

## Review Article

---

# Adherence to Treatment Among Children with Cardiac Disease

Richard F. Ittenbach, Amy E. Cassidy, Bradley S. Marino, Robert L. Spicer, Dennis Drotar

Cincinnati Children's Hospital Medical Center, Cincinnati, OH

**Abstract** *Objective:* Our purpose was to review the literature with respect to issues of adherence to treatment among children with congenital and acquired cardiac disease. *Materials and Methods:* Databases used for this review included MEDLINE, Pub Med's Single Citation Manager, Cochrane Library, Cochrane Central Register of Controlled Trials, Scopus, and Google Scholar. We did not use any restrictions on date when locating peer-reviewed articles published worldwide through December of 2008. *Results:* There exists a lack of published research regarding adherence to medical treatment for children with cardiac conditions. Of the few published studies, rates of adherence for children with congenital and acquired cardiac disease ranged from a high of 96% for an in-patient exercise programme, to a low of 33% among those who made all of their medical appointments. Risk factors for nonadherence included older age, one as opposed to two parents in the home, lack of emotional availability of parents, smoking, sedentary lifestyle, use of illicit drugs, presence of tattoos, and multiple body piercings. Clinical outcomes associated with non adherence in the population of children undergoing transplantation included mortality, acute episodes of rejection, lower levels of Cyclosporine A, and lower values for the International Normalised Ratio of prothrombin. *Conclusions:* For children with congenital and acquired heart disease, the challenges of adherence to treatment can often be overwhelming. Recommendations designed to maximize the impact and scientific rigour of future studies include obtaining quantitative and qualitative measures of adherence, identifying primary and secondary endpoints, emphasizing factors of interest, planning studies with sufficient power to impact on the adherence to treatment, and developing epidemiologic foundations.

Keywords: Therapeutics; congenital heart disease; adolescents

Received: 10 April 2009; Accepted: 1 August 2009; First published online: 23 October 2009

**A**DHERENCE TO MEDICAL TREATMENT REMAINS difficult for many segments of the general population. For children with congenital and acquired cardiac disease, the challenges associated with adherence can often be overwhelming. For some children with cardiac disease, failure to adhere to the prescribed regime may even be life-threatening.

Advances in medical and surgical management of cardiac disease have prolonged and improved the lives of children with potentially life-threatening conditions. Haemodynamic and electrophysiologic residues, nonetheless, may require long-term treatment with complex medical regimes that may

include diuretics, drugs to reduce afterload, beta blockers, antiarrhythmics, and anticoagulation. These medications, although potentially life-saving, may have serious side effects if administered inappropriately. In addition, physical, neurodevelopmental, and psychosocial morbidities are not uncommon in children with serious forms of cardiac disease, and can result in complex needs for long-term management, potentially affecting adherence to treatment. For those with life-threatening disease not amenable to medical or surgical therapies, cardiac transplantation exists as a well recognized option. Once transplanted, strict adherence to a rigorous follow-up protocol and complex immunosuppressive drug regime is required.

Not surprisingly, clinicians have observed that the process of adherence to treatment is complex.

---

Correspondence to: Amy Cassidy, PhD., Division of Biostatistics and Epidemiology (MLC 5041), 3333 Burnet Avenue, Cincinnati, OH 45229; E-mail: amy.cassedy@cchmc.org

If interventions are to be successful, clinicians recommend that future studies will need to be multidimensional in nature, and include a combination of biological, cognitive, and psychological factors.<sup>1-3</sup> Those researching adherence to treatment in children are generally cognizant of important developmental and age-related differences with respect to responsibility. For example, the providers of care are generally responsible for adherence to treatment for infants and very young children. As children mature, responsibilities quite naturally shift to the developing adolescent and young adult.<sup>4</sup> A number of qualitative studies are beginning to accrue identifying communication, positive self-concept, social support systems, and knowledge of and ability to identify with the disease process, as potentially important factors in the process of adherence to treatment.<sup>1,2,5-7</sup>

Despite the importance of adherence to treatment for children with cardiac disease, and more specifically for children with cardiac failure, there remains little in the way of generalizable information for the practicing clinician. Of those studies that have been published, the majority have focused on adults,<sup>8</sup> paediatric subspecialties other than cardiology,<sup>9</sup> or narrowly defined segments of the paediatric cardiac population.<sup>10-14</sup> The purpose our review was to scan the literature with respect to adherence to treatment for children with congenital and acquired cardiac disease, paying particular attention to rates of adherence, risk factors for nonadherence, and the relationship between adherence to treatment and clinical outcomes. We then provide recommendations designed to maximize both the impact and scientific rigours of future studies in the field of paediatric cardiology.

## Method

### *Literature Search*

We used 3 groupings of keywords to search the current literature, specifically:

- Heart disease, heart defects, congenital, card\*, or heart\*";
- Children, adolescent, or pediatrics;
- And adherence, self-management, self care, compliance, patient compliance, or self administration.

Databases used for this review included MEDLINE, Pub Med's Single Citation Manager, Cochrane Library, Cochrane Central Register of Controlled Trials, Scopus, and Google Scholar. We identified those peer-reviewed articles published worldwide through December of 2008. In an effort to expand the scope of

the search beyond the available electronic databases, and to ensure as much as possible that we would not miss articles not indexed by the aforementioned databases, we also reviewed and obtained papers cited within relevant articles.

### *Criteria for Inclusion and Exclusion*

We included peer-reviewed articles written in English that defined, measured, and investigated adherence to regimes of medical treatment in a systematic way, and that included children or adolescents with cardiac disease or cardiac failure as definable samples. Articles that primarily dealt with adults, or for which cardiac disease was not a primary focus, were excluded.

## Results

We identified a total of 8 articles in which adherence to treatment had been investigated within the context of a cohort of children with cardiac disease. Of these studies, 2 involved children with congenitally malformed hearts, while 6 included children with cardiomyopathy, cardiac failure, or children who had undergone transplantation of the heart (Table 1).

### *Rates of Adherence*

Not all the studies reported general rates of adherence. Of those that did, the percentage of children and adolescents who were reported to be adherent to medical treatments varied greatly. Among a sample of children with end-stage heart failure awaiting transplantation, a rate of adherence of 96% was reported for a sustained, low intensity, in-patient exercise programme.<sup>15</sup> In a sample of 50 children receiving either heart, or heart-lung transplants, it was reported that almost half, specifically 18 of 40 of their sample, disclosed that they were either intentionally, in 18%, or unintentionally in 28%, nonadherent to their prescribed treatment.<sup>14</sup> Substantially higher rates of 63% for missed medications, and 67% for missed appointments, were reported in another study for patients 10 years after transplantation.<sup>13</sup> Conversely, another group reported a rate of adherence of 70% to both medication and completion of diaries in a sample of 53 children followed for up to 12 months after heart and lung transplantation.<sup>16</sup>

### *Risk Factors for Nonadherence*

Several risk factors for nonadherence were identified in the 8 studies evaluated. The most prominent finding with respect to risk factors for nonadherence appeared to be related to age. Older children and adolescents evidenced lower rates of adherence to treatment than younger children.<sup>14,16,17</sup> For recipients of heart and/or

Table 1. Description of Studies Used in the Review of Literature.

Author	Research question	Study design	Clinical population	Sample size	Age range	Observation time	Measures of Adherence	Clinical outcome
Chartrand et al. (2001)	What are the major risk factors for acute rejection?	Observational	Recipients of Heart Transplantation	42	0.8 to 19.0 yrs	0.2 to 15.0 yrs	Levels of medication	Acute rejection, Mortality
Christensen et al. (2001)	Is self-management of oral anticoagulation therapy possible in children with congenital heart disease?	Case series	Patients with congenitally malformed hearts	14	2.2 to 15.6 yrs	0.6 to 2.6 yrs	Levels of medication	Value of international normalized ratio
Christensen et al. (2004)	Is self-management a successful strategy for oral anticoagulation therapy?	Case series	Patients with congenitally malformed hearts	22	1.8 to 18.6 yrs	0.9 to 5.8 yrs	Levels of medication	Value of international normalized ratio
McBride et al. (2007)	Is inpatient exercise training safe for heart transplant patients?	Observational	Recipients of Heart Transplantation	20	6.0 to 22.2 yrs	2 to 18 Months	Attendance at training sessions	Compliance with protocol, Adverse events
Ringwald et al. (2001)	What is the impact of nonadherence on late rejection after pediatric heart transplantation?	Observational	Recipients of Heart Transplantation	50	0.8 to 22.8 yrs	10 yrs	Variability in levels of cyclosporin	Drug variability, Acute rejection, Mortality
Serrano-Ikkos et al. (1998)	Will there be similar rates of unsatisfactory adherence among patients receiving transplanted hearts and hearts and lungs?	Observational	Recipients of Heart Transplantation	53	5 to 17 yrs	1 yr	Levels of medication and completion of diaries	Compliance with protocol, Mental illness, Family functioning
Stilly et al. (2006)	What is the relationship between social immaturity and failure to appreciate consequences of risky behaviour?	Questionnaire	Recipients of Heart Transplantation	27	15 to 31 yrs	Not applicable*	Self-report	Compliance with protocol, Risky behaviour, Maturity and mood
Wray et al. (2006)	Can intentional and unintentional adherence be measured in patients undergoing transplantation?	Questionnaire	Recipients of Heart Transplantation	50	1.4 to 14.9 yrs	Not applicable*	Self-report	Compliance with protocol, Heart transplantation, Family Support

Note: \* Cross-sectional data received at one time point.

heart-lung transplantation, all 7 episodes of intentional nonadherence were observed in those aged from 14 to 18 years, with 4 of the 7 episodes occurring in the most recent year.<sup>14</sup> The second most prominent risk factor pertained to family structure. For example, more acute rejections were reported among patients living in single-parent households than among those living in two-parent households.<sup>17</sup> Similarly, children living with both biological parents reported higher rates of adherence than did children living with single-parent or blended families.<sup>16</sup> Children of parent dyads, where one of the parents was critical of the emotional availability of the partner during the period of transplantation, appeared to be less adherent than children of parent dyads who considered each other to be emotionally available.<sup>16</sup>

Other notable risk factors and correlates with nonadherence for an adolescent and young adult sample included smoking in one-tenth, tattoos in one-third, a sedentary lifestyle in nine-tenths, multiple body piercings in one-third, and illicit use of street drugs in one-tenth, as well as difficulty maintaining the dietary requirements of an adult diet.<sup>13</sup> During the portion of the study involving a clinical interview, Stille et al.<sup>13</sup> found that poor adherers scored lower than good adherers across six inductively derived themes of maturity, specifically trusting others, family support, involved with others, optimistic outlook, long-term goals, evolving development, and a clinical measure of self concept that integrated the transplant experience with self concept.<sup>13</sup> Conversely, Wray and colleagues<sup>14</sup> found no statistically significant associations between adherence and beliefs about medication, perceptions of illness, or transplant related variables, such as the time since transplantation, the type of transplant, the age at transplantation, or the diagnosis prior to transplantation.

### *Relationships with Clinical Outcomes*

Several studies confirmed a strong relationship of poor outcomes in terms of morbidity, mortality, or rejection with nonadherence. A total of 49 episodes of acute rejection were observed in 15 of 50 children receiving heart transplants, 7 of whom died.<sup>17</sup> Of the episodes, three-quarters could be attributed to nonadherence. Self reports of nonadherence corroborated the finding based on levels of anti-rejection drugs in nine-tenths of cases.<sup>17</sup> Others reported a poor rate of adherence based on levels of cyclosporin.<sup>16</sup> In another study, it was found that 3 of 4 adolescent and young adults who adhered poorly had died, while all 5 patients showing good adherence group were alive and well 10 years after transplantation.<sup>13</sup> A statistically significant relationship was found between compliance with immunosuppressive

medications and acute rejection, with no deaths among 25 children who were compliant compared with almost half of children who were noncompliant dying following transplantation.<sup>10</sup> Episodes of rejection were very uncommon among children aged less than 5 years, but significantly more common among those aged 15 years and older.<sup>10</sup>

In the lone study involving intervention, 14 children with congenitally malformed hearts were taught strategies of self-management to use Coumadin, an oral anticoagulation medication that reduces the risk of thromboembolic events.<sup>12</sup> The authors found that, after 27 weeks in the study, all patients, or the parents in the case of very young children, were capable of operating the equipment and adjusting the levels of Coumadin levels.<sup>12</sup> Values for the international normalized ratio were in an appropriate range from one-sixth to nine-tenths of the time, with the median being two-thirds.<sup>12</sup> In a follow-up study 3 years later, the group reported that children were within the therapeutic range almost three-quarters of the time.<sup>11</sup> Additionally, in the first study, all 14 patients and parents reported complete satisfaction with the programme of treatment, and all but one patient wanted to continue with treatment following the study.<sup>12</sup>

### **Summary and Recommendations**

We identified, from our review of the literature, a number of different outcomes related to adherence for children with congenital and acquired cardiac disease. From attendance rates at an in-patient exercise programme to a study providing self-management in anti-coagulation, the spectrum of adherence-related outcomes for children with cardiac disease remains quite broad. In some studies, the outcomes are absolute, such as mortality, cardiac failure, or rejection of transplanted organs, while for others, informative surrogates are used, such as levels of anti-rejection drugs and levels of prothrombin. The risk models themselves have tended to follow suit, with an equally broad range of related factors, such as diet, variables related to the patients, the level of family support, risk-taking behaviours, and indicators of mental illness. The absence of a prior predictive model is a significant weakness, as it capitalizes on sample-specific variation that may not be generalizable.

We detected 3 notable themes from our review of the literature. First, levels of adherence vary widely, from relatively low to very high. Equally important is the realization that, although values of adherence are reported, they reflect a wide range of conditions and options for treatment across different age groups, from toddlers to adolescents and young adults. Second, relationships between measures of

adherence and established clinical outcomes often seem to be study-specific and, in many cases, dependent upon uniquely defined variables of interest. Third, many of the studies we reviewed use imprecisely delineated methodologies, such that it would be hard to replicate methods, let alone generalize findings to other segments of the population of children with cardiac disease.

Our review also indicated that adherence to treatment in children with cardiac disease is understudied relative to many other chronic health conditions suffered by children.<sup>18,19</sup> Despite this rather sobering realization for clinicians who treat children with cardiac disease, some promising trends are also noted. Most importantly, all 8 studies reviewed have acknowledged that adherence to treatment plays a critical role in achieving a successful medical outcome. In addition, even among the less well executed studies, the established and fairly well recognized outcomes of prothrombin times and levels of cyclosporine can be acknowledged as objective indicators of adherence. Another contribution to the literature is the number of different measures of adherence used in these studies, ranging from self-reported information to specific biochemical markers, thereby creating a fairly diverse pool of measures that future researchers can draw upon when developing their own studies.

Despite these early and important contributions to the literature, children with cardiac disease remain a vastly understudied segment, one that could surely benefit from promotion. Future researchers should strive to describe the incidence and prevalence of nonadherence to treatment for children with cardiac disease using valid and reliable measures. Recently published works involving children with cystic fibrosis,<sup>20</sup> and children with diabetes,<sup>21</sup> serve as examples in this regard.

Another area of need in future research concerns the study of the relationship between adherence and clinical outcomes. Although causal connections between adherence to treatment, control of illness, and health-related clinical outcomes are relatively well-established with Type I diabetes, and infectious diseases such as infection with the human immunodeficiency virus, the relationship between adherence in children with cardiac disease has not been well documented. For this reason, there is an important opportunity in the field of paediatric cardiology to describe the impact of adherence to treatment in a range of relevant outcomes, through such methodologies as clearly defined clinical cutoffs that delineate positive versus negative outcomes, and validated clinical thresholds below which medication may be less effective, or ineffective altogether.<sup>22</sup> Finally, very little is known about the efficacy of strategies for intervention to reduce nonadherence and negative

outcomes in vulnerable populations, or the efficacy of preventative strategies to promote adherence to prescribed medications.

In order to maximize the scientific rigour and clinical impact of future research in adherence to medical treatment for children with cardiac diseases, researchers should consider the following recommendations, not simply to enhance the quality of science, but to begin the process of laying the foundation for future strategies for intervention:

- *Obtain both quantitative and qualitative measures of adherence.* While it is crucial to gather information on the rates of adherence using the most up-to-date objective systems and technology,<sup>19</sup> it is also important to ask respondents or their parents for verbal confirmation or validation of adherence, as well as their perceptions of barriers to, or facilitators of adherence to treatment.<sup>23</sup> Objective methods are useful to document the rates of adherence in an unbiased manner. Subjective measures, such as interviews or questionnaires are very well suited to describe the situational context and factors that reflect the decision making of both the patient and his or her family
- *Clearly identify primary and secondary endpoints of nonadherence.* In many of the studies we reviewed, it was difficult to distinguish primary from secondary endpoints. For example, are levels of cyclosporine the endpoint of interest, or is it acute rejection? It may well depend on whether one is interested in mortality of the person or rejection of the transplanted organ, or simply an indicator of morbidity, which increases the likelihood of future complications. Hence, the selection of endpoints can have a profound impact on the strength of the relationships and generalizations made from them. Moreover, authors are encouraged to focus on a single, primary, operationally well-defined endpoint for which the outcome of interest has a basis in the professional literature. Where appropriate, two or three additional, secondary endpoints, also operationally well-defined, may be used to extend our understanding of the process of adherence to treatment.
- *Emphasis on the factor of interest.* Extending the notion of primary versus secondary endpoints, it was often difficult for us to understand the basis for the comparisons made in the studies we reviewed. For example, it matters greatly whether rates of adherence are being compared with respect to episodes of rejection, or, conversely, whether the episodes of rejection are being compared with respect to the level of adherence.<sup>14</sup> The results, and subsequent interpretations, are not the same. In some studies we reviewed, it appears that the

comparisons were made both ways, producing difficulty in identifying explicitly the comparisons of interest. Much of this can be handled with well-written sections detailing methods and analysis of data. Investigators are encouraged to follow closely the reporting guidelines of their respective journals and/or professional associations. Alternative and well-respected documents that investigators may consult for guidance include the Consolidated Standards of Reporting Trials<sup>24,25</sup> and the Transparent Reporting of Evaluations with Nonrandomized Designs.<sup>26</sup>

- *Plan studies with sufficient power to impact on adherence to treatment.* Being able to detect a statistically significant difference between the groups studied when it is present is a function of the size of the sample. Among the 8 studies we reviewed, none indicated that they were sufficiently powered to detect differences, and none identified the effect sizes of interest. Given the multidimensional nature of adherence and the psychological, social, and environmental influences at any one time, it will be necessary to identify from the outset the anticipated effect sizes of specific influences, alone and in combination with other potential confounding variables in a given study.<sup>23</sup> Multi-centered studies, although much more difficult to conduct, may be needed to obtain sufficient numbers of children with very specific types of cardiac disease such as children with functionally univentricular physiology, electrophysiologic abnormalities, cardiomyopathies, and cardiac failure requiring transplantation of the heart.
- *Develop an epidemiologic foundation for the study of adherence.* Prior to estimating the strength of existing relationships between measures of adherence and other clinical correlates and predictors, we must first know the extent of the problem, and patterns of behaviors related to adherence in the children we treat. Hence, we recommend that investigators first report and clearly describe the rates of adherence for their sample as a whole and for relevant subgroups, for example by age, gender, cardiac diagnosis, before moving on to other, more complicated situations.<sup>23</sup>

### Acknowledgement

The authors wish to extend a special note of thanks to Ms Alison Kissling, Medical Librarian, for her assistance with this process.

### References

1. Bunchman TE. Compliance in pediatric transplant. *Pediatr Transplant* 2000; 4 (3): 165–169.
2. Sherry DC, Simmons B, Wung SF, Zerwic JJ. Noncompliance in heart transplantation: a role for the advanced practice nurse. *Prog Cardiovasc Nurs* 2003; 18 (3): 141–146.
3. Hsu DT. Biological and psychological differences in the child and adolescent transplant recipient. *Pediatr Transplant* 2005; 9 (3): 416–421.
4. Roberts MC. *Handbook of Pediatric Psychology*. Guilford Publications, Inc., New York, NY, 2003.
5. Kools S, Kennedy C, Engler M, Engler M. Pediatric hyperlipidemia: child and adolescent disease understandings and perceptions about dietary adherence. *J Spec Pediatr Nurs* 2008; 13 (3): 168–179.
6. Lawrence K, Stillely CS, Olshansky E, Bender A, Webber SA. Further exploration: maturity and adherence in adolescent and young adult heart transplant recipients. *Prog Transplant* 2008; 18 (1): 50–54.
7. McAllister S, Buckner EB, White-Williams C. Medication adherence after heart transplantation: adolescents and their issues. *Prog Transplant* 2006; 16 (4): 317–323.
8. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004; 42 (3): 200–209.
9. Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. *J Pediatr Psychol* 2008; 33 (6): 590–611.
10. Chartrand C, Servando ES, Chartrand S. Risk factors for acute rejection after pediatric heart transplantation. *Transplant Proc* 2001; 33 (1–2): 1732–1734.
11. Christensen TD, Andersen NT, Maegaard M, Hansen OK, Hjortdal VE, Hasenkam JM. Oral anticoagulation therapy in children: successfully controlled by self-management. *Heart Surg Forum* 2004; 7 (4): E321–E325.
12. Christensen TD, Attermann J, Hjortdal VE, Maegaard M, Hasenkam JM. Self-management of oral anticoagulation in children with congenital heart disease. *Cardiol Young* 2001; 11 (3): 269–276.
13. Stillely CS, Lawrence K, Bender A, Olshansky E, Webber SA, Dew MA. Maturity and adherence in adolescent and young adult heart recipients. *Pediatr Transplant* 2006; 10 (3): 323–330.
14. Wray J, Waters S, Radley-Smith R, Sensky T. Adherence in adolescents and young adults following heart or heart-lung transplantation. *Pediatr Transplant* 2006; 10 (6): 694–700.
15. McBride MG, Binder TJ, Paridon SM. Safety and feasibility of inpatient exercise training in pediatric heart failure: a preliminary report. *J Cardiopulm Rehabil Prev* 2007; 27 (4): 219–222.
16. Serrano-Ikkos E, Lask B, Whitehead B, Eisler I. Incomplete adherence after pediatric heart and heart-lung transplantation. *J Heart Lung Transplant* 1998; 17 (12): 1177–1183.
17. Ringewald JM, Gidding SS, Crawford SE, Backer CL, Mavroudis C, Pahl E. Nonadherence is associated with late rejection in pediatric heart transplant recipients. *J Pediatr* 2001; 139 (1): 75–78.
18. Drotar D. Promoting adherence to treatment in childhood chronic illness: Concepts, methods, and interventions. Erlbaum, Mahwah, N.J., 2000.
19. Rapoff MA. *Adherence to pediatric medical regimens*. Kluwer Academic/Plenum Publishers, New York, N.Y., 1999.
20. Modi AC, Lim CS, Yu N, Geller D, Wagner MH, Quittner AL. A multi-method assessment of treatment adherence for children with cystic fibrosis. *J Cyst Fibros* 2006; 5 (3): 177–185.
21. Harris MA, Wysocki T, Sadler M, et al. Validation of a structured interview for the assessment of diabetes self-management. *Diabetes Care* 2000; 23 (9): 1301–1304.
22. Pai A, Drotar D. Treatment adherence impact: The systematic assessment and quantification of the impact of treatment

- adherence on pediatric medical and psychological outcomes. *J Pediatr Psychol* Submitted 2009.
23. Fine RN, Becker Y, De Geest S, et al. Nonadherence consensus conference summary report. *Am J Transplant* 2009; 9 (1): 35–41.
  24. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; 285 (15): 1987–1991.
  25. Stinson JN, McGrath PJ, Yamada JT. Clinical trials in the *Journal of Pediatric Psychology*: applying the CONSORT statement. *J Pediatr Psychol* 2003; 28 (3): 159–167.
  26. Des Jarlais DC, Lyles C, Crepaz N. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. *Am J Public Health* 2004; 94 (3): 361–366.