Observation studies vs therapeutic trials in three journals over three decades of pediatric critical care: a systematic review.

John Scott Baird (jsb106@cumc.columbia.edu)

Research article

Keywords: impact factor, citation count, PICU

Posted Date: December 18th, 2019

DOI: https://doi.org/10.21203/rs.2.19219/v1

Abstract

Background: Pediatric critical care developed rapidly as a medical subspecialty over the three decades since 1987, concurrent with a decline in Pediatric ICU mortality rates. It would be interesting to know if research characterized as observation studies or therapeutic trials had a greater impact on this subspecialty during this time. Methods: Three journals with a broad range of impact factors which published pediatric critical care research between 1988 and 2017 were chosen for a systematic review, including a PubMed search for all pediatric critical care studies in these journals during the study period. Studies were characterized as either observation studies or therapeutic trials. Each study's impact was assessed using citation counts collected from Google Scholar.

Results: Therapeutic trials as a percentage of research studies increased with a journal's impact factor; in addition, therapeutic trials were cited more frequently than observation studies. However, there were more observation studies than therapeutic trials, the citation count increased for both observation studies and therapeutic trials as a journal's impact factor increased, and the citation count was similar for some or all observation studies and therapeutic trials in two of the study journals. The 10 most cited studies included 7 observation studies and 3 therapeutic trials.

Conclusions: This systematic review of three journals suggests that both observation studies and therapeutic trials contributed to the impact of research in pediatric critical care during the three decades following 1987.

Background

The development of pediatric critical care as a medical subspecialty acquired momentum in the 1980's, including the first major textbook and the first subspecialty board examination for physicians, both in 1987. In the three decades since, the Pediatric ICU (PICU) mortality rate has progressively declined[1–3]; the impact of research in pediatric critical care on that decline is unknown. Randomized controlled trials (RCTs) have been considered superior to observation studies in the evaluation of medical therapies[4], and over several decades RCTs have increased in frequency in some journals with high impact factors[5]. It would be interesting to know if observation studies or therapeutic trials- including RCTs- had more of an impact on this subspecialty during these three decades, prompting this systematic review.

Three journals which represent important forums for pediatric critical care research were selected for this systematic review; their impact factors span a broad range. Citation counts have been used to assess the impact of medical research[6]; they were reviewed for all observation studies and therapeutic trials identified in these three journals during the study period.

Methods

The New England Journal of Medicine (N Engl J Med), the American Journal of Respiratory and Critical Care Medicine (Am J Resp Crit Care Med), and Pediatric Critical Care Medicine (Pediatr Crit Care Med)

published pediatric critical care research during at least some of the study period (1988 to 2017), and were selected for review as their impact factors span a broad range. The American Review of Respiratory Diseases (Am Rev Respir Dis) was renamed in 1994 as the American Journal of Respiratory and Critical Care Medicine (Am J Resp Crit Care Med); both journal titles were searched, and results included for both journals as Am J Resp Crit Care Med. Pediatr Crit Care Med did not begin publication until 2000; it is included as it was the first peer-reviewed journal to focus exclusively on pediatric critical care, and it has been an important forum for research in this field. The impact factors for 2017 were collected from Journal Citation Reports from Clarivate Analytics (www.clarivate.com).

A MEDLINE/PubMed search limited to human studies and using the terms “pediatric critical care” or “pediatric intensive care” with each journal abbreviation during the study period was performed in May and June, 2019. Studies for inclusion were those characterized as either a therapeutic trial (in which a novel therapy or intervention is compared to a standard, either current or historical, not limited to prospective or randomized or blinded studies) or an observation study (in which a novel observation of physiology, a disease, or its therapy is presented). Therapeutic trials with a negative result included those which failed to show a benefit to a novel therapy or intervention. RCTs were always characterized as therapeutic trials (and included those in which the patient served as his/her own control), while case reports (up to 3 patients per report; case records or discussions were considered case reports only if they satisfied criteria for observation studies) were always characterized as observation studies. Other study types- including cohort, case-control, cross-sectional studies, and case series (including more than 3 patients)- all required a review of the published study to determine if the primary goal of the study was to report a comparison consistent with a therapeutic trial or instead satisfied criteria for an observation study. A reanalysis of a previously published study was always characterized as an observation study. Studies exclusively in a NICU or adult ICU or on a pediatric ward, or focused exclusively on neonates or adults in a PICU, were excluded, as were editorials, letters to the editor, quality improvement studies, reviews, simulation studies, training materials, and surveys.

Google Scholar (www.scholar.google.com) is a freely accessible web search engine, and was used to determine citation counts on the Google Scholar database in May and June, 2019.

Statistical methods:

Data are presented as medians; 95% confidence intervals are included in the figures. Statistical testing was performed using nonparametric methods whenever possible. Continuous variables were compared using Mann-Whitney tests. Dichotomous variables were compared using Fisher’s exact or Chi-square tests, or Chi-square tests for trend as appropriate. Correlations were analyzed by Spearman or Kruskal-Wallis tests, as appropriate. Statistical tests were two-sided, with significance set at $p < 0.05$. All calculations were obtained using Prism 8 for MacOS (GraphPad Software, Inc; San Diego, CA).

Results

2482 records for possible inclusion in this review were identified from the PubMed search, and 1113 of these records satisfied criteria for either observation studies or therapeutic trials (Fig. 1). A PubMed search using Pediatr Crit Care Med did not yield any results prior to 2003, so the PubMed search for this journal included 2003 to 2017 only; the table of contents for each issue of this journal from 2000 to 2002 was then reviewed to identify studies which also satisfied inclusion criteria: 90 studies were identified, yielding a total of 1203 studies from the three journals during the study period.

From this total, there were more observation studies than therapeutic trials (1092 vs 111, 91 vs 9% of studies; Table I). Case reports made up 15% (162 of 1092) of all observation studies, while RCTs made up 48% (53 of 111) of all therapeutic trials. All therapeutic trials were RCTs in N Engl J Med and Am J Resp Crit Care Med, but only 39% (37 of 95) of therapeutic trials were RCTs in Pediatr Crit Care Med. Negative results of therapeutic trials were noted in 31% (34 of 111), and this was similar across journals (N Engl J Med combined with Am J Resp Crit Care Med vs Pediatr Crit Care Med: 7 of 16 vs 27 of 95; $p = 0.22$). Therapeutic trials as a percentage of total studies (observation studies and therapeutic trials) in a journal increased with that journal's impact factor ($p < 0.0001$; Table I).

Observation studies were cited less than therapeutic trials (medians: 21 vs 36; $p < 0.0001$; Fig. 2A), and case reports were cited less than other observation studies (medians: 15 vs 22; $p < 0.0001$). RCTs were cited more than other therapeutic trials (medians: 59 vs 26; $p = 0.003$). Negative therapeutic trials were cited as often as positive therapeutic trials (medians: 30 vs 36; $p = 0.42$); the difference was not quite significant when negative therapeutic trials were compared to observation studies (medians: 30 vs 21; $p = 0.05$).

The citation count for observation studies differed across journals ($p < 0.0001$; Fig. 2B), and increased with a journal's impact factor: observation studies in N Engl J Med were cited more than observation studies in Am J Resp Crit Care Med (medians: 261 vs 78; $p = 0.004$), and observation studies in Am J Resp Crit Care Med were cited more than observation studies in Pediatr Crit Care Med (medians: 78 vs 20; $p < 0.0001$). The citation count for therapeutic trials also differed across journals ($p < 0.0001$; Fig. 2C): therapeutic trials in N Engl J Med and Am J Resp Crit Care Med were cited more than therapeutic trials in Pediatr Crit Care Med (N Engl J Med and Am J Resp Crit Care Med vs Pediatr Crit Care Med medians: 145 vs 27; $p < 0.0001$).

Observation studies in N Engl J Med had a similar median citation count compared to therapeutic trials in N Engl J Med (medians: 261 vs 155; $p = 0.41$), while observation studies in Am J Resp Crit Care Med or Pediatr Crit Care Med were cited less than therapeutic trials in each journal (Am J Resp Crit Care Med medians: 78 vs 124; $p = 0.04$; Pediatr Crit Care Med medians: 20 vs 27; $p = 0.008$). However, when case reports were excluded, the citation count was similar in Am J Resp Crit Care Med for observation studies compared to therapeutic trials (medians: 93 vs 124; $p = 0.07$).

The 10 studies with the greatest impact included 7 observation studies[7–13] and 3 therapeutic trials[14–16]. These studies were each cited between 470 to 883 times.

Discussion

Using a definition of observation studies which excluded studies comparing therapeutic outcomes, this systematic review of pediatric critical care research suggests that both observation studies and therapeutic trials contributed to the impact of this research during the study period. In summary:

1.
The percentage of therapeutic trials increased with a journal's impact factor, and all therapeutic trials were RCTs in the 2 journals with the highest impact factors. Therapeutic trials were also cited more frequently than observation studies, and RCTs were cited more than other therapeutic trials. Therapeutic trials- and RCTs in particular- thus appeared to contribute more than observation studies to a journal's impact, suggesting a hierarchy of research study designs, with RCTs near the apex.
2.
However, there were more observation studies overall, and the citation count increased for both observation studies and therapeutic trials as a journal's impact factor increased. In addition, several observation studies were among the most cited studies overall. Moreover, the citation count was similar for some or all observation studies and therapeutic trials in the 2 journals with the highest impact factors, suggesting a similar contribution of observation studies compared to therapeutic trials in these journals; this is inconsistent with a hierarchy of research study designs. A "halo" effect[17], in which a journal's impact factor contributes to a study's citation count independent of research study design, could explain these findings.

Limitations to the data generated in this systematic review include the arbitrary definitions used to categorize studies: observation studies have previously included (by definition) non-RCT therapeutic trials[18, 19]. The separation of observation studies from therapeutic trials in this review helped reveal the impact of observation studies not focused on specific medical therapies. An additional limitation is that the impact of research not characterized as an observation study or a therapeutic trial (e.g., letters to the editor, quality improvement studies, reviews, simulation studies, training materials, and surveys; also: animal or laboratory studies, or pediatric critical care studies performed in a non-PICU setting) was not assessed. Finally, the quality of medical research is only indirectly related to its impact[20], and accepted metrics for quality assessment of medical research are not yet available: no assessment of the quality of observation studies or therapeutic trials was made in this review.

In a defense of case reports in critical care, Mark Helfaer wrote: "We are left with the two sets of tools of medical knowledge: the clinical trials and the observational reports. It is up to the clinicians to be able to meld these two sets of tools so that our patients can benefit from the science and the powers of observation[21]." After three decades of research in pediatric critical care, declining PICU mortality rates suggest that our patients have indeed benefitted from both the science and the powers of observation.

Conclusions

This systematic review of three journals with a broad range of impact factors suggests that both observation studies and therapeutic trials contributed to the impact of research in pediatric critical care during the three decades following 1987.

Declarations

Abbreviations:

Am J Resp Crit Care Med: American Journal of Respiratory and Critical Care Medicine

N Engl J Med: New England Journal of Medicine

Pediatr Crit Care Med: Pediatric Critical Care Medicine

PICU: pediatric intensive care unit

RCT: randomized controlled trial

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The author declares that he has no competing interests.

Funding: Not applicable (none).

Author’s contributions: JSB formulated the study, analyzed and interpreted all data, and takes sole responsibility for the manuscript.

Acknowledgements: Not applicable.

References

1.

Pollack MM, Ruttimann UE, Getson PR. Accurate prediction of the outcome of pediatric intensive care. A new quantitative method. N Engl J Med. 1987;316(3):134–9.
2.
Namachivayam P, Shann F, Shekerdemian L, Taylor A, van Sloten I, Delzoppo C, Daffey C, Butt W. Three decades of pediatric intensive care: Who was admitted, what happened in intensive care, and what happened afterward. Pediatr Crit Care Med. 2010;11(5):549–55.
3.
Pollack MM, Holubkov R, Funai T, Berger JT, Clark AE, Meert K, Berg RA, Carcillo J, Wessel DL, Moler F, et al. Simultaneous Prediction of New Morbidity, Mortality, and Survival Without New Morbidity From Pediatric Intensive Care: A New Paradigm for Outcomes Assessment. Crit Care Med. 2015;43(8):1699–709.
4.
Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? N Engl J Med. 2000;342(25):1907–9.
5.
McDermott MM, Lefevre F, Feinglass J, Reifler D, Dolan N, Potts S, Senger K. Changes in study design, gender issues, and other characteristics of clinical research published in three major medical journals from 1971 to 1991. J Gen Intern Med. 1995;10(1):13–8.
6.
Garfield E. Which medical journals have the greatest impact? Ann Intern Med. 1986;105(2):313–20.
7.
Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med. 2003;167(5):695–701.
8.
Libster R, Bugna J, Coviello S, Hijano DR, Dunaiewsky M, Reynoso N, Cavalieri ML, Guglielmo MC, Areso MS, Gilligan T, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med. 2010;362(1):45–55.
9.
Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, Charpie JR, Hirsch JC. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med. 2010;11(2):234–8.
10.
Kipper DJ, Piva JP, Garcia PC, Einloft PR, Bruno F, Lago P, Rocha T, Schein AE, Fontela PS, Gava DH, et al. Evolution of the medical practices and modes of death on pediatric intensive care units in southern Brazil. Pediatr Crit Care Med. 2005;6(3):258–63.
11.
Zawistowski CA, DeVita MA. A descriptive study of children dying in the pediatric intensive care unit after withdrawal of life-sustaining treatment. Pediatr Crit Care Med. 2004;5(3):216–23.
12.

Althabe M, Cardigni G, Vassallo JC, Allende D, Berrueta M, Codermatz M, Cordoba J, Castellano S, Jabornisky R, Marrone Y, et al. Dying in the intensive care unit: collaborative multicenter study about forgoing life-sustaining treatment in Argentine pediatric intensive care units. Pediatr Crit Care Med. 2003;4(2):164–9.
13.
Tsai E, Shemie SD, Cox PN, Furst S, McCarthy L, Hebert D. Organ donation in children: role of the pediatric intensive care unit. Pediatr Crit Care Med. 2000;1(2):156–60.
14.
Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, et al. Hypothermia therapy after traumatic brain injury in children. N Engl J Med. 2008;358(23):2447–56.
15.
Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano BJ, Robillard P, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007;356(16):1609–19.
16.
Groothuis JR, Simoes EA, Levin MJ, Hall CB, Long CE, Rodriguez WJ, Arrobio J, Meissner HC, Fulton DR, Welliver RC, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. N Engl J Med. 1993;329(21):1524–30.
17.
Zhang Z, Poucke SV. Citations for Randomized Controlled Trials in Sepsis Literature: The Halo Effect Caused by Journal Impact Factor. PLoS One. 2017;12(1):e0169398.
18.
Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000;342(25):1887–92.
19.
Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med. 2000;342(25):1878–86.
20.
Garfield E. How can impact factors be improved? BMJ 1996, 313(7054):411–413.
21.
Helfaer MA. Role of case reports in medical literature: bathwater has not been shown to cleanse babies. Pediatr Crit Care Med. 2002;3(3):311–2.

Table 1

Table I: Pediatric critical care observation studies and therapeutic trials in 3 journals over 3 decades.

	Total number of observation studies (number of case reports)	Total number of therapeutic trials (number of RCTs)	Therapeutic trials/therapeutic trials + observation studies, %	2017 impact factor
New England Journal of Medicine	4 (0)	11 (11)	73	72
American Review of Respiratory Diseases/ American Journal of Respiratory and Critical Care Medicine	39 (4)	5 (5)	11	15
Pediatric Critical Care Medicine	1049 (158)	95 (37)	8	3

Figures

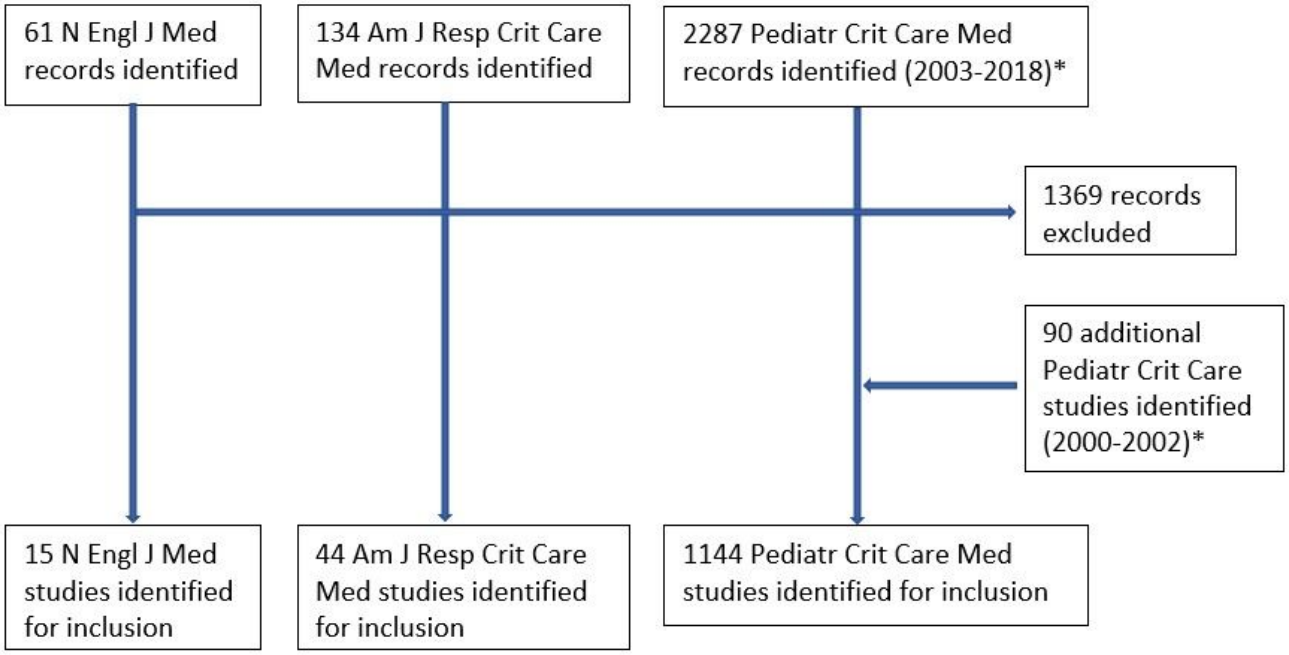

Figure 1

Flowchart of study selection for systematic review. *: see text in Results.

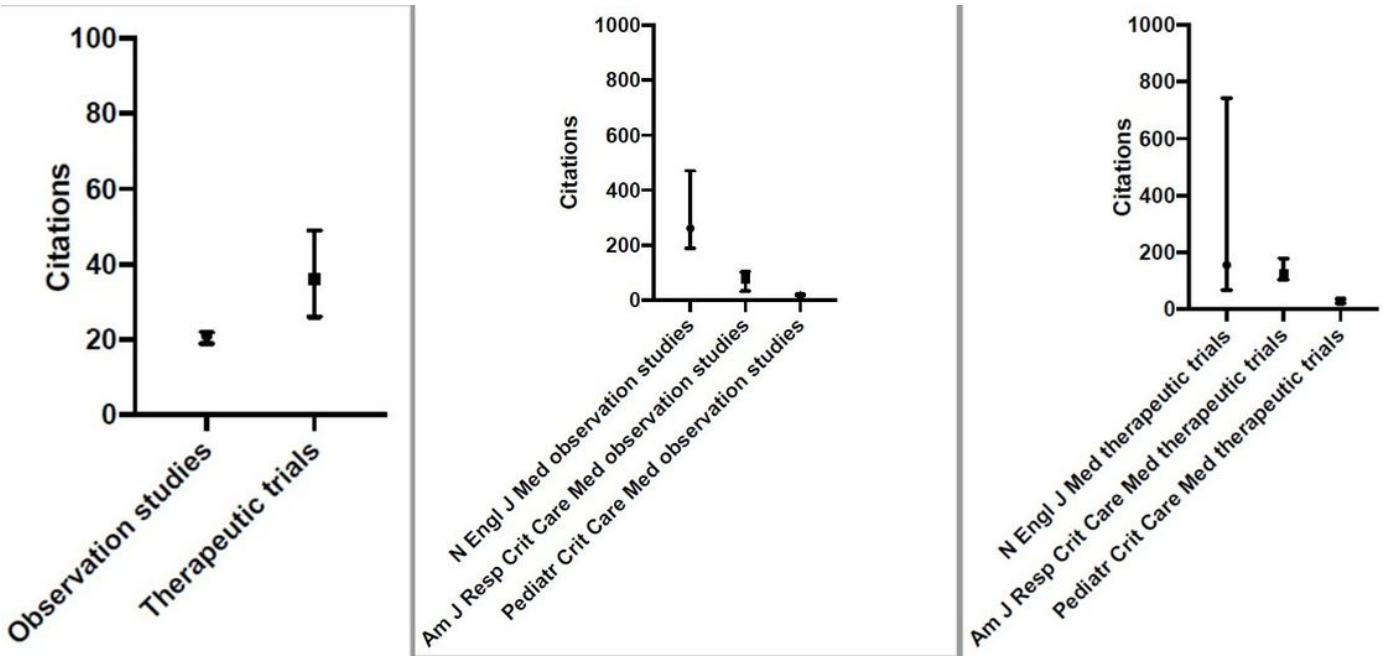

Figure 2

Figure 2A: Citation counts for pediatric critical care observation studies vs therapeutic trials in 3 journals over 3 decades (medians with 95% confidence intervals). Figure 2B: Citation counts for pediatric critical care observation studies in 3 journals over 3 decades (medians with 95% confidence intervals). Figure 2C: Citation counts for pediatric critical care therapeutic trials in 3 journals over 3 decades (medians with 95% confidence intervals).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc