Citation Article: Suieubekov B., Yeshmanova A. New research and changing paradigms of coagulopathy in children after cardiac surgery: A narrative review. *Futur Med [Internet]*. 2022;1(1): 29-36.
Available from: https://doi.org/10.57125/FEM.2022.03.25.03

New research and changing paradigms of coagulopathy in children after cardiac surgery: A narrative review

Suieubekov Bekzat [1*], Ainur Yeshmanova [2]

[1] *Kazakh Medical University "Higher School of Public Health", Utepova 19, Almaty, Kazakhstan, 050060*

[2] *Asfendiyarov Kazakh National Medical University, Tole bi street 94, Almaty, Kazakhstan, 480012*

Abstract

Background: Congenital heart disease (CHD) is a disorder and abnormality of the heart or the great vessels of the thorax, which usually occurs during fetal development. It has been reported that CHD is a common condition. Nearly 25% of newborns with critical types of CHD require surgical intervention in the first year of life. Hence, increasing numbers of the annually conducted cardiopulmonary bypass (CPB) cardiac surgeries are usually associated with postoperative bleeding and coagulopathy. Bleeding after CPB usually requires a replacement therapy, including the transfusion of whole blood, red blood cells, coagulation factors, or platelets.

Aim: to identify the pathophysiology of coagulopathy following cardiac surgery, how it impacts the clinical outcomes, and the available management options.

Methods: In this review, we only included English articles from common electronic databases such as PubMed /MEDLINE, Web of Science, Scopus, and the Cochrane Library with the keywords "congenital heart disease", "cardiac surgery" combined with keywords involving "coagulopathy" The end date for this review is February 2022.

Scientific novelty: This review aims to briefly review the problem of post-CPB bleeding in the pediatric population regarding multiple aspects. The medical literature lacks a comprehensive review regarding the problem of CHD, its prevalence, types, surgical options, post-cardiac surgery complications such as coagulopathy, the pathophysiology of the coagulopathy, and the preventive and therapeutic measures.

The practical significance of the result obtained: This review may help surgeons and pediatricians deeply understand post-CPB coagulopathy's pathophysiology and how to anticipate, prevent, and manage it properly. Antifibrinolytic pharmaceuticals represent the mainstay for managing this problem; their administration during CPB reduces the risk of postoperative bleeding. Blood component transfusion is also an alternative option.

Conclusion: Post-cardiac surgery, coagulopathy, and bleeding are major problems facing cardiothoracic surgeons. Postoperative bleeding, especially in the pediatric population, is one of the common causes of surgical re-exploration, leading to a higher risk of morbidities and mortalities. Meticulous preoperative examination, investigation, and intraoperative protective measures are important factors in avoiding and properly managing postoperative bleeding risk.

Keywords: congenital heart disease, cardiopulmonary bypass, coagulopathy, cardiac surgery.

Received: Novemer 2 , 2021
Revised: December 10, 2021
Accepted: February 16, 2022
Published: March, 30, 2022

* **Corresponding author**: Suieubekov Bekzat
bekzat.suieubekov@gmail.com
DOI: https://doi.org/10.57125/FEM.2022.03.25.03

Introduction

Congenital heart disease (CHD) is the disorder and abnormality of either the heart or the great vessels of the thorax, which usually occurs during fetal development. CHD may be classified to cyanotic CHD or non-cyanotic CHD according to the nature of the structural malformation. It can be further categorized into three types of lesions such as left heart obstructive lesions, right heart obstructive lesions, and mixed lesions [1,2]. It has been reported that CHD is a common condition affecting about 1% of all live births and approximately 40,000 newborns annually in the United States [3]. Nearly 25% of newborns with critical types of CHD require surgical intervention in the first year of life. In children with transposition of the great arteries, a major and complex surgical correction is mandatory in the first week of life [4]. In spite of the great advances in the early detection programs and the rapid progress in the surgical management of CHD. It is considered one of the leading causes of mortality among pediatrics suffering from various congenital disorders [5].

Therefore, there are increasing numbers of the annually conducted cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) support in the various cardiac surgeries. CPB and ECMO are usually associated with post-operative bleeding and coagulopathy, which may be attributed to decreased levels of coagulants and as a complication from CHD. Bleeding after CPB usually requires a replacement therapy, including the transfusion of whole blood, red blood cells, coagulation factors, or platelets [6,7].

Research Problem

There are many complications encountered during complex cardiac surgeries in children. Post-operative coagulopathy is one of the common and serious sequences of these surgeries. Physicians cannot determine how to prevent such complications.

Research Focus

Assessing and determining the causes, consequences, and new paradigms of coagulopathy in children undergoing cardiac surgeries.

Research Questions

1. What are CHDs occurring in newborns?
2. Do all CHDs require cardiac surgery?
3. What are the causes and pathophysiology of coagulopathy encountered after cardiac surgeries in children?
4. What is the proper management of post-operative bleeding and coagulopathy encountered after cardiac surgeries in children?

Research Aim

Therefore, we performed this study to investigate the changes in coagulation profile in children undergoing cardiac surgeries due to CHD.

Research Methodology

In our review, we only included English articles from common electronic databases such as PubMed /MEDLINE, Web of Science, Scopus, and the Cochrane Library with the keywords "congenital heart disease" and "cardiac surgery" combined with keywords, involving "coagulopathy" The end date for this review is February 2022. The studies that were found using each set of keyword combinations were then pooled to create an impartial collection of publications. Studies and/or articles that weren't subjected to peer review, as well as proposals, procedures, reviews, letters, and opinions, were eliminated. The references include publications that were chosen because they are related to our topic. We concentrated on providing an overview of CHDs and its surgery-related coagulopathy.

Research Results

The result of the search using our search strategy was 1482 articles. We screened these articles to choose the articles related to our topic. We conducted a full-text screening of 173 articles after excluding the remaining article by title and abstract screening. Finally, we used 50 articles to gather information about our topic and write this review.

Literature review

CHD represents a wide range of cardiac malformations, from mild and simple disorders with good prognosis to severe and complex defects requiring difficult surgical intervention with a variable prognosis. Despite the fact that

CHD is one of the leading causes of childhood morbidity and mortality, the prevalence of CHD in adults is increasing. Previous studies demonstrated that nearly 90% of pediatrics with CHD may survive into adulthood due to the recent improvement in disease identification, medical, and surgical management [8,9]. It is reported that there is a significant percentage of patients requiring at least one surgical management during their life [10,11].

Etiology

To the best of our knowledge, the cause of CHD is still unknown. However, there is evidence that it is multifactorial occurring due to combined environmental factors and genetic predisposition [12]. Recent research found that critical CHD may develop either isolated or as a consequence of a specific genetic syndrome. More than 20% of children with critical CHD were found to have a specific chromosomal abnormality, such as Turner syndrome, trisomy 21, 13, and 18. At the same time, environmental factors that showed a contributing role include maternal diabetes, infections, phenylketonuria, or exposure to toxins. It was found that the overall incidence of CHD increases by 4% if one parent is diseased or in cases of the second pregnancy after the first diseased child [13].

Epidemiology

Based on the recent data from the American Heart Association, tetralogy of Fallot (TOF), ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), aortic stenosis, coarctation of aorta, pulmonary stenosis, and atrioventricular septal defect represent about 85% of all CHDs [14]. Critical CHDs represent about 25% of all CHDs. TOF is the most prevalent critical CHD, while TGA is the second most prevalent critical CHD. Cardiovascular anomalies are responsible for about 35% of children dying due to congenital disorders [13].

Patients may present with variable clinical manifestations from the first weeks of life according to the type of lesion. However, the proper identification of the specific etiology may be difficult as other diseases, such as pulmonary diseases, sepsis, or inborn error of metabolism may share similar manifestations. Therefore any child with suspected CHD should perform a fetal echocardiogram and other diagnostic methods [15–17].

According to the Society of Thoracic Surgeons' database, about 28,000 cardiac surgeries are performed in children in North America each year, while about five thousand cardiac surgeries, including three thousand CPB are performed per year in the United Kingdom. There is a growing number of cardiosurgical procedures every year worldwide [18,19].

Management of CHDs

The primary aim in managing children with CHDs is to stabilize the general condition and vital signs by providing appropriate oxygen therapy and prostaglandin E1 infusion in cases of malformation affecting ducts [20]. The mild and trivial lesions usually don't require surgical intervention. However, strict follow-up, prophylactic antibiotics, and lifestyle modifications are required [21]. Patients could be managed with various techniques according to the type, location, and severity of the cardiac defect. Pulmonary stenosis is the most common lesion causing right ventricular valvular outflow obstruction representing about 9% of all CHDs [22]. Surgical intervention is required if the pressure gradient across the pulmonary valve exceeds 50mmHg. Pulmonary valvuloplasty using a balloon is the gold standard technique in this defect [23]. Aortic stenosis is regarded as the most common defect causing left ventricular outflow obstruction, accounting for about 6% of all CHDs [23]. Similar to pulmonary stenosis, mild lesions could be managed conservatively, while cases with severe symptoms and pressure gradient above 50mm Hg are candidates for surgical intervention. The first line therapeutic option was surgical commissurotomy. However, balloon valvuloplasty replaced it [24]. Regarding coarctation of aorta, it is a common anomaly accounting for 5% to 8% of all CHDs. Many cases with mild or no symptoms could be treated conservatively. However, there is recommendation that urgent intervention by balloon angioplasty and stents are required when children are stabilized [25].

CHDs often require difficult and challenging surgical procedures. For open heart surgeries to be performed successfully, safety protocols and checklists must be followed. In order to achieve success in patients, especially those with narrow safety margin, safe and proper CPB is essential [26]. The principle of CPB is to isolate the patient's cardiopulmonary system, allowing better visualization of the heart and the great vessels by providing most functions of the cardiopulmonary system, such as adding oxygen, eliminating carbon dioxide, and providing proper perfusion to all body organs.

Coagulopathy after cardiac surgery

Impact of the problem

One of cardiac surgery's most frequent side effects is postoperative bleeding [27,28]. Following cardiac surgeries, 20% of patients experience substantial bleeding, and 5% of them need to be reoperated/reexplored [29]. The need for re-exploration is one of the significant factors predicting the adverse outcomes following cardiac surgery. It is associated with higher postoperative mortality, mechanical ventilation use, acute respiratory distress syndrome, arrhythmia, sepsis, and susceptibility to surgical site infection and transfusion-related infections [29].

Reducing the risk of postoperative bleeding is important for better clinical outcomes. Many factors influence the incidence of bleeding and the need for re-exploration. This includes patients' age, renal function status, CPB duration, and intracardiac repair. Surgical causes could be identified in only 50% of patients needing reoperation. Other causes are related to certain factors during the procedure, like surgical trauma, prolonged contact between the blood and the synthetic surface of the CBP machine, a higher dosage of heparin, and hypothermia. These factors aggravate the dysfunction of coagulation and the inflammatory systems [29].

So, a deep understanding of the causes, pathophysiology, and factors associated with postoperative bleeding is critical to apply the best protective measures and to help choose the suitable management approach for each case.

Pathophysiology

Many factors can explain coagulopathy following cardiac surgeries. This includes using anticoagulation for operative preparation, inflammation, fibrinolysis, and platelet dysfunction. Additionally, the hemodilution caused by the primer fluid of the bypass circuit, blood loss during surgery, activation of the extrinsic coagulation pathway by the tissue factor, activation of the intrinsic system by the contact with the CPB circuits, and the remaining of the heparin used as a part of the systemic anticoagulation preparation [30,31].

Regarding the role of inflammation, CPB extensively activates the inflammatory system. As a result, leukocytes are activated and release their granule contents. The relationship between the activation of the coagulation system and the inflammatory system during the CPB is complicated and not easy to understand. Since CPB causes acute phase reactions resembling those occurring during septic conditions, this relationship may be explained on this bases [32,33]. The marked release of the leukocytes' granules contents leads to the monocytes' activation. This, in turn, causes tissue factor (TF) subendothelial expression generation of thrombin, which finally lead to "paradoxical" activation of the coagulation cascade, causing its consumption and then its impairment. Tissue factor pathway inhibitor is a crucial TF coagulant activity suppressor. (TFPI). Heparin stimulates the release of TFPI. TFPI poses highly positive charges that strongly attract the negatively charged glycosaminoglycan, like heparin. So, post-cardiac surgery bleeding may be caused by heparin-induced TFPI.

Physiologically, the thrombolysis process inhibits the further growth of the thrombus. The fibrinolytic system is activated when the plasminogen is cleaved to plasmin. Fibrin stimulates the endothelial cells to synthesize the tissue plasminogen activator (t-PA). Additionally, fibrin stimulates the urokinase plasminogen activator (u-PA) synthesis in monocytes, macrophages, and fibroblasts. Both elements act through the extrinsic pathway that activates the plasminogen. In addition, plasminogen can be activated through an intrinsic pathway by an active factor 12 during the coagulation cascade [34,35]. The plasmin is an endopeptidase that splits the fibrinogen and fibrin into smaller fragments incapable of clotting. One of these fragments is D-dimer, which is a marker for the fibrin fragmentation process. An inhibitor of the fibrinolytic system called plasminogen activator inhibitor (PAI-1) is released after the release of t-PA and u-PA [34,35]. It was reported that patients undergoing cardiac surgery with CPB have higher levels of t-PA, D-dimer, and t-PA-PAI-1 complex and lower levels of PAI-1. And the levels of these components were higher in those undergoing CPB than in those undergoing cardiothoracic surgeries without CPB [34,35]. T-PA is released from the endothelial walls leading to external activation of the fibrinolytic system. It is important to note that the activation of the fibrinolytic system is related to the degree of activation for the coagulation system, as the thrombin and fibrin activates the fibrinolytic system. This was evidenced by the correlation between the thrombin levels and the fibrinolytic markers at the end of the operation.

Moreover, inflammatory mediators like cytokines and endotoxins activate the plasminogen and its inhibitors [34,35]. Despite the previously reported explanations, a clear relation between fibrinolysis and post-CPB bleeding remains a query. Few studies report a correlation between fibrinolytic markers and post-CPB bleeding [34,35].

Platelet dysfunction is considered one of the major causes of bleeding following CPB, As evidenced by the prolonged bleeding time and platelet contractile force tests after CPB. Moreover, a noticeable but brief decrease in platelet count is noted. This may be due to hemodilution, which is not a direct cause of platelet dysfunction. CPB-associated platelet dysfunction may be attributed to external factors. Hypothermia may impair platelet function, as reported by many studies. In patients undergoing CPB, temperature affects the bleeding time, which reflects the overall platelet function. Moreover, the hypothermia was linked to reduced protein C and S levels, elevated thrombin levels, and thrombomodulin release indicating an overall coagulopathy [34,35].

Management approaches

Based on the understanding of the pathophysiology of post-CBP coagulopathy, several investigations have shown that administering antifibrinolytic substances during CPB reduces the stimulation of the inflammatory and fibrinolytic systems. Additionally, it reduces postoperative blood loss and the need for blood transfusion. Pharmaceutical agents include tranexamic acid, aprotinin, and aminocaproic acid. Data from a meta-analysis found that aprotinin led to a twofold reduction of mortality and decreased the number of patients needing a blood transfusion and re-exploration rates without raising the possibilities of myocardial infarction [36,37]. It is noted that plasminogen and t-PA reduce

the platelets' activity. Thrombolytic agents act through the degradation of the fibrin, von Willebrand factor, and platelets surface glycoproteins (GPIb and GPIIb/IIIa). A similar action was noted during and after CPB, leading to platelet dysfunction. Therefore, the fibrinolytic-induced platelet defect may be reduced by introducing antifibrinolytic drugs like aprotinin that decrease the activation of fibrinolytic enzymes [38]. Patients undergoing CPB who receive aprotinin therapy have normal levels of 2-antiplasmin, preserved GP1b platelet receptors, improved platelet aggregation, and less blood loss than patients who do not receive aprotinin treatment. Similar effects are produced by other antifibrinolytic medications like tranexamic acid and aminocaproic acid, but they are less efficient than aprotinin against platelet dysfunction and receptors lysis [38]

Discussion

Nearly 25% of newborns with critical types of CHD require surgical intervention in the first year of life. Additionally, in children with transposition of the great arteries, a major and complex surgical correction is mandatory in the first week of life [4]. Therefore, there is an increasing number of CPB cardiac surgeries, which are usually associated with postoperative bleeding and coagulopathy [6,7]. Unlike adults, the pediatric population has relatively less circulatory blood volume [39]. So, bleeding leads to losing most of their blood components quickly, making bleeding control more challenging. This makes post-cardiac surgery bleeding prevalent in the pediatric population and needs special attention.

Control of the postoperative coagulopathy and bleeding following cardiac surgery is the mainstay for the success of cardiac surgeries, reducing the incidence of re-exploration and subsequent complications. Therapeutic and protective options are not limited to the use of the ant antifibrinolytic agents. In surgical settings, post-CPB bleeding and coagulopathy are the most frequent causes of blood product transfusion. Replacement therapy includes the transfusion of whole blood, red blood cells, coagulation factors, or platelets [6,7].

Other options include prothrombin complex concentrate (PCC) and plasma transfusion. In a randomized controlled trial of 100 patients by Smith et al. [40], there was no significant difference between both treatment options regarding postoperative bleeding and adverse effects. But, in the PCC group, fewer patients required intraoperative blood transfusion than in the plasma transfusion group [40]. We could not find any data regarding the coagulopathy paradigms changes after cardiac surgery in children in Kazakhstan.

Conclusions and Implications

1. Post-cardiac surgery bleeding is one of the major problems for cardio-thoracic surgeons.
2. Postoperative bleeding is one of the common causes of surgical re-exploration.
3. Re-exploration itself leads to a higher risk of morbidities and mortalities.
4. Meticulous preoperative examination, investigation, and intraoperative protective measures are important factors in preventing postoperative bleeding.
5. Antifibrinolytic pharmaceuticals represent the mainstay for managing this group of patients; their administration during CPB reduces the risk of postoperative bleeding. Blood component transfusion is an alternative option.

Declarations

Author contributions

All authors have sufficiently contributed to the study and agreed with the results and conclusions.

Funding

No funding source is reported for this study.

Ethical statement

This study does not require IRB approval as it does not involve human subjects/data.

Declaration of interest

No conflict of interest is declared by authors.

Data sharing statement

Data supporting the findings and conclusions are available upon request from the corresponding author.

References

1. Desai K, Rabinowitz EJ, Epstein S. Physiologic diagnosis of congenital heart disease in cyanotic neonates. Curr Opin Pediatr [Internet]. 2019 Apr;31(2):274–83. Available from: http://journals.lww.com/00008480-201904000-00019
2. Mohammad Nijres B, Samuel BP, Vettukattil JJ. Subclinical atherosclerosis in patients with cyanotic congenital heart disease. Int J Cardiol [Internet]. 2019 May;282:44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167527318359412
3. Jain S. Congenital heart disease: Saving lives and securing liveliness with early primary care and expert family care. J Fam Med Prim Care [Internet]. 2021;10(9):3178. Available from: https://journals.lww.com/jfmpc/Fulltext/2021/10090/Congenital_heart_disease__Saving_lives_and.4.aspx
4. Valleley MS, Buckley KW, Hayes KM, Fortuna RR, Geiss DM, Holt DW. Are there benefits to a fresh whole blood vs. packed red blood cell cardiopulmonary bypass prime on outcomes in neonatal and pediatric cardiac surgery? J Extra Corpor Technol [Internet]. 2007 Sep;39(3):168–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17972451
5. Meshram RM, Gajimwar VS. Prevalence, profile, and pattern of congenital heart disease in Central India: A prospective, observational study. Niger J Cardiol [Internet]. 2018 [cited 2022 January 17];15(1):45. Available from: https://www.nigjcardiol.org/article.asp?issn=0189-7969;year=2018;volume=15;issue=1;spage=45;epage=49;aulast=Meshram
6. Bishop JC, Blakemore K, Vricella L, Sekar P, Sagaser K, Crino J, Ness P, Kogutt BK, Boyd J, Aucott S, Jelin AC, Chiu J, Gehrie E, McMillan KN. Prenatal ABO/RHD Genotyping: A New Paradigm to Allow for Fresh Whole Blood for Cardiopulmonary Bypass in the Immediate Newborn Period. Fetal Diagn Ther [Internet]. 2018;44(2):156–9. Available from: https://www.karger.com/Article/FullText/487592
7. Keene SD, Patel RM, Stansfield BK, Davis J, Josephson CD, Winkler AM. Blood product transfusion and mortality in neonatal extracorporeal membrane oxygenation. Transfusion [Internet]. 2020 Feb 14;60(2):262–8. Available from: https://onlinelibrary.wiley.com/doi/10.1111/trf.15626
8. Raissadati A, Nieminen H, Jokinen E, Sairanen H. Progress in Late Results Among Pediatric Cardiac Surgery Patients. Circulation [Internet]. 2015 Jan 27;131(4):347–53. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.114.011190
9. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing Mortality in Congenital Heart Disease. J Am Coll Cardiol [Internet]. 2010 Sep;56(14):1149–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109710026422
10. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease. J Am Coll Cardiol [Internet]. 2008 Dec;52(23):e143–263. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109708033044
11. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal Trends in Survival to Adulthood Among Patients Born With Congenital Heart Disease From 1970 to 1992 in Belgium. Circulation [Internet]. 2010 Nov 30;122(22):2264–72. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.110.946343
12. Yasuhara J, Garg V. Genetics of congenital heart disease: a narrative review of recent advances and clinical implications. Transl Pediatr [Internet]. 2021 Sep;10(9):2366–86. Available from: https://tp.amegroups.com/article/view/77549/html
13. Rohit M, Shrivastava S. Acyanotic and Cyanotic Congenital Heart Diseases. Indian J Pediatr. 2018 Jun;85(6):454-460. doi: 10.1007/s12098-017-2454-6. Epub 2017 Sep 30. PMID: 28963608.
14. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart Disease and Stroke Statistics–2012 Update. Circulation [Internet]. 2012 Jan;125(1). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0b013e31823ac046
15. Van De Bruaene A, Meier L, Droogne W, De Meester P, Troost E, Gewillig M, Budts W. Management of acute heart failure in adult patients with congenital heart disease. Heart Fail Rev [Internet]. 2018 Jan 25;23(1):1–14. Available from: http://link.springer.com/10.1007/s10741-017-9664-x
16. Tulloh RMR, Medrano-Lopez C, Checchia PA, Stapper C, Sumitomo N, Gorenflo M, Jung Bae E, Juanico A, Gil-Jaurena JM, Wu MH, Farha T, Dodge-Khatami A, Tsang R, Notario G, Wegzyn C. CHD and respiratory syncytial virus: global expert exchange recommendations. Cardiol Young [Internet]. 2017 Oct 16;27(8):1504–21. Available from: https://www.cambridge.org/core/product/identifier/S1047951117000609/type/journal_article
17. Di Filippo S. Antibioprophylaxie de l'endocardite infectieuse dans les cardiopathies congénitales. Presse Med [Internet].

2017 Jun;46(6):606–11. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0755498217302543

18. Jacobs JP, Mayer JE, Mavroudis C, O'Brien SM, Austin EH, Pasquali SK, Hill KD, He X, Overman DM, St. Louis JD, Karamlou T, Pizarro C, Hirsch-Romano JC, McDonald D, Han JM, Dokholyan RS, Tchervenkov CI, Lacour-Gayet F, Backer CL, Fraser CD, Tweddell JS, Elliott MJ, Walters H, Jonas RA, Prager RL, Shahian DM, Jacobs ML. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2016 Update on Outcomes and Quality. Ann Thorac Surg [Internet]. 2016 Mar;101(3):850–62. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497516000709

19. Hoffman JIE. The global burden of congenital heart disease : review article. Cardiovasc J Afr [Internet]. 2013 Jun 21;24(4):141–5. Available from: http://www.cvja.co.za/onlinejournal/vol24/vol24_issue4/#43/z

20. Ismail SR, Almazmi MM, Khokhar R, AlMadani W, Hadadi A, Hijazi O, Kabbani MS, Shaath G, Elbarbary M. Effects of protocol-based management on the post-operative outcome after systemic to pulmonary shunt. Egypt Hear J [Internet]. 2018 Dec;70(4):271–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1110260818300541

21. Rao PS. Management of Congenital Heart Disease: State of the Art; Part I—ACYANOTIC Heart Defects. Children [Internet]. 2019 Mar 8;6(3):42. Available from: https://www.mdpi.com/2227-9067/6/3/42

22. Syamasundar P. Congenital Heart Defects – A Review. In: Congenital Heart Disease - Selected Aspects [Internet]. InTech; 2012. Available from: http://www.intechopen.com/books/congenital-heart-disease-selected-aspects/congenital-heart-defects-a-review

23. Rao PS. Percutaneous balloon pulmonary valvuloplasty: State of the art. Catheter Cardiovasc Interv [Internet]. 2007 Apr 1;69(5):747–63. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ccd.20982

24. C. Agu N. Balloon Aortic Valvuloplasty. Pediatr Ther [Internet]. 2012;01(S5). Available from: https://www.omicsonline.org/balloon-aortic-valvuloplasty-2161-0665.S5-004.php?aid=9081

25. R Doshi A. Coarctation of Aorta-Management Options and Decision Making. Pediatr Ther [Internet]. 2012;01(S5). Available from: https://www.omicsonline.org/coarctation-of-aorta-management-options-and-decision-making-2161-0665.S5-006.php?aid=9082

26. Kumar TKS. Practical conduct of open heart procedures for congenital heart lesions. J Thorac Dis [Internet]. 2020 Mar;12(3):1235–59. Available from: http://jtd.amegroups.com/article/view/37145/html

27. Pereira KMFSM, de Assis CS, Cintra HNWL, Ferretti-Rebustini REL, Püschel VAA, Santana-Santos E, Rodrigues ARB, de Oliveira LB. Factors associated with the increased bleeding in the postoperative period of cardiac surgery: A cohort study. J Clin Nurs. 2019;

28. Petrou A, Tzimas P, Siminelakis S. Massive bleeding in cardiac surgery. Definitions, predictors and challenges. Hippokratia. 2016;20(3):179–86. PMID: 29097882. PMCID: PMC5654433

29. Elassal AA, Al-Ebrahim KE, Debis RS, Ragab ES, Faden MS, Fatani MA, et al. Re-exploration for bleeding after cardiac surgery: revaluation of urgency and factors promoting low rate. J Cardiothorac Surg [Internet]. 2021;16(1):166. Available from: http://dx.doi.org/10.1186/s13019-021-01545-4

30. Ranucci M, Baryshnikova E, Ciotti E, Ranucci M, Silvetti S. Hemodilution on cardiopulmonary bypass: Thromboelastography patterns and coagulation-related outcomes. J Cardiothorac Vasc Anesth [Internet]. 2017;31(5):1588–94. Available from: http://dx.doi.org/10.1053/j.jvca.2017.04.014

31. Bartoszko J, Karkouti K. Managing the coagulopathy associated with cardiopulmonary bypass. J Thromb Haemost [Internet]. 2021;19(3):617–32. Available from: http://dx.doi.org/10.1111/jth.15195

32. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg [Internet]. 2002;21(2):232–44. Available from: http://dx.doi.org/10.1016/s1010-7940(01)01099-5

33. ten Cate JW, Poll T van der, Levi M, Cate HT, van Deventer SJH. Cytokines: Triggers of clinical thrombotic disease. Thromb Haemost [Internet]. 1997;78(01):415–9. Available from: http://dx.doi.org/10.1055/s-0038-1657562

34. Heissig B, Salama Y, Takahashi S, Osada T, Hattori K. The multifaceted role of plasminogen in inflammation. Cell Signal [Internet]. 2020;75(109761):109761. Available from: http://dx.doi.org/10.1016/j.cellsig.2020.109761

35. Sugioka K, Mishima H, Kodama A, Itahashi M, Fukuda M, Shimomura Y. Regulatory Mechanism of Collagen Degradation by Keratocytes and Corneal Inflammation: The Role of Urokinase-Type Plasminogen Activator. Cornea. 2016 Nov;35 Suppl 1:S59-S64. doi: 10.1097/ICO.0000000000000995. PMID: 27661072.

36. Levi M, E.Cromheecke M, Jonge E de, Prins MH, Mol BJM de, Briët E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: Meta-analysis of clinically relevant endpoints. Transfus Altern Transfus Med [Internet]. 2001;3(5):13–22. Available from: http://dx.doi.org/10.1111/j.1778-428x.2001.tb00045.x

37. Kuepper F, Dangas G, Mueller-Chorus A, Kulka PM, Zenz M, Wiebalck A. Fibrinolytic activity and bleeding after cardiac surgery with cardiopulmonary bypass and low-dose aprotinin therapy. Blood Coagul Fibrinolysis [Internet]. 2003;14(2):147–53. Available from: http://dx.doi.org/10.1097/00001721-200302000-00005

38. Paparella D, Brister SJ, Buchanan MR. Coagulation disorders of cardiopulmonary bypass: a review. Intensive Care Med [Internet]. 2004;30(10):1873–81. Available from: http://dx.doi.org/10.1007/s00134-004-2388-0

39. Saikia D, Mahanta B. Cardiovascular and respiratory physiology in children. Indian J Anaesth [Internet]. 2019;63(9):690–7. Available from: http://dx.doi.org/10.4103/ija.IJA_490_19

40. Smith MM, Schroeder DR, Nelson JA, Mauermann WJ, Welsby IJ, Pochettino A, et al. Prothrombin complex concentrate vs plasma for post-cardiopulmonary bypass coagulopathy and bleeding: A randomized clinical trial: A randomized clinical trial. JAMA Surg [Internet]. 2022;157(9):757–64. Available from: http://dx.doi.org/10.1001/jamasurg.2022.2235