Tetralogy of Fallot: A Comprehensive Review of Pathophysiology, Diagnosis, and Management

Hashim Mahmood¹, Hamza Javed², Syed Abdullah Haider³, Abeeha Mahmood⁴, Muhammad Wali⁵

¹MBBS, University College of Medicine and Dentistry, Pakistan, Medical Student
²MBBS, University College of Medicine and Dentistry, Pakistan, Medical Student.
³MBBS, University College of Medicine and Dentistry, Pakistan, Medical Student
⁴MBBS, CMH, Medical College, Pakistan, Medical Student
⁵Assistant Professor Cardiology, University of Lahore Teaching Hospital, Pakistan


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*Corresponding author: Syed Abdullah Haider, MBBS, University College of Medicine and Dentistry, Pakistan, Medical Student

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ABSTRACT

Tetralogy of Fallot (TOF) is a congenital heart defect characterized by four anatomical abnormalities: pulmonary stenosis, ventricular septal defect, overriding aorta, and right ventricular hypertrophy. This comprehensive review examines the pathophysiology, diagnosis, and management of TOF. Pathologically, TOF results from an anterocephalad deviation of the infundibular septum during fetal development, leading to the four defining features. Clinical presentation varies, including cyanosis, dyspnea, heart failure, and arrhythmias. Diagnosis relies on clinical evaluation, imaging (especially echocardiography), and cardiac catheterization. Early diagnosis is crucial for timely intervention. Surgical correction is the primary treatment, aiming to relieve right ventricular outflow tract obstruction and repair the ventricular septal defect. Surgical approaches include complete repair and palliative shunting, selected based on age, symptoms, and anatomy of patient. Postoperative care and long-term follow-up in these patients is crucial, monitoring for complications like pulmonary regurgitation, arrhythmias, and residual defects. A multi-disciplinary approach is required for the management of TOF patients. Early diagnosis, timely surgery, and comprehensive postoperative care are vital for improving outcomes and quality of life. Advances in surgical techniques and perioperative care have significantly improved TOF prognosis. However, lifelong follow-up are essential due to the risk of late complications. Further research into the long-term outcomes of different surgical strategies and the impact of newer interventions is needed to enhance TOF management further.
INTRODUCTION

Tetralogy of Fallot is the most common cyanotic congenital cardiac condition that occurs in approximately 3 out of 10,000 live births.\(^1\) It consists of: ventricular septal defect, obstruction of the right ventricular outflow tract, right ventricular hypertrophy and overriding of the ventricular septum by the aortic root. Most of the patients are neonates with varying degrees of cyanosis proportionate to the level of blood flow obstruction to the lungs. The diagnosis is made using diagnostic tests such as electrocardiogram, echocardiogram and chest radiographs. \(^1\) Genetic factors have a great contribution to TOF. Transcription factors and signaling molecules responsible for cardiogenesis \(^2\) which include gata4, nkx2.5, jag1, foxc2, tbx5, and tbx1\(^3\) have been implicated. Chromosomal anomalies such as trisomies 21 (Down syndrome), 18 (Edwards syndrome), and 13 (Patau syndrome) have been reported to be associated with TOF. Recent experiences show a more frequent association between microdeletions on chromosome 22 and TOF. Initial treatment may be palliative but ultimately surgical interventions are required. Palliative procedures include surgical creation of a systemic-to-pulmonary arterial shunt. Timing and type of surgical intervention depend on factors such as patient age, heart anatomy, and its associated anomalies. TOF requires lifelong monitoring and management. Treatment strategies have improved greatly over time however, residual problems such as right ventricular dysfunction, arrhythmia, and pulmonary regurgitation are common.

Clinical Picture and Symptoms

Clinical features of a patient vary depending on the severity of the disease. Most common clinical presentations may consist of Cyanosis (bluish lips, nails, and skin) due to mixing of oxygen poor and oxygen rich blood. Other features include clubbing, tachypnea, murmurs (due to abnormal heart structure), episodes of cyanotic spell (in response to feeding, crying or exertion which lead to increased right to left shunting of blood) \(^4\), Poor growth with fatigue and exercise intolerance (due to poor oxygen supply to body). The patient may obtain a unique squatting position which increases systemic vascular resistance and reduces right-to-left shunting, temporarily improving oxygen levels.\(^5\)

Pathology

The development of heart starts with fusion of outer endocardial tubes that form a cardiac tube later. The Cardiac tub folds upon itself and forms cranial dorsal aorta and downwards ventricle. Ventricular septal defects ate peri membranous and an association has been found in the form of anterior and cephalic deviation of infundibular septum that causes TOF \(^6\).

The causes of most congenital heart diseases are unknown but in case of TOF, Methylene Tetrahydrofolate reductase inhibitor (MTFHR) may be a susceptible gene. VEGF genetic polymorphisms may also play a role. Alcohol usage, diseases such as Rubella in mother may be the cause as well. VSD if non restrictive may not be harmful as the pressures in the ventricles would be same. In case restrictive outflow of right ventricle hypertrophy of
RV occurs and causes right to left shunt. In complete RORV pulmonary blood flow is dependent on PDA. Additionally atrial septal defect, atrioventricular septal defect, anomalous origin of the left inter ventricular coronary artery from right coronary artery and right sided aortic arch are most common associated abnormalities. Right sided aortic arch is mostly associated with micro deletion of chromosomes 22q11\(^7\). Associated chromosomal anomalies may include trisomies of 21, 18 and 13 \(^8\).

Tetralogy of Fallot accounts for 7-10 percent of all the congenital defects in children affecting both sexes and occurs in 3 to 5 of every 10 000 live births.

Conditions associated with tetralogy of Fallot include left superior vena cava, anomalies of tricuspid valve, anomalies of mitral valve, stenosis of left pulmonary artery, bicuspid pulmonary valve, coronary artery anomalies, anomalous pulmonary venous return, forked ribs, scoliosis, cleft lip, cleft palate, hypospadias, skeletal and cranial facial abnormalities \(^9\).
Figure 1. In this figure laid out by the University of Calgary we see the genetic impact on a patient regarding Tetrology of Fallot followed by the clinical presentation. The signs and symptoms are also laid out.\[10\]

In pulmonary stenosis a narrowing is seen at or just below the pulmonary valve. Stenosis is mostly seen at the level of septoparietal trabeculae due to its hypertrophy. Stenosis is the major cause of malformations and while the other abnormalities acting as compensatory processes, TOF with pulmonary atresia or pseudotruncus arteriosus is so severe that there is complete that is complete right ventricular obstruction and agenesis of pulmonary trunk \[11\]

In overriding aorta the aortic valve is not only present in left ventricle but is biventricular. The aortic valve is present above the septal defect and on the right of the pulmonary artery; most are joining the right ventricle.

Ventricular septal defect is the presence of a hole or discontinuity present in the wall connecting the two ventricles. It is located around the outlet septum and on its upper side. The defect is usually single and large.

Figure 2: [We see here a transverse plane of a fetal chest in gray scale at the level at which all 4 chambers of the heart are visible in view A and a five chamber view in view B. In setting A we can appreciate the normal cardiac anatomy. In view B we see a large ventricular septal defect (VSD) leading to a left to right ventricle blood shunt. RA (right atrium), LA (left atrium), LV (left ventricle), RV (right ventricle) \[12\]]
In Right ventricular hypertrophy the wall of the right ventricle is hypertrophied and more muscular than normal. A boot shaped heart is present on x-ray of right ventricular hypertrophied heart. Due to the disarrangement of the septum the right ventricle hypertrophies to compensate the obstruction of outflow\(^{[13]}\).

**Diagnostic Imaging**

Transthoracic echocardiography (TTE) always plays a vital role in managing patients with tetralogy of Fallot (TOF) across their lifespan, ranging from prenatal detection to evaluating late complications of the congenital condition in adulthood. With the imaging having widespread availability, cost-effectiveness, and lack of contraindications, it make it indispensable for both pre- and post-operative assessment\(^{[14]}\).

TTE protocol for TOF should always include the use of standard echocardiograph imaging from the subcostal, parasternal, apical, and suprasternal windows, along with complete sweeps and selected single planes, to ensure a comprehensive evaluation.

Transthoracic echocardiography (TTE) offers a detailed visualization of the anomalies and measurement of cardiac structures, providing vital insights into the severity of the pulmonary stenosis, size, and morphology of the ventricular septal defect (VSD), over-riding aorta, and right ventricular outflow tract (RVOT) obstruction. In tetralogy of Fallot (TOF), the typical VSD is an anterior misalignment type of outlet VSD, where the conal septum diverges anteriorly from the muscular septum of the ventricular septum, contributing to a <50% overriding of the aorta over the muscular ventricular septum, muscular obstruction of the RVOT, and right ventricular hypertrophy (RVH)\(^{[15]}\). Spectral Doppler as well as color flow mapping analysis can provide additional valuable information in helping clinicians’ better treat, and properly diagnose the severity of the patients TOF. In cases of mild RVOTO, the interventricular shunt is left-to-right. As the obstruction of the outflow tract worsens, the shunt can become bidirectional and eventually left to right (Eisenmenger syndrome)\(^{[16]}\), potentially leading to hypercyanotic spells. The high parasternal and suprasternal views allow assessment of additional blood flow sources, such as patent ductus arteriosus and aortopulmonary collaterals. The pulmonary valve is often dysplastic and thickened, with a hypoplastic annulus. Severe annulus hypoplasia may require a transannular patch extension during surgical correction. TTE also helps identify associated lesions, such as anomalous coronary arteries and additional VSD(s). As a result, this significantly influences surgical planning and outcomes\(^{[17]}\), impacting post-operative intensive care and necessitating additional surgery if overlooked.

Real-time transesophageal echocardiography (TEE) is critical during surgical correction of TOF, providing intraoperative guidance for assessing the surgical repair, including ventricular septal defect closure, ensuring adequate relief of RVOTO, and evaluating residual intracardiac shunts.
Successive echocardiographic evaluations will aid in monitoring the effectiveness of surgical interventions and evaluating any other possible remaining issues, such as lingering shunts, right ventricular outflow tract obstruction (RVOTO), or pulmonary regurgitation (Figure 3).

Figure 3: (Evaluating a patient with tetralogy of Fallot (TOF) who has undergone transcatheter pulmonary valve replacement (Melody) involves several echocardiographic assessments. These include a right-ventricular focused four-chamber view in the left upper corner, color Doppler imaging of the right ventricular outflow tract with the Melody valve implantation in the right upper corner, global longitudinal strain of the right ventricle in the left lower corner, and TAPSE evaluation with gradient assessment through the Melody valve in the right lower corner) \(^{[18]}\)

Variations in treatment strategies

Tetralogy of Fallot and its final treatment indication is always surgical. Patients as they grow older require greater contractility and hence greater cardiac output in order to meet the body’s metabolic requirements. Generally
it is thought that a primary repair of Tetralogy of Fallot which occurs earlier in a neonate’s life can limit the high right ventricular pressure that it would have been exposed to without the repair. This non repair would lead to the classic ventricular hypertrophy, and a decrease in oxygen saturation leading to possible hypoxia and anoxic brain injury. Our main purpose in different treatment regiments is to not only allow the heart of the neonate to develop and grow but to preserve both cardiac [19] and brain [20] function by preventing the blood between the left and right chambers from mixing. Neonatal repair has acceptable results but is not used as widely as non-neonatal repair [21] due to further repairs needed beyond the neonatal period. However for most patients, the period of the primary repair can be extended to 6 months [22] to allow the heart to grow and allows for very good outcomes for the patient in the postoperative period [23].

Symptomatic Tetralogy of Fallot unfortunately does require a primary neonatal repair and this is where various treatment modalities come into play for the neonate. The modified blalock- taussig shunt also known as the mBT shunt has been used to increase pulmonary flow via systemic to pulmonary shunting. The mBT shunt not only increases pulmonary flow, but reduces the risk of hypoxemia and allows for the pulmonary artery to grow, allowing the heart to increase in size and develop further while also not risking the patient’s life with cyanotic symptoms. Current mortality rates of the mBT systemic to pulmonary shunt sits between 3-5% [24], however the mBT shunt being better than the primary neonatal repair has not been established [25].

Another treatment modality we have seen that increases systemic to pulmonary blood flow is Ductus Arteriosus (DA) stenting. Recent literature helps us compare the outcomes between mBT shunting and DA stenting which showed that long term survival outcomes have shown a reduced mortality rate before the DA stent but a higher risk of re-intervention requirement [26]. Some papers showed that there was no difference in risk between mBT shunting and DA stenting when primary outcome of death and “unplanned reintervention to treat cyanosis” were compared [27]. Although current literature may not show a significant mortality risk between the 2 procedures, DA stenting has been proven to be both complicated and unsuitable for cyanotic congestive heart disease (CHD) with severe complications including acute thrombosis, with a rate of 2-3% [28]. Other complications have included ductus arteriosus spasm (very rare with a <1% chance of occurrence) along with stent migration which, although may not be life threatening, an occurrence of a stent migration requires a semi-elective surgical procedure [29].

Another, more controversial [30] systemic to pulmonary shunting procedure that may be used is palliative balloon dilation of the pulmonary annulus which both helps grow pulmonary vasculature and may act as a conduit for future surgical TOF repair procedures [29,30].
Overall survival rate

![Graph showing cumulative survival rates](image)

**Figure 4:** (the Graph explains survival rates since time repair with a 95% Confidence Interval) \(^{(31)}\)

Early mortality rates in both European and American congenital cardiac surgical journals have reported a substantial decrease in peri-operative mortality rates, being under 3% \(^{(32,33)}\). Operative outcomes are determined by the size of the pulmonary valve, pulmonary artery, pressure gradient between Right ventricular and pulmonary artery pressure \(^{(34)}\) and patient oxygen saturation \(^{(35)}\). Mortality rates during the procedure depends on several factors, including the patients oxygen saturation levels, the pressure variation between the right ventricle and pulmonary artery, and the size of the pulmonary artery before surgery \(^{(36,37)}\). TOF surgical repair which includes a transannular patch has shown to have higher rate of peri-operative deaths \(^{(38)}\). Coronary stenosis, premature birth, children with growth retardation as well as congenital anomalies all play a role in increasing the rates of death during TOF repair \(^{(39,40,41)}\).

With current advances in surgical techniques the rate of peri operative mortality have been dwindling and the number of adults that require care into old age with a history of TOF repair has been steadily on the rise \(^{(42)}\).

Cuypers et al. has made a significant finding by revealing that 44% of patients required at least one re-intervention; either through surgical or catheter-based procedures, throughout a 35-year monitoring period \(^{(43)}\). In comparison, D’Udekem et al. conducted a study \(^{(44)}\) and established in the study that approximately 24 ± 5% of the patients in the
study underwent re-operative procedures for TOF after a 30-year follow-up duration. It's highly noteworthy to extrapolate that there has been a substantial decrease in the incidence of re-interventions among individuals who underwent transatrial transpulmonary repair as a result of advanced technology in the surgical field which has allowed for a decrease in mortality rates and higher numbers of children living into adulthood. Luijten et al., in a 10-year investigation, observed an 80% absence of both re-intervention and mortality [45].

In a more compact case-control study, a clear trend emerged, demonstrating a reduced frequency of surgeries for pulmonary valve replacement (PVR) subsequent to transatrial repair, in contrast to the transventricular approach. The utilization of a transannular patch (TAP) corresponds to an elevated likelihood of needing re-intervention, as does the severity of Tetralogy of Fallot (ToF) [45] at the time of the initial repair. The specific factors contributing to the necessity for re-interventions will be detailed in upcoming sections of this article.

Patients will be closely observed in the ICU ward after the surgery before being discharged. The length of stay in the hospital will depend on the patient's response to surgery and their overall condition. This stay will consist of vital signs monitoring, post surgical pain management, fluid/nutrition management, wound care, respiratory care (to help prevent lung complications like atelectasis and pneumonia) and Cardiac monitoring (to track heart rhythm and function). Ideally, the patient will be vaccinated for flu and pneumonia to reduce infections [46]. Patient and family education are crucial to ensure safety of the patient. Patient’s activity will be strictly restricted for a stated length of time and the patient will be closely monitored for warning signs such as fever, increased pain, and changes in skin color, difficulty breathing, or abnormal heart rhythms. Regular follow-up appointments with the cardiac surgeon/cardiologist are essential to monitor the patient's progress and make any necessary adjustments to the treatment plan.

Immediately Post operation, the patient should be moved to the cardiac care unit (CCU) so that close monitoring of immediate post operative complications may continue. The most important part of immediate post operative care is to see that the patient is hemodynamically stable, is on respiratory support, is having their pain being managed, fluid and diuresis is occurring, the patient is no longer bleeding and the patient is not showing any signs of post operative infections leading to fever, infected wound/ sutures etc... [47]. During this time period the most common complications include Junctional Ectopic Tachycardia (Figure. 5) [48], Post operative bleeding, and Low Cardiac Output Syndrome. Low cardiac output syndrome remains vital to avoid as it is life threatening. Causes include tamponade, systolic or diastolic cardiac dysfunction, arrhythmias, and possible residual lesions such as pulmonary artery branch stenosis, residual right ventricular hypertrophy or a new ventricular septal defect. Later complications include Post operative ileus, poor oral intake, and pain or irritability [47]. The patient's taken out of the CCU if they are stable off of milrinone for 4-6 hours, stable with supplemental oxygen, stable off of dexamethasone and is off of pentobarbital for at least 4 hours prior to CCU discharge.
CONCLUSION

In conclusion, this literature review has provided a comprehensive and insightful overview of Tetralogy of Fallot (TOF), a complex congenital heart defect that presents significant challenges in diagnosis, management, and long-term care. Through the synthesis of numerous studies, clinical reports, and advancements in the field, we have gained a deeper understanding of the multifaceted nature of TOF.

We have also explored the embryological basis of TOF, highlighting the intricate developmental processes that can lead to the characteristic anatomical abnormalities seen in this condition. Additionally, we have examined the diverse clinical presentations of TOF, ranging from mild to severe forms, and the importance of early and accurate diagnosis through various imaging modalities, including echocardiography, cardiac MRI, and CT angiography.

Surgical management plays a crucial role in the treatment of TOF, with corrective surgery being the standard of care. Advances in surgical techniques, such as total repair in infancy, have significantly improved outcomes and survival rates. However, challenges remain, including the management of residual lesions, such as pulmonary valve regurgitation and right ventricular outflow tract obstruction, which can lead to an impact on long-term prognosis.

Furthermore, this review has highlighted the importance of long-term follow-up and monitoring for individuals with TOF. Regular echocardiographic evaluations are essential for assessing cardiac function, detecting complications, and guiding further management strategies. Additionally, ongoing research efforts are essential to improve our
understanding of TOF, develop novel treatment approaches, and enhance long-term outcomes and quality of life for individuals living with this condition.

While significant progress has been made in the diagnosis, management, and outcomes of TOF, continued research, collaboration, and innovation are paramount to further advance our understanding and care of individuals affected by this complex congenital heart defect.

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