care Database (epicc.mcmaster.ca). This is a database of published pediatric critical care RCTs found by searching MEDLINE, EMBASE, LILACS and CENTRAL (Updated July 4, 2013).

Inclusion criteria: RCTs or quasi-RCTs that:

- were published in English
- administered any intervention to children in an intensive care or critical care unit

Exclusion criteria: We excluded studies that were:

- trials enrolling exclusively pre-term infants
- cross-over trials
- only published as an abstract

Data extraction: Pairs of reviewers independently screened trials for eligibility and abstracted data. Discrepancies were resolved by consensus. We used the Cochrane Risk of Bias Tool to rate each of the following: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.

Analysis and reporting: We then classified the overall risk of bias for each trial as low (low risk of bias in all domains), high (high risk of bias in at least one domain), or unclear.

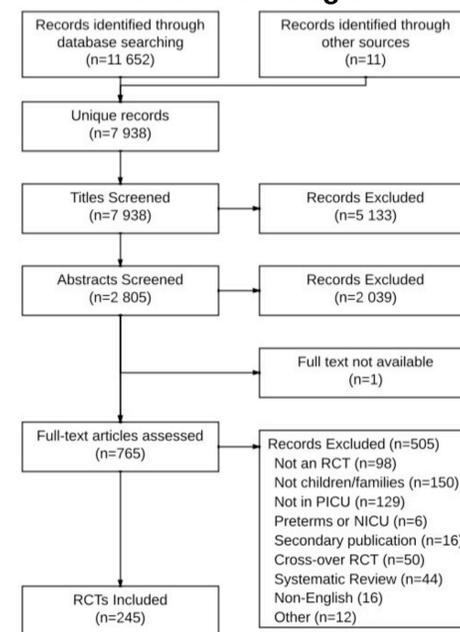
We used chi-square and t-tests to compare studies at high risk of bias to other studies. To assess for changes over time we divided the trials into quintiles based on the year of publication.

Included trials

We included 245 trials. Trials were conducted in 34 different countries and published in 86 different journals. The number of trials published per year increased between 1987 and 2012.

Trials most commonly studied medications (58%) and were single centred (20%). The median (Q1, Q2) number of children randomized was 48 (30, 96).

Review flow diagram



Risk of bias

12 trials (5%) were at low risk of bias for all domains, all published since 2006. The proportion at low risk of bias increased over time (p for trend <0.001).

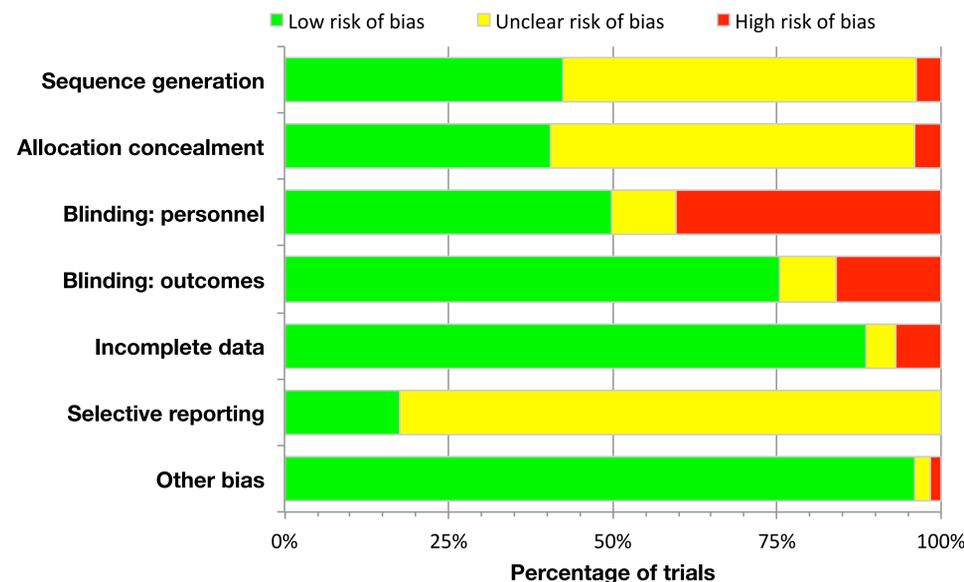
109 trials (44%) were at high risk of bias for at least one domain, most frequently lack of blinding.

Trials of non-pharmacological interventions less frequently reported blinding than those studying medications, 55% and 35% respectively ($p=0.001$).

124 trials (51%) were at unclear overall risk of bias. The majority of trials were assessed as unclear risk of bias with respect to sequence generation, allocation concealment and selective reporting.

Reporting was more complete in the more recent trials. The mean number of domains assessed as unclear decreased from 3.4 in the first quintile to 1.6 in the most recent quintile (p for trend <0.001). 64% of trials published since 2011 reported that the trial was registered.

Risk of bias in 245 pediatric critical care RCTs

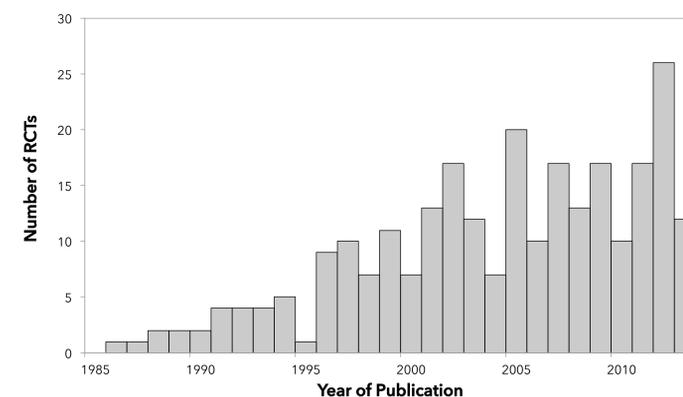


RCTs at high risk of bias compared to those at low or unclear risk of bias

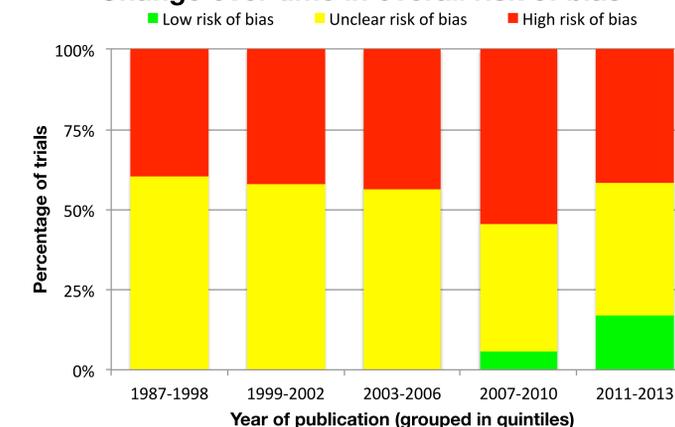
Characteristic	High risk of bias (n=109)	Low or unclear risk of bias (n=136)	P value
Commercial funding	16 (15)	22 (16)	0.75
Studied medications	50 (46)	91 (67)	<0.01
Reported blinding	31 (28)	100 (74)	<0.01
Children randomized/trial	48 (30, 97)	50 (30, 97)	0.94
Multicentre design	20 (18)	28 (21)	0.66
Stopped early	10 (9)	22 (16)	0.11
Positive results	30 (28)	33 (24)	0.56

Data are presented as number (%) or median (Q1, Q2)

Number of trials published per year



Change over time in overall risk of bias



Conclusions

Many trials in pediatric critical care are at high risk of bias, most commonly because of lack of blinding. Trials studying non-pharmacological interventions less frequently report blinding. While the proportion of trials at low risk of bias is small, these are increasing over time.

The majority of these trials are at unclear overall risk of bias, primarily due to incomplete reporting. The reporting of key elements required to assess the risk of bias is improving over time but remains sub-optimal.