DOI: https://doi.org/10.54393/pjhs.v4i11.1106

PAKISTAN JOURNAL OF HEALTH SCIENCES

https://thejas.com.pk/index.php/pjhs

Volume 4, Issue 11 (November 2023)

Review Article

A Narrative Review on Management of Cyanosis in Neonates

Maria Fayyaz[1*] and Sumbal Shahbaz[1]

[1]Department of Health Professional Technologies, The University of Lahore, Lahore, Pakistan

ARTICLE INFO

Key Words:
Cyanosis, Etiology, Evaluation, Management

How to Cite:
Fayyaz, M., & Shahbaz, S. (2023). A Narrative Review on Management of Cyanosis in Neonates: Management of Cyanosis in Neonates. Pakistan Journal of Health Sciences, 4(11). https://doi.org/10.54393/pjhs.v4i11.1106

***Corresponding Author:**
Maria Fayyaz
Department of Health Professional Technologies, The University of Lahore, Lahore, Pakistan
mariafayyaz58@gmail.com

Received Date: 10th September, 2023
Acceptance Date: 5th November, 2023
Published Date: 30th November, 2023

ABSTRACT

A bluish coloring of the skin or mucous membrane that is characteristic of the medical condition cyanosis can be visible around the lips, fingers, and toes. It is one of the indications of respiratory distress in infants that can be brought on by inadequate circulation and low levels of oxygenated blood. There are two basic causes of cyanosis, cardiac and pulmonary. Medical professionals are constantly very concerned about accurately diagnosing and treating newborns with congenital heart disease (CHD), despite the fact that prenatal diagnostic methods have significantly improved. Although they are physiologically entirely different from one another, ductus dependent congenital cardiac abnormalities can be divided into the ductus dependent systemic or pulmonary sickness. When developing the treatment plan, the clinical state and cardiac abnormalities must be taken into consideration. Many life-threatening conditions may not show signs right away after delivery, and the majority of clinical and physical symptoms are ambiguous, which makes a diagnosis difficult. Careful evaluation is required, and when clinical data, electrocardiograms, and chest X-rays are used. The newborn must be identified as being at such high risk right once, and prompt medical attention is essential to reducing mortality and morbidity.

INTRODUCTION

Cyanosis is a bluish-purple blotch confined to the skin, for instance the area around the lips fingers and toes. When the actual amount of reduced hemoglobin in the capillaries exceed 3g/dl cyanosis develops [1]. Cyanosis is one of the most prominent indicators of newborn respiratory distress. Most of the research point out that if a baby's skin or lips becomes blue, it is most often related with lack of deoxygenation of blood that leading to hypoxia. In this condition, the apparent color of the blood goes from a brilliant red to a darker blue [2]. The main oxygen messenger in the blood is hemoglobin, which consist of four smaller components two alpha and beta polypeptide chain. Iron containing heme group is situated in the center. The potential of the blood to deliver oxygen is seriously hampered by presence of aberrant hemoglobin. This may develop tissue hypoxia, which may be clinically observed as cyanosis [3]. Although the oxygen level improved about 85-95% within 10 minutes of delivery, newborns generally experience central cyanosis after childbirth. So this should be treated and assessed as early as possible. This can be associated with potentially fatal illness due to cardiac, infectious, metabolic, parenchymal and non-parenchymal disease [4]. Central, peripheral, differential and acrocyanosis are four basic types of cyanosis. Central cyanosis causes mucosal layers to prominently turn blue-purple as a result of low level of oxygen in the blood, as a consequence of circumstances that increase the amount of deoxygenated Hb or divergent Hb. Peripheral cyanosis is a condition in which extremities develop a distinctive bluish contusion on the distal extremities because they are

DOI: https://doi.org/10.54393/pjhs.v4i11.1106

not receiving enough oxygenated blood. Peripheral cyanosis is rarely serious medical condition. Differential cyanosis causes the hands and feet to turn blue in color that is unsymmetrical. It usually means that there are substantial underlying cardiopulmonary diseases [5]. Acrocyanosis often seen surrounding the lips or upper and lower limbs, commonly occurring in healthy neonates. It is a gentle disorder produced by vasomotor alterations that can cause vasoconstriction and enriched tissue oxygen extraction [6]. Cyanosis typically happens when Hb has very minimal amount of oxygen. There are two physical conditions in which oxygen is transported in the blood. Only 2% of the total oxygen carried in the blood is dissolved directly in the plasma; the majority, around 98%, is linked to hemoglobin [7]. Absence of adequate oxygen supply to the peripheral tissues might be identified by the appearance of cyanosis. The higher oxygen intake by peripheral tissues possibly a contributing factor. Several factors are crucial for the transportation of oxygen to the internal organs. The amount of the oxygen delivered depends on heart rate and arterial oxygen level. The preload, after-load and contractility are factors that affects heart rate. High level of deoxygenated Hb probably makes cyanosis highly visible. Jaundice, skin tone, the environment, or lighting may influence the detection of cyanosis. Anemia or polycythemia can have a significant impact on cyanosis. When Hb concentration is insufficient, it is more complicated to detect cyanosis. In other word, in a patient with severe anemia, cyanosis cannot be made clinically visible [8]. A comprehensive clinical assessment and detailed history help the doctor to diagnose the cause of the cyanosis. The clinical indications are verified by laboratory test reports such as CBC, pulse oximetry, chest radiography, arterial blood gas and echo-cardiographs [9].

Etiology

Heart failure, genetically inherited heart disease (right-to-left shunting), and valvular heart disorder, for example, complete transposition of the great arteries (TGA), coarctation of the aorta (CoA), critical pulmonary and aortic valvular stenosis/atresia, tricuspid atresia (TA), hypoplastic left heart syndrome (HLHS), arterial septal defect (ASD), patent ductus arteriosus (PDA) might be unnoticed for a long time before manifesting as severe acidosis, cyanosis, shock, or death. Chronic heart diseases are categorized into two types: ductus dependent cardiac lesions and non-ductus dependent cardiac lesions [10]. The predominance of congenital cardiac abnormalities are involved in 10% of all occurrences of cyanosis in children over the age of one year. Fallot syndrome is characterized by four defects: right ventricular hypertrophy, ventricular septal defect, pulmonary stenosis, and aortic dextroposition [11]. Respiratory depression can arise as a result of a central nervous system illness. There is acute alveolar hypoventilation when central nervous system illness manifests as cyanosis [12]. A temperature less than 36.5C is normally referred as neonatal hypothermia, it is correlated with neonatal mortality and morbidity especially in premature and low birth weight babies. Hypothermia is infrequently a direct cause of death. It also does play a significant role in mortality due to asphyxia, prematurity, infection as well as intraventricular hemorrhage [13]. In polycythemia and hyper viscosity blood flow reduced in brain, lungs, heart and intestine. Although renal plasma is impacted, there is no reduction in renal blood flow, which lowers glomerular filtration rate. A higher arterial oxygen content is associated with higher Hb and hematocrit levels. The higher arterial oxygen content, not hyper viscosity, is fully responsible for the diminished blood flow to the brain and heart [14]. Hyperventilation, COPD (chronic obstructed pulmonary disease), bronchiolitis, bronchospasm, and pulmonary hypertension are a few examples of pulmonary illnesses that are indicated by poor alveolar-arterial diffusion and ventilation perfusion mismatches [15]. When pulmonary vascular resistances (PVR) leftover excessively high after birth, blood shunts right to left across fetal circulatory pathway that provoke persistent pulmonary hypertension in a newborn (PPHN). As a consequence, severe hypoxia develops that may or may not response to conventional respiratory support in a newborn. PPHN is expected to impact 1.9 per 1000 live births [16]. Three main categories can be used to classify the reason of persistent pulmonary hypertension in newborn PPHN. The most common form of PPHN is driven by parenchymal disorders such as pneumonia, severe respiratory distress syndrome, and meconium aspiration syndrome (MAS). This is mostly caused by inadequate entry into the alveolar space, especially in cases of MAS with airway obstruction. PPHN patients with congenital hernia have decrease blood vessel thickness, a smaller cross- section of the pulmonary vasculature and higher pulmonary vascular resistance [17]. When the iron in hemoglobin transforms from Fe^{2+} to Fe^{3+} state, it results in methemoglobinemia, a disorder that leads to congenital acquired cyanosis. In this condition only 2 percent hemoglobin is present. The skin tone might be taken on a bluish tinge when methemoglobin is present. This disorder can brought on by contact with the topical anesthetic such as dapsone, nitroglycerine or other strong oxidizing substances. Genetically inherited methemoglobinemia type I or II is caused by a mutagenicity in the gene encoding the cytochrome b5 reductase enzyme. This ailment does not occur frequently. When cytochrome b5 reductase is not enzymatically active, methemoglobin reduction is restricted [18]. Peripheral cyanosis can be caused by a variety of factors, including heart failure and

DOI: https://doi.org/10.54393/pjhs.v4i11.1106

shock, benign vasoconstriction caused on by cold exposure, and regional ischemia from arterial blockage brought on by peripheral vascular disease [19]. Peripheral cyanosis occurs when the body continues to fail providing oxygen-rich blood to the peripheral tissues. Vasoconstriction induces ischemic peripheral cyanosis by reducing blood flow to the extremities. During peripheral cyanosis, arterial saturation is completely natural; but, due to vascular constriction and decreased blood flow, the peripheral tissues in the capillary receive more oxygen. Since there is more de-oxygenated blood on the venous side of the capillary bed, there seems to be a significant difference in saturation between venous and arterial blood [20].

Evaluation

The evaluation should be carefully done by examining the infant's airways, lungs and heart. Risk factors for pregnancy, labor pains and the birth of the baby should be assessed as the part of history. Maternal diabetes increases the chance of polycythemia, which can cause respiratory distress as well as congenital heart problems. Polyhydramnios may signify bronchial, esophageal or neurological disorders and the occurrence of oligohydramnios may reveal renal issues linked to hypoplastic lungs. It is essential to keep in consideration that infection is still possible even if the prenatal culture for group B streptococcus was negative when examining for reports findings for cervical infection. A history of complicated birth may produce cerebral bleeding or phrenic nerve paralysis [21]. Clinical diagnosis should be done once the infant has prepped. It is important to monitor the growth parameters of the infant because babies who are large or little according to the weeks of pregnancy are at a higher risk of developing polycythemia. Common indications of respiratory insufficiency are pulmonary disease including meconium aspiration, persistent pulmonary hypertension, fast breathing, retractions and nasal flaring [22]. Because of hypoventilation, neurologic disorders are possible potential reason of cyanosis and may be associated with lethargic or irregular breathing rate. Additionally it is crucial to assess the infant's activity, tone and irregular respiration. An Erb's palsy or harsh cry are instance of birth trauma signs that may be identified during assessment [23]. The newborn's oxygenation and pulse rate must be closely monitored during the cardiac assessment. The S2 heart sound, which will be continuous and narrow split in pulmonary hypertension, transposition, and pulmonary atresia, should be the major focus of heart auscultation [24]. Blood oxygenation refers to the amount of hemoglobin that has been chemically bonded with oxygen, or the fraction of blood containing oxygen. An ideal non-surgical and persistent method of measuring oxygen saturation is pulse oximetry. The first finger of the right hand should be used for pulse oximetry. In many micro sample blood gas analyzers, the examination of lactate now gives additional, crucial data on global perfusion and oxygenation [25]. A chest X-ray is a crucial aspect of assessment of the baby with cyanotic CHD. In order to find out situs inversus and dextrocardia, the placements of the stomach, liver, and heart should be recognized. While investigating the lungs, one might identify parenchymal lungs illness or abnormalities including cystic adenomatous malformation. Any hemi-diaphragm that is inflated more than two intercostal spaces may be an indication of phrenic nerve damage related to diaphragmatic paralysis. Frequently, lobar emphysema appear with hyper inflated lungs field. Reduced pulmonary vascular markings are a sign of pulmonary stenosis or pulmonary atresia with inappropriate ductal shunting in infants with idiopathic severe pulmonary hypertension. Certain medical signals can be provided by the size and form of the heart, such as the TOF (boot shape) heart, the impression of transposition (like an egg on a string), and the recognizable massive cardiomegaly of Ebstein's anomaly (Figure 1) [26]. Evaluation of newborns with significant conditions like transposition usually benefits from an ECG. A notable example is a newborn with left axis deviation induced by left ventricular hypertrophy [27]. When medical findings is combined with ECG and chest X-ray (CXR) readings, it is typically easy to distinguish between a cardiac and respiratory cause of cyanosis. Unfortunately, some problems remain tough, and in these cases, a hyperoxia test may be useful. Instead of a pulse oximeter, ABG (arterial blood gas) testing should be employed for this test. At room temperature, ABGs are commonly done through the right radial artery. After 10 minutes of 100% oxygen levels, the ABG is performed. Partial pressure of oxygen should raise greatly in the absence of a left-to-right shunt [28].

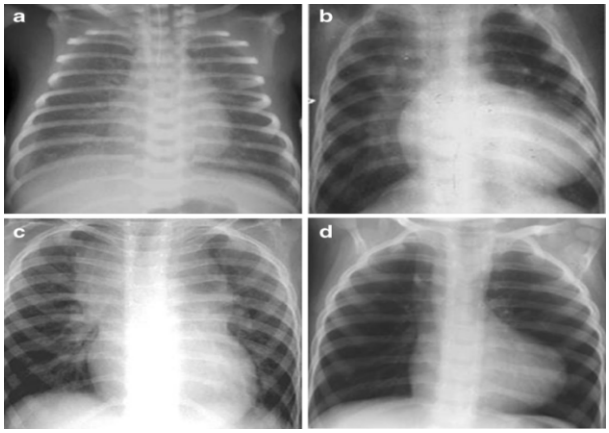

Figure 1: Chest X-ray in numerous cases of cyanotic CHD, **A:**

DOI: https://doi.org/10.54393/pjhs.v4i11.1106

Occluded TAPVC showing no cardiomegaly and extreme pulmonary veins high blood pressure, **B:** Harmonic progression of Great Arteries- cardiac hypertrophy, narrow pedicle with pulmonary plethora, e.g., egg on side elegance, **C:** Supra cardiac TAPVC characteristic snowman look, and **D:** Tetralogy of Fallot, no cardiomegaly, oligemic[26].

Management

Complete transposition of the great arteries (TGA)

The procedure often used for cure of TGA is termed as balloon arterial septostomy. In this procedure, medical specialist inserts a device with a balloon tip into left atrium through the oval fossa. To rupture the fragile atrial septum, the balloon is inflated and dragged back into the right atrium. For this treatment to be effective, the final ASD (atrial septal defect) width must exceed than 5 mm, along with an improvement in O_2 concentration. This method is efficient for developing reliable inter-atrial connectivity. High oxygen rates should be resisted because they can induce ductal closer, have a negative effect on inter-circulatory mixing, and also cause intense alveolar inflation when used with an extremely high ventilator mode like, positive inspiratory pressure (PIP) and positive end expiratory pressure (PEEP) [29]. Reconstructive surgery with an arterial switch is the suggested treatment to achieve total anatomical and physiological repair[30].

Tetralogy of Fallot

The entire surgical treatment of the disease with the lowest possible rate of death and morbidity is the aim of care for patients with TOF. It seeks to treat any side effects that TOF and other cyanotic cardiac problems may cause. Hyper-cyanotic episodes are a disorder that affects children with TOF and causes them to weep uncontrollably, breathe deeply quickly, and become blue and pale. The following is a detailed explanation of how to handle hyper cyanotic episodes. To increase systemic arterial resistance, which encourages pulmonary flow, the infant should be positioned with the knees to the chest. In order to breathe humid oxygen, put on a face mask. To end the trance, subcutaneous morphine sulphate 0.1 mg/kg is needed. At this stage, it is necessary to address metabolic acidosis, fluid transfusion-induced anemia, and sodium bicarbonate-induced dehydration. Propranolol can also be gently administered intravenously in a solution of 0.1 mg/kg combined with 50 ml of water and 5% dextrose. Surgery should be done if none of the aforementioned therapies improve the infant's condition. Many physicians conducted balloon pulmonary valvuloplasty in TOF patients to increase respiratory blood flow as well as allow for the establishment of the left ventricle and pulmonary artery system[31].

Pulmonary circulatory lesions that depend on the ductus

A typical characteristic of right-sided lesions such TOF and its variants is central cyanosis. The stability of the ductus would determine the extent of cyanosis. It is straightforward to differentiate between cardiac and respiratory origin utilizing an arterial blood gases hyperoxia test [32]. As ductal tissues tighten, cyanosis could exacerbate. These newborns must start receiving PGE1 injections immediately. Keeping the ductus arteriosus completely open, up to the Blalock taussing shunt surgery, which aids in improving respiratory flow for pulmonary atresia. PGE1 infusions are essential for stabilizing the airways because they reduce pulmonary vascular resistance, enhance left to right shunting, and ultimately increase respiratory blood flow. PGE1 is first administered at 0.05 g/kg/min. Increase the dosage by 0.1 g/kg/min once the infant's condition has stabilized and there hasn't been any improvement. The dosage should then be adjusted to 0.025 g/kg/min. maintaining the patient's airway is essential for determining whether or not they have septic shock because of its complicated side symptoms, which would include apnea, bradycardia, hypotension, fluid electrolyte imbalance, and pyrexia. PGE1 is not harmful for CHD, but it can lead to limited atrial septal rupture, transposition of the great arteries, and complete atypical pulmonary vascular return(TAPVR)[33].

Ductus dependent systemic circulatory lesions

Therapy for this patient should concentrate on improving metabolic acidosis, which could be harmful to the patient's operative status, and increasing systemic oxygenation. The way in which these people are treated is based on two key concepts. Initially, keep the ductus open. For survival, PGE1 must be supplied. The flow balance between the systemic and pulmonary circulation should be considered when ductal patency has been achieved. When pulmonary blood flow rises, systemic and coronary blood flow are reduced. Oliguria, metabolic acidosis, and cardiovascular failure are signs of inadequate perfusion. To reduce pulmonary over circulation, ventilation techniques are employed to improve pulmonary vascular resistance. The systemic and myocardium systems can both get appropriate perfusion when two competing circulations are kept equal. By carefully adjusting the PEEP (4-6 cm H_2O), regulating the inspiratory rate, pressure, and peak flow to sustain an arterial CO_2 pressure of 5-6 kpa, minimize unnecessary O2 delivery, retaining the systemic arterial concentration at around 80%, and preventing respiratory alkalosis. Low or high partial pressures of CO_2 have the potential to overload the pulmonary circulation with volume and cause heart failure by reducing the pulmonary vascular resistance to blood flow [34]. Neonatal who develop tachypnea from shock require morphine sedation; in this situation, a muscle relaxant should be taken into consideration. Utilizing vasodilators will provide the

DOI: https://doi.org/10.54393/pjhs.v4i11.1106

greatest possible systemic perfusion. If poor cardiac output persists despite all of these attempts, the availability of PGE1 infusions, intravascular volume, and anemia should be reevaluated. If the blood pressure is manageable, metabolic acidosis can be treated with a modest dose of nitroprusside infusion [35].

CONCLUSIONS

When an infant with cyanosis shows up at the emergency room, prompt evaluation, diagnosis, and treatment is necessary. Technology, resources, a lack of time, and a lack of competence are all factors that prevent a baby with suspected cyanosis from receiving a prompt postnatal diagnosis. When diagnosing newborn cyanosis, a methodical and logical approach is crucial. The emergency department practitioner will be able to determine whether the underlying cause is related to airway obstruction, parenchymal disease, hypoventilation due to CNS disease or apnea, or due to cardiac disease by having a thorough understanding of the normal transitional physiology and how diseases of the airway, lung, and circulatory system may disrupt these processes. The clinical diagnosis, careful consideration of hemodynamic stability, prudent oxygen supply, and referral to the most suitable inpatient hospital setting form the basis of management. Although the prognosis varies depending on the diagnosis, it is typically favorable with early detection and treatment.

Authors Contribution

Conceptualization: MF
Writing-review and editing: MF, SS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Lees MH. Cyanosis of the newborn infant: recognition and clinical evaluation. The Journal of Pediatrics. 1970 Sep; 77(3): 484-98. doi: 10.1016/S0022-3476(70)80024-5.
[2] Azmi NF, Delbressine F, Feijs L. Conceptual determination and assessment of cyanosis. Int. J. Bioscience, Biochemistry and Bioinformatics. 2016 Jul; 6(3): 75-83. doi: 10.17706/ijbbb.2016.6.3.75-83.
[3] Adeyinka A and Kondamudi NP. Cyanosis. StatPearls Publishing; 2018.
[4] Eichenwald E and Kim M. Overview of cyanosis in the newborn. UpToDate. 2021 Apr; 2.
[5] Pahal P and Goyal A. Central and peripheral cyanosis. StatPearls publishing; 2021.
[6] Sasidharan P. An approach to diagnosis and management of cyanosis and tachypnea in term infants. Pediatric Clinics. 2004 Aug; 51(4): 999-1021. doi: 10.1016/j.pcl.2004.03.010.
[7] Lundsgaard C. Studies on Cyanosis: I. Primary Causes of Cyanosis. The Journal of Experimental Medicine. 1919 Sep; 30(3): 259-69. doi: 10.1084/jem.30.3.259.
[8] Lees MH and King DH. Cyanosis in the newborn. Pediatrics in Review. 1987 Aug; 9(2): 36-42. doi: 10.1542/pir.9-2-36.
[9] Hiremath G and Kamat D. Diagnostic considerations in infants and children with cyanosis. Pediatric Annals. 2015 Feb; 44(2): 76-80. doi: 10.3928/00904481-20150203-12.
[10] Mutlu B, Keskin EY, Oliveira AC, Relvas L, Bento C. A Rare Cause of Cyanosis since Birth: Hb M-Iwate. Turkish Journal of Hematology. 2019 Dec; 36(4): 299. doi: 10.4274/tjh.galenos.2019.2019.0123.
[11] Wilson R, Ross O, Griksaitis MJ. Tetralogy of fallot. BJA Education. 2019 Nov; 19(11): 362. doi: 10.1016/j.bjae.2019.07.003.
[12] Benson JM and Therrell Jr BL. History and current status of newborn screening for hemoglobinopathies. Seminars in Perinatology. 2010 Apr; 34(2): 134-44. doi: 10.1053/j.semperi.2009.12.006.
[13] Horn EP, Bein B, Steinfath M, Ramaker K, Buchloh B, Höcker J. The incidence and prevention of hypothermia in newborn bonding after cesarean delivery: a randomized controlled trial. Anesthesia & Analgesia. 2014 May; 118(5): 997-1002. doi: 10.1213/ANE.0000000000000160.
[14] Jyotsna M, Srinivas B, Lalita N. Cyanosis–Part 1. Indian Journal of Cardiovascular Disease in Women-WINCARS. 2016 Dec; 1(04): 069-74. doi: 10.1055/s-0038-1656488.
[15] Sattar SBA, Sharma S, Headley A. Bacterial Pneumonia(Nursing). StatPearls Publishing; 2021.
[16] Stark AR and Eichenwald EC. Persistent pulmonary hypertension of the newborn. UpToDate. 2018; 10.
[17] Teng RJ and Wu TJ. Persistent pulmonary hypertension of the newborn. Journal of the Formosan Medical Association. 2013 Apr; 112(4): 177-84. doi: 10.1016/j.jfma.2012.11.007.
[18] Taleb M, Ashraf Z, Valavoor S, Tinkel J. Evaluation and management of acquired methemoglobinemia associated with topical benzocaine use. American Journal of Cardiovascular Drugs. 2013 Oct; 13: 325-30. doi: 10.1007/s40256-013-0027-2.
[19] McMullen SM and Patrick W. Cyanosis. The American

DOI: https://doi.org/10.54393/pjhs.v4i11.1106

Journal of Medicine. 2013 Mar; 126(3): 210-2. doi: 10.1016/j.amjmed.2012.11.004.
[20] Das S and Maiti A. Acrocyanosis: an overview. Indian Journal of Dermatology. 2013 Nov; 58(6): 417. doi: 10.4103/0019-5154.119946.
[21] Steinhorn RH. Evaluation and management of the cyanotic neonate. Clinical Pediatric Emergency Medicine. 2008 Sep; 9(3): 169-75. doi: 10.1016/j.cpem.2008.06.006.
[22] Geggel RL. Diagnosis and initial management of cyanotic heart disease in the newborn. UpToDate. 2021.
[23] Murty VY and Ram KD. Phrenic nerve palsy: a rare cause of respiratory distress in newborn. Journal of Pediatric Neurosciences. 2012 Sep; 7(3): 225. doi: 10.4103/1817-1745.106487.
[24] Geggel R and Armsby C. Cardiac causes of cyanosis in the newborn. UpToDate. 2021 Apr; 11.
[25] Movahedian AH, Mosayebi Z, Sagheb S. Evaluation of pulse oximetry in the early detection of cyanotic congenital heart disease in newborns. The Journal of Tehran University Heart Center. 2016 Apr; 11(2): 73.
[26] Kitterman JA. Cyanosis in the newborn infant. Pediatrics in Review. 1982 Jul; 4(1): 13-23. doi: 10.1542/pir.4-1-13.
[27] Gupta SK. Clinical approach to a neonate with cyanosis. The Indian Journal of Pediatrics. 2015 Nov; 82: 1050-60. doi: 10.1007/s12098-015-1871-7.
[28] Cloherty JP, Eichenwald EC, Stark AR. Manual of neonatal care. Lippincott Williams & Wilkins; 2008.
[29] Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. The Lancet. 2008 Jun; 371(9629): 2039-41. doi: 10.1016/S0140-6736(08)60872-7.
[30] Choi BS, Kwon BS, Kim GB, Bae EJ, Noh CI, Choi JY, *et al*. Long-term outcomes after an arterial switch operation for simple complete transposition of the great arteries. Korean Circulation Journal. 2010 Jan; 40(1): 23-30. doi: 10.4070/kcj.2010.40.1.23.
[31] Rao PS. Diagnosis and management of cyanotic congenital heart disease: part I. The Indian Journal of Pediatrics. 2009 Jan; 76: 57-70. doi: 10.1007/s12098-009-0030-4.
[32] Krishnan US. Approach to congenital heart disease in the neonate. The Indian Journal of Pediatrics. 2002 Jun; 69: 501-5. doi: 10.1007/BF02722652.
[33] Lin AE, Di Sessa TG, Williams RG, Leighton J, Gross K, Wong AL. Balloon and blade atrial septostomy facilitated by two-dimensional echocardiography. The American Journal of Cardiology. 1986 Feb; 57(4): 273-7. doi: 10.1016/0002-9149(86)90904-5.
[34] Barron DJ, Kilby MD, Davies B, Wright JG, Jones TJ, Brawn WJ. Hypoplastic left heart syndrome. The Lancet. 2009 Aug; 374(9689): 551-64. doi: 10.1016/S0140-6736(09)60563-8.
[35] Tweddell JS, Hoffman GM, Fedderly RT, Berger S, Thomas Jr JP, Ghanayem NS, *et al*. Phenoxybenzamine improves systemic oxygen delivery after the Norwood procedure. The Annals of Thoracic Surgery. 1999 Jan; 67(1): 161-7. doi: 10.1016/S0003-4975(98)01266-1.