Clinical cardiac regenerative studies in children

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Abstract

Although the incidence of pediatric heart failure is low, the mortality is relatively high, with severe clinical symptoms requiring repeated hospitalization or intensive care treatment in the surviving patients. Cardiac biopsy specimens have revealed a higher number of resident human cardiac progenitor cells, with greater proliferation and differentiation capacity, in the neonatal period as compared with adults, demonstrating the regeneration potential of the young heart, with rising interest in cardiac regeneration therapy in critically ill pediatric patients. We review here the available literature data, searching the MEDLINE, Google Scholar and EMBASE database for completed, and www.clinicaltrials.gov homepage for ongoing studies involving pediatric cardiac regeneration reports. Because of difficulties conducting randomized blinded clinical trials in pediatric patients, mostly case reports or cohort studies with a limited number of individuals have been published in the field of pediatric regenerative cardiology. The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure. Congenital heart disease, myocarditis, and idiopathic hypertrophic or dilated cardiomyopathy leading to congestive heart failure are some possible areas of interest for pediatric cardiac regeneration therapy. Autologous bone marrow mononuclear cells, progenitor cells, or cardiospheres have been applied either intracoronary or percutaneously intramyocardially in severely ill children, leading to a reported clinical benefit of cell-based cardiac therapies. In conclusion, compassionate use of autologous stem cell administration has led to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

Key words: Congenital heart disease; Heart failure; Cardiac regeneration; Cell-based therapy; Hospitalization; Children

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Core tip: This review summarizes the available literature data involving pediatric cardiac regeneration reports.
Due to lack of randomized blinded clinical trials in pediatric cardiology patients, mostly case reports with limited number of individuals have been published in the pediatric regenerative cardiology. The majority of pediatric autologous cell transplantation into the cardiac tissue have been performed in children with severe or terminal heart failure, and led to the conclusion, that compassionate use of autologous stem cell administration may lead to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

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INTRODUCTION

Epidemiology of heart failure in children

The overall prevalence of pediatric heart failure is largely unknown because of the non-unique definition and classification of this disease. According to statistical estimations and pediatric registries, 2.5 million children annually are born with congenital heart disease (CHD) worldwide, and among these children, 15%-25% eventually develop heart failure [1-4].

The incidence of pediatric dilated cardiomyopathy with consequent heart failure is low, calculated as 0.57-2.6 per 100000 children under age 18 years [5,6]. In this group, approximately two thirds of cases are idiopathic, and the remaining involve postmyocarditis syndrome or musculoskeletal diseases [7]. Dilated cardiomyopathy dominates myocardial disease-related heart failure, followed by hypertrophic cardiomyopathy, with restrictive cardiomyopathy identified least frequently [8]. The median age of the patients with dilated cardiomyopathy is approximately 1.8 years when the initial diagnosis is made [9].

The mortality of pediatric heart failure is high, and approximately one third of patients die in the first year following diagnosis [9,10]. The surviving children develop progressive heart failure requiring intensive medical care and heart transplantation [11]. For those surviving at least 2 years after the diagnosis, mortality and the need for heart transplantation are somewhat lower (13.6%) [6]. Approximately 18 of every 100000 children are hospitalized annually because of heart failure, with 0.87 new cases per 100000 children per year [11]. The hospital mortality of these pediatric patients is 7%, and numbers are much higher compared to the adult population (4%) [11,12]. After the first hospitalization, only 21% of pediatric patients remain free from serious adverse events (rehospitalization, death, or heart transplantation) [13]. The lack of sufficient numbers of young donor organs and the relatively high post-transplantation mortality limit the incidence and success of pediatric heart transplantation.

In addition, the cost of hospital treatment for pediatric heart failure is usually extremely high, exceeding 135000 USD per patient. Underlying CHD involving a single ventricle, for example, expands the costs of in-hospital treatment for heart failure to over 200000 USD [14].

The medical therapy for pediatric heart failure includes the whole armamentarium used in adults; however, the benefit cannot be clearly demonstrated for all interventions in children [15]. Some established methods for adult cardiology, such as diverse regenerative therapies or left ventricular assist devices, are rarely available for young patients because of incompatibilities of implant size in growing children. Medical treatment might be insufficient because, as noted, many children end up requiring heart transplantation [16].

Spontaneous cardiac regeneration capacity in children

Newborn mice can regenerate the cardiac apex after resection but only if the resection occurs within the first 7 d after birth [17]. Lineage tracing investigations have revealed that cell cycle entry of pre-existing cardiomyocytes in mice is responsible for this regeneration. Gene expression analysis indicates that neonatal cardiomyocytes maintain proliferation capacity only up to 7 d post-birth, this regeneration property is then lost [17]. Mishra et al. [18] investigated the prevalence and proliferation capacity of different stem cell-like cells acquired from cardiac biopsy specimens of children undergoing open heart surgery. They showed that plenty of resident human cardiac progenitor cells (hCPCs, a subpopulation of cardiospheres, CDCs) can be found in the neonatal period but that the number of these cells decreases rapidly with advancing age, from 8.9% to 3.2% in the right atrium and from 0.4% to 0.1% in the right ventricle. In addition, c-kit + hCPCs were three times more frequently found in neonates than in children over age 2 years. The proliferation and differentiation potential of the hCPCs was also greater in neonates, as shown by the higher expression levels of c-kit and Ki67, as well as the expression of NCK2, NOTCH1, and NUMB, the genes responsible for proliferation and differentiation. Furthermore, heart tissue samples of children with CHD contained an increased number of c-kit + hCPCs and CD133 + cells, and these cells expressed cardiac lineage and endothelial transcription factors during differentiation under in vitro conditions [19]. CDCs are a rich source of secreted regenerative substances, such as cytokines and growth factors, e.g., vascular endothelial growth factor, hepatocyte growth factor, or insulin-like growth factor, and exert anti-apoptotic and proangiogenic effects in the myocardium [20,21]. CDCs found in infant hearts have higher telomerase activity compared with those of adults.

Together, these data suggest that the regenerative capacity of the heart in children is much greater than that of adults. Additional evidence comes from clinical observations that the younger heart can exhibit morphological changes after volume unloading by surgical correction of CHD [22]. Additionally, pressure overload from
a single right ventricle leads to an increase in the number of cardiac stem cells (0.41% ± 0.24%) compared to
dilated cardiomyopathy (0.15% ± 0.09%)²³.

Clinical pediatric cardiac regeneration studies
To establish standardized therapy and guidelines for
treatment of diseases, randomized double-blinded cli-
cial studies delivering evidence-based medicine are
necessary. In contrast with the huge number of adult
clinical trials, in pediatric cardiology, especially for cardiac
regenerative therapy, large randomized trials are lacking.
In addition to the understandable ethical reasons,
other factors also preclude such trials: The relative
rarity of heart failure with a limited number of pediatric
patients in the stable clinical condition necessary for
randomization, a divergence in terminology, proprietary
and often incompatible informatics platforms, and
variability in data standards in growing children²⁴. In
2012, the United States Food and Drug Administration
Safety and Innovation Act intensified pediatric product
development, also enhancing the number of pediatric
clinical trials. In Europe, the Pediatric Regulation and
Pediatric Therapeutics programs have strengthened
the applications of new medicines in evidence-based
pediatric clinical studies. In contrast with the very spare
pediatric regenerative cardiology studies, pediatric cancer
and HIV/AIDS treatment networks have already been
successfully established and developed with standardized
data validity and consistency²⁴. We review here the
available literature data, searching the Medline, Google
Scholar and Embase database for completed, and
available literature data, searching the Medline, Google
Scholar and Embase database for completed, and
www.clinicaltrials.gov homepage for ongoing studies involving
pediatric cardiac regeneration reports.

DISCUSSION
Cardiac diseases for pediatric cardiac regeneration
In most cases, cardiac cell-based therapy has been
applied in children with severe heart failure caused by
diverse diseases, predominantly idiopathic dilated
cardiomyopathy, post-myocarditis, or chemotherapy-
induced dilated cardiomyopathy (Table 1 and Figure 1).
Severe heart failure has been described also with post-
myocardial infarction in cases of an anomalous origin
of the left coronary artery from the pulmonary artery
or Takayasu’s arteritis, treated with different kinds of
reparative cells. Other congenital diseases such as double
outlet right ventricle, pulmonary atresia with ventricular
septal defect, or hypoplastic left heart syndrome (HLHS)
causing severely depressed heart function, have been
considered for treatment with non-committed cells. Table
2 lists the pediatric diseases for which cardiac cell-based
regenerative studies might be considered.

For the reasons described, to date, only two ran-
domized clinical cardiac regenerative trials with a low
number of included children have been conducted. Both
have revealed benefits of cardiac cell-based therapy²⁶-²⁹.
In addition to these currently finished trials, case reports
or pilot trial results have been published, mainly based on
an indication of compassionate use in severely ill pediatric
patients. The majority of children receiving cardiac cell-
based therapy were in a critical or terminal status of
cardiac decompensation, as evidenced by the fact that
some of the children had to undergo heart transplants
afterwards²².

Cell types and delivery modes
Different types of cells have been used for cardiac
regenerative cell therapy in children, such as bone
marrow-derived mononuclear cells, cells from leukocyte
apheresis, and mesenchymal stem cells. In all cases, auto-
logous cells were used.

Most of the children received the reparative cells
via intracoronary injections. To ensure retention of the
injected cells, echocardiography-guided transcutaneous
intramyocardial delivery was also used, or a transapical
delivery mode was applied³⁰.

Clinical studies
The evidence for pediatric cardiac regeneration is mostly
anecdotal, deriving from case reports or cohort studies
including very limited number of patients (max. nine
repeated children in Rupp et al³¹). In addition, the only
comparative study, published by Ishigami et al³² allocated

Table 1  Pediatric cardiac diseases treated with cells

| Cell-based cardiac regenerative treatment | Ongoing studies |
|------------------------------------------|----------------|
| Dilated cardiomyopathy (Dil. CMP)        | Dilated cardiomyopathy (Dil. CMP) |
| Idiopathic dilated CMP                   |                |
| Cytostatics-induced dilated CMP          |                |
| Postmyocarditis dilated CMP              |                |
| Ischemic heart failure (myocardial infarction) |            |
| Anomalous origin of the left coronary arteries |             |
| Takayasu arteritis                       |                |
| Congenital heart disease                 |                |
| DORV after surgical correction           |                |
| Pulmonary atresia with ventricular septal defect |         |
| HLHS                                     |                |

CMP: Cardiomyopathy; DORV: Double outlet right ventricle; HLHS: Hypoplastic left heart syndrome.
intracoronary injections of autologous bone marrow mononuclear cells (BM-MNCs). The reasons for terminal heart failure in these children were anthracycline-induced dilated cardiomyopathy; post-myocarditis, idiopathic, or congenital cardiomyopathy; CHD with poor ventricular function, such as hypoplastic left heart or double outlet right ventricle; and pulmonary atresia with ventricular septal defect after surgical corrections. Three of the nine patients received a heart transplant and one patient died after cell treatment. The surviving children showed an improvement in clinical status during the 24 to 52 mo of follow-up.

De Lezo et al.\[35\] presented a case of a 5-mo-old infant with severe heart failure due to extensive myocardial infarction because of an anomalous origin of the left coronary artery. After surgical re-implantation of the left coronary artery to the aorta, the artery was occluded, then stented, then dilated after stent occlusion. Because of the critical clinical situation, during the second percutaneous procedure, autologous bone marrow-origin mononuclear cells were injected into the left main branch, using a stop-flow technique. The cardiac cell therapy led to an increase in the left ventricular ejection fraction from 24% to 45% at 6 mo of follow-up in the first case, and to reverse remodeling and marked improvement in clinical status in the second case.

Rupp et al.\[33,34\] reported two cases of bone marrow-origin progenitor cell intracoronary injection, one involving a 2-year-old boy with dilated cardiomyopathy and the other an 11-mo-old infant with HLHS; both of them were in a critical clinical condition of heart failure. The bone marrow progenitor cells were injected into the left anterior descending and left circumflex coronary arteries in the first case and into the dominant right coronary artery in the second case, using a stop-flow technique. The cardiac cell therapy led to an increase in the left ventricular ejection fraction from 24% to 45% at 6 mo of follow-up.

In further work, Rupp et al.\[34\] published a somewhat larger cohort study of nine pediatric patients receiving intracoronary injections of autologous bone marrow mononuclear cells (BM-MNCs). The reasons for terminal heart failure in these children were anthracycline-induced dilated cardiomyopathy; post-myocarditis, idiopathic, or congenital cardiomyopathy; CHD with poor ventricular function, such as hypoplastic left heart or double outlet right ventricle; and pulmonary atresia with ventricular septal defect after surgical corrections. Three of the nine patients received a heart transplant and one patient died after cell treatment. The surviving children showed an improvement in clinical status during the 24 to 52 mo of follow-up.

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After mobilizing stem cells from the bone marrow with granulocyte colony-stimulating factor (G-CSF), Olguntürk et al.\[36\] selected peripheral blood-origin stem cells and performed intracoronary injections of these cells into both the left and right coronary arteries in two patients both with dilated cardiomyopathy and severe
Congestive heart failure. At the 4-mo follow-up, both children showed impressive improvement, and one of them could be removed from the heart transplantation list.

Similarly, Limsuwan et al. applied the first daily injections of G-CSF, followed by bone marrow aspiration and selection of CD34+/CD33+ cells in an 8.5-year-old girl who had had an acute extensive anterior myocardial infarction related to Takayasu arteritis one year earlier. The selected stem cells were injected into the left anterior descending artery with the stop-flow technique. The 3-mo follow-up showed an increase in ejection fraction from 30% to 47.8% by cardiac magnetic resonance imaging.

Zeinaloo et al. selected autologous bone marrow mesenchymal stem cells in an 11-year-old boy with a diagnosis of dilated cardiomyopathy and injected them into the left and right coronary arteries. The one-year clinical check-up revealed an improvement of the left ventricular ejection fraction from 20% to 42%.

Lacis et al. treated a 3-mo-old child, who was in critical clinical condition with dilated cardiomyopathy, with autologous BM-MNCs via echocardiography-guided transcutaneous transapical intramyocardial injections. The ejection fraction increased from 20% to 41% at the 4-mo follow-up, and the child's clinical well-being was obvious.

Rivas et al. treated two children who both had dilated cardiomyopathy and were ages 3 and 4 mo, respectively, by administering peripheral blood progenitor cells, mobilized by G-CSF treatment. One month later, both children presented improvement, but one child developed progression later. This article described a temporary effect of the cell-based cardiac regenerative therapy.

Ishigami et al. published a nonrandomized prospective cohort study comparing data for seven patients treated with intracoronary injection of cardiosphere-derived cells and seven controls treated with standard therapy. All children had HLHS with planned stage 2 or 3 surgical palliation, which allowed the collection of autologous tissue for selection of CDCs in the treated group. The intracoronary injection of CDCs proved to be safe, and the right ventricle ejection fraction increased and remained constant at the 18 mo follow-up.

Bergmane et al. treated seven children with dilated cardiomyopathy with autologous bone marrow cells administered transcutaneously and intramyocardially by subxyphoid needle puncture under echocardiographic guidance. Six of the seven patients showed dramatically improved LV EF from 33.5% to 54%, BNP and NYHA decreased.
increased left ventricular ejection fraction at one year after the treatment, paralleled by a decrease in N-terminal proBNP and improved clinical status.

Burkhart et al.\textsuperscript{[46]} injected autologous umbilical cord blood-derived cells directly into the right ventricle during a second palliative operation of a child with HLHS. Three months later, the ejection fraction had increased to 45% with a marked decrease in plasma pro-BNP. Ongoing registered clinical studies are listed in Table 3.

### CONCLUSION

Cell-based cardiac regeneration therapy in pediatric patients has led to at least transient improvement of heart function and improvement of heart failure symptoms in a limited number of pediatric patients included in mostly non-randomized studies or case reports.

The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure, indicating that at the moment, this treatment strategy is a supplement after standard therapies have been exhausted. Whether specific age groups or those with structural heart diseases may benefit more than others has to be elucidated.

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**REFERENCES**

1. Bernstein HS, Srivastava D. Stem cell therapy for cardiac disease. *Pediatr Res* 2012; 71: 491-499 [PMID: 22430385 DOI: 10.1038/pr.2011.61]

2. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Lackland D, Lyon J, Muntner P, Nichol G, O’Keefee J, Roger VL, Sitzer M, Sorlie P, Stone PH, Taler SJ, Thom TD, Vaccaro ST, Witcher E, Wood HD, Wright EP, Zhang M, Zogaj M. Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; 119: 480-486 [PMID: 19171871 DOI: 10.1161/CIRCULATIONAHA.108.191259]

3. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004; 43: 317-327 [PMID: 15013109 DOI: 10.1016/j.jacc.2003.07.046]

4. Madriago E, Silberbach M. Heart failure in infants and children. *Pediatr Rev* 2010; 31: 4-12 [PMID: 20408034 DOI: 10.1097/PRR.0b013e3181d1-4]

5. Kaushal S, Jacobs JP, Gossett JG, Steele A, Steele P, Davis CR, Pahl E, Vijayan K, Asante-Korang A, Boucek RJ, Backer CL, Wold LE. Innovation in basic science: stem cells and their role in the treatment of paediatric cardiac failure–opportunities and challenges. *Cardiol Young* 2009; 19 Suppl 2: 74-84 [PMID: 19857353 DOI: 10.1017/S104795110999165X]

6. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med* 2003; 348: 1647-1655 [PMID: 12171739 DOI: 10.1056/NEJMoa021715]

7. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, Canter C, Wilkinson JD, Lipshultz SE. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA* 2006; 296: 1867-1876 [PMID: 17047217 DOI: 10.1001/jama.296.15.1907]

8. Selem SM, Kaushal S, Hare JM. Stem cell therapy for pediatric dilated cardiomyopathy. *Curr Cardiol Rep* 2013; 15: 369 [PMID: 23666883 DOI: 10.1007/s11886-013-0369-z]

9. Alvarez JA, Wilkinson JD, Lipshultz SE. Outcome Predictors for Pediatric Dilated Cardiomyopathy: A Systematic Review. *Prog Pediatr Cardiol* 2007; 23: 25-32 [PMID: 19701490 DOI: 10.1016/j.ppedcard.2007.05.009]

10. Arola A, Tuominen J, Ruuskanen O, Jokinen E. Idiopathic dilated cardiomyopathy in children: prognostic indicators and outcome. *Pediatrics* 1998; 101: 369-376 [PMID: 9480999]

11. Burns KM, Byrne BJ, Gelb BD, Kühn B, Leinwand LA, Mital S, Pearson GD, Rodefeld M, Rossano JW, Stauffer BL, Taylor MD, Towbin JA, Redington AN. New mechanistic and therapeutic targets for pediatric heart failure: report from a National Heart, Lung, and Blood Institute working group. *Circulation* 2014; 130: 79-86 [PMID: 24982119 DOI: 10.1161/CIRCULATIONAHA.113.007980]

12. Rossano JW, Kim JJ, Decker JA, Price JF, Zafar F, Graves DE, Morales DL, Heinle JS, Bozkurt B, Towbin JA, Denfield SW, Dreyer WJ, Jeffries JL. Prevalence, morbidity, and mortality of heart failure-related hospitalizations in children in the United States: a population-based study. *J Card Fail* 2012; 18: 459-470 [PMID: 22633380 DOI: 10.1016/j.cardfail.2012.03.001]

13. Hollander SA, Bernstein D, Yeh J, Dao D, Sun HY, Rosenthal D. Outcomes of children following a first hospitalization for dilated cardiomyopathy. *Circ Heart Fail* 2012; 5: 437-443 [PMID: 22570362 DOI: 10.1161/CIRCHEARTFAILURE.111.964510]

14. Rossano JW, Goldberg DJ, Mott AR, Lin KY, Shaddy RE, Kaufman BD, J. Rychik. Heart failure related hospitalizations in children

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**Table 3 On-going registered clinical studies**

| ClinicalTrials.gov ID | Diagnosis | Intervention | Study design | No. of patients to enroll | Age eligible | Status |
|----------------------|-----------|--------------|--------------|--------------------------|--------------|--------|
| NCT01354594          | Dilated CMP | Intracoronary autologous stem cell infusion | Single Group Assignment | 10 | 1 to 16 | Suspended |
| NCT012256501         | CMP       | Intracoronary intramyocardial injection of allogeneic mesenchymal cells during the Bi-Directional Cavopulmonary Anastomosis | Randomized | 32 | 1 to 16 | Recruiting |
| NCT012398604         | HLHS      | Intracoronary injections of autologous umbilical cord blood cells into the right ventricle of HLHS children undergoing a scheduled Glenn surgical procedure. | Randomized | 30 | to 28 d | Recruiting |
| NCT01883076          | HLHS      | efficacy of intracoronary infusion of cardiac progenitor cells in patients with univentricular heart disease | Safety Study | 10 | < 18 mo | Recruiting |
| NCT01829750          | HLHS      | efficacy of intracoronary infusion of cardiac progenitor cells in patients with univentricular heart disease | Randomized | 34 | < 20 yr | Recruiting |

HLHS: Hypoplastic left heart syndrome; CMP: Cardiomyopathy.
with single ventricle heart disease in the United States: costly and more expensive. J Card Fail 2012; 18: S73 [DOI: 10.1016/j.cardfail.2012.06.473]

15 Shaddy RE, Bovecek MM, Hsu DT, Bovecek RJ, Canter CE, Mahony L, Ross BD, Patel E, Blume ED, Dodd DA, Rosenthal DN, Burr J, LaSalle B, Holahoks R, Lukas MA, Tani LY. Cardioidil for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007; 298: 1171-1179 [PMID: 17848651 DOI: 10.1001/jama.298.10.1171]

16 Lipshultz SE. Ventricular dysfunction diagnostic method in infants, children and adolescents. Prog Pediatr Cardiol 2000; 12: 1-28 [PMID: 1114543]

17 Polizotti BD, Gannapathy B, Walsh S, Choudhury S, Ammananunchi N, Bennett DG, dos Remedios CG, Haubner BJ, Penninger JM, Kühn B. Neuregulin stimulation of cardiomyocyte regeneration in mice and human myocardium reveals a therapeutic window. Sci Transl Med 2015; 7: 281ra45 [PMID: 25834111 DOI: 10.1126/scitranslmed.aab5171]

18 Mishra R, Vijayan K, Colletti EJ, Harrington DA, Matthiesen TS, Simpson D, Goh SK, Walker BL, Almeida-Porada G, Wang D, Backer CL, Dudley SC, Wold LE, Kaushal S. Characterization and functionality of cardiac progenitor cells in congenital heart patients. Circulation 2011; 123: 364-373 [PMID: 21242485 DOI: 10.1161/CIRCULATIONAHA.110.971622]

19 Ghazizadeh Z, Vahdat S, Fattahi F, Fonoudi H, Omranii G, Gholampour M, Aghdamii N. Isolation and characterization of cardiogenic, bone marrow-derived progenitor cells in a critically ill two-year-old child with dilated cardiomyopathy. J Heart Lung Transplant 2010; 29: 574-577 [PMID: 20044280 DOI: 10.1016/j.healun.2009.10.006]

20 Rupp S, Zehir AM, Diller M, Schranz D. Intracoronary administration of autologous bone marrow-derived progenitor cells in critically ill two-year-old child with dilated cardiomyopathy. Pediatr Transplant 2009; 13: 620-623 [PMID: 19067928 DOI: 10.1111/j.1399-3046.2008.01024.x]

21 de Lezo JS, Pan M, Herrera C. Combined percutaneous revascularization and cell therapy after failed repair of congenital heart defects. Curr Heart Lung Med 2010; 2: 151-153 [PMID: 20470359 DOI: 10.1111/j.1399-3046.2009.01306.x]

22 Pavo IJ, Teragawa H, Ueda H. Pediatric cardiac regeneration studies. Pavo IJ et al. Pediatr Cardiol 2010; 32: 2-4 [DOI: 10.1007/s00246-015-1209-x]

23 Patel P, Mital S. Stem cells in pediatric cardiology. Eur J Pediatr 2010; 172: 1287-1292 [PMID: 23292032 DOI: 10.1007/s00431-012-1920-4]

24 Yang Q, Zhang J, Jiang J. Intracoronary transplantation of genetically modified mesenchymal stem cells, a novel method to close muscular ventricular septal defects. Med Hypotheses 2011; 77: 505-507 [PMID: 21788104 DOI: 10.1016/j.mehy.2011.06.020]

25 Pillekamp F, Reppel M, Brockmeier K, Heschler J. Stem cells and their potential relevance to paediatric cardiology. Cardiol Young 2006; 16: 117-124 [PMID: 16553971 DOI: 10.1017/S10477597100060023]

26 Pillekamp F, Khalil M, Emmel M, Brockmeier K, Heschler J. Stem cells in pediatric heart failure. Minerva Cardioangiol 2008; 56: 335-348 [PMID: 18509294]

27 Tobita K. Autologous cellular cardiomyoplasty for pediatric dilated cardiomyopathy patients: new therapeutic option for children with failing heart? Pediatr Transplant 2010; 14: 151-153 [PMID: 20470356 DOI: 10.1111/j.1399-3046.2010.01307.x]

28 Lasic A, Erglis A. Intramyocardial administration of autologous bone marrow mononuclear cells in a critically ill child with dilated cardiomyopathy. Cardiol Young 2011; 21: 110-112 [PMID: 20977823 DOI: 10.1017/S1047751110001435]

29 Rupp S, Jux C, Böning H, Bauer J, Ewell SR, Dimmeler S, Zehir AM, Schranz D. Intracoronary bone marrow cell application for terminal heart failure in children. Cardiol Young 2012; 22: 558-563 [PMID: 22329889 DOI: 10.1017/S104775112000066]

30 Ishigami S, Ohtsuki S, Tarui S, Osaka D, Eitoku K, Yamaoka T, Kondo M, Okuyama M, Kobayashi J, Baba K, Arai S, Kawabata T, Yoshizumi K, Tateishi A, Kuroko Y, Iwasaki T, Sato S, Sahasara S, Sano S, Oh H. Intracoronary autologous cardiac progenitor cell transfer in patients with hypoplastic left heart syndrome: the TICAP prospective phase 1 controlled trial. Circ Res 2015; 116: 653-664 [PMID: 25403163 DOI: 10.1161/CIRCRESAHA.116.304671]

31 Rupp S, Zehir AM, Diller M, Schranz D. Intracoronary administration of autologous bone marrow-derived progenitor cells in critically ill two-year-old child with dilated cardiomyopathy. Pediatr Transplant 2009; 13: 620-623 [PMID: 19067928 DOI: 10.1111/j.1399-3046.2008.01024.x]

32 de Lezo JS, Pan M, Herrera C. Combined percutaneous revascularization and cell therapy after failed repair of anomalous origin of left coronary artery from pulmonary artery. Catheter Cardiovasc Interv 2009; 73: 833-837 [PMID: 19180653 DOI: 10.1002/ccd.21891]

33 Olguutürk R, Sula, S usek GT, Ozoğlan ME, E r e D, S aygili A. Peripheric stem cell transplantation in children with dilated cardiomyopathy: preliminary report of first two cases. Pediatr Transplant 2010; 14: 257-260 [PMID: 20470359 DOI: 10.1111/j.1399-3142.2009.01215.x]

34 Lim Susan, Pinyachit P, Limpijankit T, Khowsathit P, Hongseg S, Pornkul R, Siripornpitak S, Boonbaichayapruk S. Transcoronary bone marrow-derived progenitor cells in a critically ill two-year-old child with dilated cardiomyopathy: the TICAP prospective phase 1 controlled trial. Pediatr Transplant 2010; 15: 40-43 [PMID: 20470359 DOI: 10.1111/j.1399-3046.2009.01306.x]

35 Rivas J, Menéndez JJ, Arrieta R, Alves J, Romero MP, García-Guerra L, Álvarez-Doforno R, Parrón M, González A, Ruza F, Gutiérrez-Larraya F. [Usefulness of intracoronary therapy with progenitor cells in patients with dilated cardiomyopathy: Bridge or alternative to heart transplantation?]. An Pediatr (Barcelona) 2011; 74: 218-225 [PMID: 21398194 DOI: 10.1016/j.anpedi.2011.02.013]

36 Bergmane I, Lasic A, Lubuana I, Jakobsens E, Erglis A. Follow-up of the patients after stem cell transplantation for pediatric dilated cardiomyopathy. Pediatr Transplant 2013; 17: 266-270 [PMID: 23458132 DOI: 10.1111/pet.12055]

37 Burkhart HM, Qureshi MY, Peral SC, O’Leary PW, Olson TM, Cetta L, Álvarez-Doforno R, Parrón M, González A, Ruza F, Gutiérrez-Larraya F. [Usefulness of intracoronary therapy with progenitor cells in patients with dilated cardiomyopathy: Bridge or alternative to heart transplantation?]. An Pediatr (Barcelona) 2011; 74: 218-225 [PMID: 21398194 DOI: 10.1016/j.anpedi.2011.02.013]
