Transfusion Medicine Reviews 30 (2016) 217–222

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Pediatric Therapeutic Apheresis: A Critical Appraisal of Evidence

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ARTICLE INFO

Available online 8 August 2016

Keywords:
Apheresis
Pediatric
Adverse events
Level of evidence

ABSTRACT

Apheresis technology has progressed significantly over the last 50-60 years from a predominately blood donation–based procedure to one that now includes a variety of therapeutic modalities. The last 25 years also has seen an increase in the number of diseases treated by therapeutic apheresis (TA) modalities. Because of ethical considerations, therapeutic modalities are often vetted first in adult populations before establishing utility in pediatric patients. TA is no different. The majority of published studies involve adult patients. Pediatric apheresis studies are traditionally retrospective, single-center experiences, single case reports, or case series. To confirm this, we evaluated the peer-reviewed published literature to assess the level of evidence of clinical pediatric apheresis studies published in the last 21 years. Adverse events experienced by pediatric patients undergoing TA procedures and procedural modifications necessary to accommodate pediatric patients receiving TA were also explored. Consideration was given to differences in disease outcomes in pediatric vs adult patients and evolution of TA treatment indications. A systematic search of the literature yielded >1000 pediatric apheresis publications. Only 370 articles specifically assessed TA in the treatment of a pediatric disease. Of those, the majority (98%) were single-center experiences, single case reports, or case series. The remaining 2% were prospective cohort studies or randomized controlled trials. This first formal assessment of the pediatric apheresis literature confirms the findings of previous anecdotal reports and expert opinion.

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Apheresis is derived from the Latin word *aphairein* which means "to remove" [1]. Originally developed for blood donation more than 50 years ago, apheresis has slowly become a treatment modality for a variety of disorders [2]. The therapeutic apheresis (TA) instrumentation used today is largely automated and traditionally uses centrifugation to separate blood elements based on density. There are several notable exceptions. One is low-density lipoprotein (LDL) apheresis where the LDL is removed from plasma via filtration/adsorption [3]. Another notable exception is the use of plasma filtration, often used in dialysis centers to remove plasma. A third exception is the performance of extracorporeal photopheresis using Latham bowl technology in a discontinuous or near-continuous fashion (Mallinckrodt Pharmaceuticals, West Chester, PA). The Latham bowl's unique conical shape allows blood to fill from the bottom with the red cells migrating to the outer wall, plasma to the inner wall, and the buffy coat in between

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http://dx.doi.org/10.1016/j.tmrv.2016.08.002
0887-7963/

(Haemonetics, Braintree, MA). These advances have established TA as an effective therapeutic option for many different diseases.

Despite TA modalities being used as first-line and second-line treatment options, the decision to perform a TA procedure is based largely on evidence compiled in the American Society for Apheresis (ASFA) guidelines [4]. The ASFA guidelines assign specific diseases to a category from I TO IV based on the strength and quality of peer-reviewed, published evidence and include both adult and pediatric studies [4]. Generally, a level I category is assigned to diseases for which a TA modality is a primary therapeutic intervention; a level II category is assigned to diseases for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment; a level III category where optimum role of apheresis therapy is not established with decision making should be individualized; and level IV category is for those in which TA is ineffective or even harmful [4].

Pediatric patients represent a heterogeneous patient population characterized by rapidly developing organ systems and small but rapidly changing blood volumes, which not only challenges practitioners from a technical perspective but also often alters the therapeutic response as compared with adults [5]. TA, particularly therapeutic plasma exchange (TPE), is often performed for pediatric diseases based on case series or anecdotal reports in the literature or an apheresis medicine specialist's personal and institutional experience [3,5-11].

In this review, we systematically examine the current published evidence that directly supports the use of TA in the pediatric patient population. We briefly assess the quality of evidence in peer-reviewed, published articles relating the use of TA modalities clinically in pediatric patients. Secondly, adverse events related to pediatric TA procedures in the context of technical challenges related to pediatric developmental changes are examined. Finally, confounders that affect the use of TA in pediatric patients are described.

Brief Systematic Assessment of Literature

A systematic assessment of the literature was performed to formally quantify the level of evidence, disease entity, and types of TA modalities used for TA in pediatric patients in the last 21 years. To identify clinical TA studies involving pediatric patients, we performed a search of MEDLINE (1/1/1995-2/16/2016) using MeSH terms *apheresis*, *therapeutic apheresis*, *cytapheresis*, *photopheresis*, *plasmapheresis*, *erythrocytapheresis*, *thrombocytapheresis*, *red cell exchange*, and *pediatric(s)*. The search was limited to articles published in the English language and involving humans specifically *pediatric patients* (defined as patients ≤18 years of age). Articles were screened against predefined inclusion and exclusion criteria using a tiered approach: first title then abstract screen and finally full article screen (Fig 1). Inclusion criteria comprised peer-reviewed, full manuscripts that reported primary or adjunct use of TA in a pediatric patient. Excluded studies were those which reported only in vitro outcomes, only adult patients or adult and pediatric data in aggregate, abstracts only, proceedings from international meetings, reviews only without clinical specificity, and expert opinion. Articles on peripheral blood stem cell collection were also excluded as were articles addressing adverse events and epidemiology. Studies were examined and categorized for level of evidence using the Oxford Center for Evidence-Based Medicine—Levels of Evidence by the 2 authors [12]. Disagreements in level assessment were resolved by consensus. Included studies were stratified by clinical specialty, disease treated, TA modality, and level of evidence.

The search of MEDLINE yielded 1172 articles for initial screen; an additional 38 articles were identified after a secondary reference search. After duplicates were removed, 1198 articles were reviewed. Using the inclusion and exclusion criteria described above, 561 articles passed the title-level screen and 386 articles passed the abstract-level screen (Fig 1). Thirteen articles specifically addressed adult and pediatric data

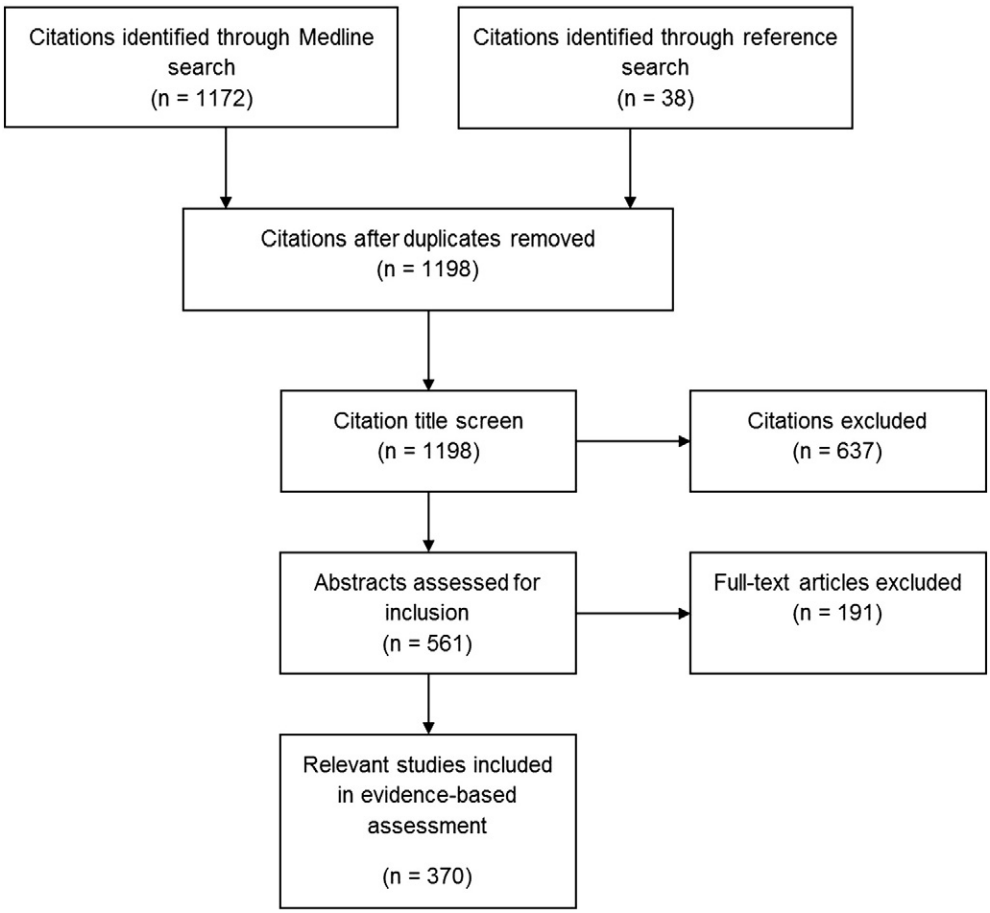

Fig 1. Article screening process and results. Flow of the articles through the systematic screening process including title, abstract, and full article assessment.