# The American Association for Thoracic Surgery (AATS) 2022 Expert Consensus Document: Management of infants and neonates with tetralogy of Fallot



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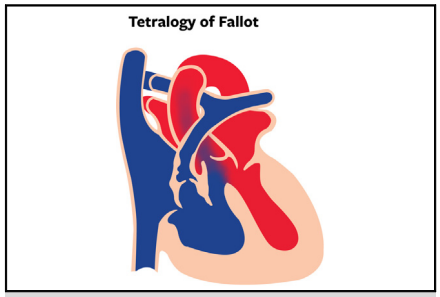
## ABSTRACT

**Objective:** Despite decades of experience, aspects of the management of tetralogy of Fallot with pulmonary stenosis (TOF) remain controversial. Practitioners must consider newer, evolving treatment strategies with limited data to guide decision making. Therefore, the TOF Clinical Practice Standards Committee was commissioned by the American Association for Thoracic Surgery to provide a framework on this topic, focused on timing and types of interventions, management of high-risk patients, technical considerations during interventions, and best practices for assessment of outcomes of the interventions. In addition, the group was tasked with identifying pertinent research questions for future investigations. It is recognized that variability in institutional experience could influence the application of this framework to clinical practice.

**Methods:** The TOF Clinical Practice Standards Committee is a multinational, multidisciplinary group of cardiologists and surgeons with expertise in TOF. With the assistance of a medical librarian, a citation search in PubMed, Embase, Scopus, and Web of Science was performed using key words related to TOF and its management; the search was restricted to the English language and the year 2000 or later. Articles pertaining to pulmonary atresia, absent pulmonary valve, atrioventricular septal defects, and adult patients with TOF were excluded, as well as nonprimary sources such as review articles. This yielded nearly 20,000 results, of which 163 were included. Greater consideration was given to more recent studies, larger studies, and those using comparison groups with randomization or propensity score matching. Expert consensus statements with class of recommendation and level of evidence were developed using a modified Delphi method, requiring 80% of the member votes with 75% agreement on each statement.

**Results:** In asymptomatic infants, complete surgical correction between age 3 and 6 months is reasonable to reduce the length of stay, rate of adverse events,




**TOF: Shown is a right-to-left shunt seen with symptomatic TOF.**

### CENTRAL MESSAGE

Although outcomes for the management of TOF are excellent, elements of the treatment strategy remain controversial.

### PERSPECTIVE

Tetralogy of Fallot with pulmonary stenosis presents on a spectrum. Additionally, institutions have preferences in treatment strategies. Therefore, the available data may be insufficient to guide the practitioner in many situations. Large, long-term, multi-institutional studies or registries are necessary for further progress.

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A full list of author relationships is provided in Appendix 1 and 2.

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and need for a transannular patch. In the majority of symptomatic neonates, both palliation and primary complete surgical correction are useful treatment options. It is reasonable to consider those with low birth weight or prematurity, small or discontinuous pulmonary arteries, chromosomal anomalies, other congenital anomalies, or other comorbidities such as intracranial hemorrhage, sepsis, or other end-organ compromise as high-risk patients. In these high-risk patients, palliation may be preferred; and, in patients with amenable anatomy, catheter-based procedures may prove favorable over surgical palliation.

**Conclusions:** Ongoing research will provide further insight into the role of catheter-based interventions. For complete surgical correction, both transatrial and transventricular approaches are effective; however, the smallest possible ventriculotomy should be utilized. When possible, the pulmonary valve should be spared; and if unsalvageable, reconstruction can be considered. At the conclusion of the operation, adequate relief of the right ventricular outflow obstruction should be confirmed, and identification of a significant fixed anatomical obstruction should prompt further intervention. Given our current knowledge and the gaps identified, we propose several key questions to be answered by future research and potentially by a TOF registry: When to palliate or proceed with complete surgical correction, as well as the ideal type of palliation; the optimal surgical approach for complete repair for the best long-term preservation of right ventricular function; and the utility, efficacy, and durability of various pulmonary valve preservation and reconstruction techniques. (J Thorac Cardiovasc Surg 2023;165:221-50)

To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.

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## INTRODUCTION

### Preamble

The combination of cardiac defects defined as tetralogy of Fallot (TOF) was originally described in 1671 by Neils Stenson.[1,2] It was more completely described, and with a better understanding of the underlying physiology, by Etienne-Louis Fallot in 1888; at the time, it was called the "maladie des enfants bleus."[2-4] It was subsequently termed TOF in 1924 by Abbot.[5] It is the most common cyanotic congenital heart defect, occurring in 3 to 5 per 10,000 live births.[3,6-8] It was the earliest palliated congenital defect in 1944 by Blalock, Taussig, and Thomas with the Blalock-Taussig-Thomas (BTT) shunt.[9] Subsequently, it was among the earliest congenital defects to undergo complete repair by Lillehei in 1954 using cross-circulation.[10] Finally, significant further surgical advances were made by Castañeda, particularly with primary neonatal repair.[11]

Despite the commonality of this lesion and the decades of experience with surgical palliation and repair, controversy persists regarding many aspects of its treatment. Even with differing approaches, it should be noted that TOF represents a great example of the advancements of medical and surgical therapies with excellent short- and long-term survival.[12] Due to this success, TOF now represents an ever-growing diagnosis among the adult congenital heart disease population. As these patients age into adulthood, reassessment of TOF treatment, sometimes performed decades previously, is being considered.

TOF exists on a spectrum encompassing mild pulmonary stenosis (PS) to pulmonary atresia (PA); however, for the purposes of this document, TOF will refer to TOF with PS unless stated otherwise. It is recognized that TOF, even when limited to those with PS, represents a wide spectrum of disease severity. Furthermore, various institutions may have particular expertise in various treatment options. Thus, interpretation of the existing literature can be complicated.

To help provide guidance to the practitioner regarding the management of infants and neonates with TOF, an expert panel was assembled to review the currently available literature. This led to the creation of this expert consensus

**Abbreviations and Acronyms**

AATS = American Association for Thoracic Surgery
BTT = Blalock-Taussig-Thomas shunt
CCRC = congenital cardiac research collaborative
COR = classification of recommendation
CTA = computed tomography angiography
ICU = intensive care unit
LAD = left anterior descending
LOE = level of evidence
LOS = length of stay
PA = pulmonary atresia
PDA = patent ductus arteriosus
PGE1 = prostaglandin E1
PHIS = Pediatric Health Information System
PS = pulmonary stenosis
RCA = right coronary artery
RV = right ventricle
RVOT = right ventricular outflow tract
t-RA = trans-right atrial
t-RV = trans-right ventricle
TAP = transannular patch
TOF = tetralogy of Fallot
VSD = ventricular septal defect

document, the aim of which was to provide practitioners, especially fellow-level trainees or early career physicians, with a framework on which to base the initial categorization of TOF patients and treatment options. We aimed to provide recommendations focused on the timing and types of interventions to be performed, the management of high-risk patients, technical considerations during palliative or complete surgical correction, and the assessment of outcomes of these interventions. Additionally, and potentially most important, areas where data are lacking were identified and noted for future research.

## METHODS

The American Association for Thoracic Surgery (AATS) Congenital Clinical Practice Standards Committee identified TOF as a topic that could benefit practitioners by providing an expert consensus document with a collection of the currently available data, expert interpretation of the data and supplementation with expert opinion where data are lacking, and identification of areas that would most benefit from future research. This document was designed with a focus on the decisions that influence the complete surgical correction of TOF. Although there are many additional preoperative and postoperative considerations such as perioperative intensive care unit (ICU) management, these important elements are not addressed in this document. Because the primary focus was directed toward surgical aspects of TOF management, AATS selected surgeon chairs (S.E. and P.E.), who in turn solicited and convened an international panel of experts consisting of practicing pediatric cardiac surgeons, pediatric cardiologists, and pediatric interventional cardiologists. In total, the group consisted of 13 pediatric cardiothoracic surgeons, two pediatric cardiologists (both interventional cardiologists), and 1 AATS member with expertise in the Delphi process. An outline was created and the participants divided into subgroups to focus on specific topics. Once the final form was reached, it was reviewed by 14 additional experts in TOF consisting of pediatric cardiac surgeons and pediatric cardiologists, including international experts. In total, 30 individuals reviewed the content of the document.

Attempts were made to identify all currently available relevant data about TOF and its treatment. With the assistance of a medical librarian, a robust search was performed using PubMed, Embase, Scopus, and Web of Science (full details about the search criteria and key words are provided in Appendix 3). Initially, the search was limited to the English language and the year 2000 or later. Additionally, from each article, the bibliography was inspected to identify additional articles worth consideration. We also considered and included other works suggested by any of the panel of reviewers and new citations during the process until April 30, 2022. Articles pertaining to PA, absent pulmonary valve, major aortopulmonary collaterals, atrioventricular septal defect (VSD), and adult patients with TOF were excluded. Articles that were compilations or nonprimary sources, such as review articles or meta-analyses were excluded with regard to statement creation, although some were utilized when composing the overall document. Particularly, meta-analyses were considered in evaluating the level of evidence (LOE). All articles were compiled into Covidence (Covidence.org) for review by the group. Greater consideration was given to more recent studies, those with larger patient populations, and those using comparison groups especially with randomization or propensity score matching. Each abstract was read by 2 members. If found to be relevant, they were collected into the applicable section. Each author within that writing section read every article.

After these articles were reviewed, clinical questions were designed using the patient intervention comparison outcome format.[13] Expert consensus statements with classification of recommendation (COR) and LOE were developed using a modified Delphi method. Throughout this process, each statement was critically examined and revised by the entire group and subsequently voted upon for validation. To consider the statement having reached consensus, 80% of members must have voted with 75% in agreement (voted as "agree" or "strongly agree").[13] Voting was blinded but allowed for comments to clarify disagreements and assist with statement modifications. Any statement in which consensus was not reached after 3 voting sessions was removed.

COR is provided primarily based on the size of the treatment effect, or estimated size of the treatment effect, or the magnitude of benefit compared with the risk of harm.[13] LOE provides an estimation on the certainty of the treatment effect based on the currently available date. Although the magnitude of the treatment effect was not considered for the LOE, consideration was given such that a higher LOE allowed for a higher COR, even with only marginal benefits. As with the formation of the statements, consensus was required before finalizing the COR or LOE for each statement with the same voting requirements. The language for each statement was chosen to be consistent with that recommended by the American College of Cardiology and American Heart Association, and at times the correlating language helped to determine the appropriate COR (Figure 1).[14] When a recommendation lacked sufficient evidence to allow for a formal statement, it was included as a Best Practices Statement.

Once the recommendations, and their COR and LOE were determined, the narrative was constructed to help fully inform the reader as to the intent and meaning of each statement, as well as the main points and any counterpoints. Furthermore, the narration supplies readers with the data used to make each recommendation. Areas lacking data and other areas for future research were noted.

### Limitations and Bias

The evaluation of different treatment strategies for TOF has been hampered by a heterogeneous patient population, significant variations in management techniques, from threshold for and timing of intervention, to types of specific

**CLASS (STRENGTH) OF RECOMMENDATION**

**CLASS I (STRONG)** — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

**CLASS IIa (MODERATE)** — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

**CLASS IIb (WEAK)** — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

**CLASS III: No Benefit (MODERATE)** — **Benefit = Risk**
***(Generally, LOE A or B use only)***

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

**CLASS III: Harm (STRONG)** — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

**LEVEL (QUALITY) OF EVIDENCE‡**

**LEVEL A**
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

**LEVEL B-R** — **(Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

**LEVEL B-NR** — **(Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

**LEVEL C-LD** — **(Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

**LEVEL C-EO** — **(Expert opinion)**

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized. widely used, and preferably validated evidence grading tools; and for systematic review; the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

**FIGURE 1.** American College of Cardiology/American Heart Association classification of recommendation and level of evidence. From: Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:1373-84. *RCT*, Randomized controlled trial; *R*, randomized; *NR*, nonrandomized; *LD*, limited data; *EO*, expert opinion; *COR*, class of recommendation; *LOE*, level of evidence. Reprinted with permission from Elsevier. Copyright 2014.

techniques of interventions, to center-level treatment strategy preferences, as well as change in practices over time and lack of long-term follow-up data. TOF, as with most congenital heart defects, exists on a spectrum. Every lesion is different, particularly with regard to the right ventricular outflow tract (RVOT) obstruction, both the level (subvalvular, valvular, or supravalvular) and the severity. Further, various institutions have preferred and championed particular approaches to the controversial aspects of management of TOF. For these reasons, the majority of available data consist of single-institution retrospective reviews of a single approach. This provides some data on general approaches but lacks the comparison groups necessary to effectively guide management strategies. Further, although it is among the most common congenital heart defects, the number of patients presenting to most single institutions is insufficient to allow for enough patients to form meaningful comparison groups or subgroup analyses.

Alternatively, reviews of larger databases have recently been published. These lack the granularity necessary to fully guide treatment for such a heterogeneous patient population. Additionally, with the field of pediatric cardiothoracic surgery and interventional cardiology rapidly progressing, the currently available literature may have comparison groups that are suboptimal; by the time a study is published, new techniques have been developed. Given that the full influence of some of these variations in treatment may not be apparent for decades, this complicates the decision on whether to adopt these modifications.

This document has a primary focus on the surgical aspects of TOF management; therefore, future endeavors expanding on this work would require additional experts in fetal and neonate cardiology, echocardiography, radiology, and critical care, among others. Technical aspects, including the decision on when/which type of catheter-based palliative procedure to pursue also are outside the scope of this document. We incorporated or addressed all reviewer suggestions; however, we were limited by constraints posed by our methodology and the desire to avoid recommendations based on personal preferences in the absence of published supporting data.

## Terminology

Because TOF itself represents a heterogeneous patient population, readers should note that for the purposes of this article, TOF refers to TOS with PS specifically, and not PA with or without major aortopulmonary collaterals, associated atrio-VSD or TOF with absent pulmonary valve, except when explicitly stated. When discussing TOF, terminology is commonly used to facilitate efficient communication in the clinical setting and to allow for more meaningful subgroup analyses when performing clinical research.

In this document, the following terms were used as defined. It should be noted, whereas the following were formulated and agreed upon by the group, they were not subjected to the Delphi voting process:

- **Symptomatic TOF:** In the absence of ductal patency, symptomatic TOF is characterized by sustained persistent desaturation or provoked episodic desaturations to <80% (hypercyanotic or "Tet spells"), in the absence of noncardiac (pulmonary or airway) causes. Although these patient cohorts, sustained but stable cyanosis versus those with episodic, sometimes-severe desaturations, represent different clinical scenarios and perhaps different urgencies in management, for the purposes of this document we considered both as symptomatic. Medical therapies such as beta-blockers or red blood cell transfusion to minimize any relative anemia may be instituted and provide some relief; these patients require a more urgent treatment plan under the symptomatic guidelines provided below.
- **Nondefinitive treatment strategies:** Includes medical management with prostaglandin as well as the palliative procedures described next. This may also refer to the use of beta-blockers to delay the need for surgical intervention.
- **Palliative procedures:** Surgical or catheter-based procedures, short of a complete surgical correction, performed with the intent to augment or stabilize pulmonary blood flow.
- **Complete surgical correction:** A surgical procedure consisting of closure of the VSD with adequate relief of RVOT obstruction with or without attempts at preserving valve competency. Relief of the RVOT obstruction may be adequate rather than complete because a decision to leave some RVOT gradient to preserve pulmonary valve function may be appropriate. The determination of what constitutes adequate relief and the amount of residual obstruction that is acceptable remains controversial and is discussed in further detail in this document. Complete surgical correction also may include the intentional maintenance of a patent foramen ovale or other atrial level communication, which may result in transient perioperative desaturation.
- **Pulmonary valve "annulus":** Although the authors concede that the pulmonary valve does not have an annulus, for the purposes of simplicity, in this document the leaflet hinge point will be referred to as an annulus.
- **Transannular incision:** Any incision across the pulmonary valve annulus.
- **Annulus-preserving repair:** A complete surgical correction consisting of RVOT repair techniques that do not disrupt the native pulmonary annulus; that is, when a transannular incision is not performed.
- **Valve reconstruction:** A complete surgical correction of TOF that includes, in addition to a transannular incision, all techniques (such as monocusp creation, leaflet augmentation, or right atrial appendage leaflet neovalve construction) intending to prevent or reduce pulmonary insufficiency.
- **Neonate:** Age younger than 1 month.

## EXPERT CONSENSUS STATEMENTS AND BEST PRACTICES

Based on the available data, the writing group developed recommendations for the preoperative evaluation, timing of elective repair, decision making regarding a staged approach versus primary complete surgical correction in both standard and high-risk patients, the decision making about type of surgical or catheter-based palliation, the technical aspects of the complete surgical correction, and finally, the postoperative evaluation of the repair and when to consider reintervention. Each statement that was presented to the group was able to reach consensus, often after significant modifications; no statements were removed.

**Preoperative echocardiography should be performed with special attention paid to the level(s) of obstruction (subvalvular, valvular, or supravalvular), pulmonary valve function and morphology, and size of the pulmonary valve annulus and main and branch pulmonary arteries as well as coronary artery anatomy. Best Practices Statement.**

Complete understanding of the anatomy and physiology of a given patient with TOF is required for a successful, durable repair. Particular attention should be paid on preoperative echocardiography to the level(s) of obstruction, specifically, the subvalvular, valvular, and supravalvular regions.[15] The surgeon should understand where turbulence and obstruction start in the RVOT and its location relative to landmarks used during the operation. They should also

**Recommendation regarding elective complete surgical correction**

| Elective | COR | LOE |
|---|---|---|
| For patients with tetralogy of Fallot undergoing elective complete surgical correction, repair between ages 3 and 6 months is reasonable | IIa | B-NR |

be aware that proximal obstruction will mask the severity of more distal obstruction.

The pulmonary valve should be thoroughly visualized. This can be challenging on transthoracic echocardiography, but the key features to be evaluated include cusp mobility (including doming and excursion), cusp dysplasia and thickening, and the pulmonary annular dimension expressed either as an absolute value or more commonly as a *z* score. Cusp number and orientation can be difficult to determine on preoperative imaging but may be informative for surgeons. These features aid in operative planning and the likelihood of a valve-sparing repair. The pulmonary arteries are typically underfilled, but attention should be paid to concerning features, such as left pulmonary artery narrowing, often secondary to the ductus insertion rather than at the pulmonary artery bifurcation.

Coronary artery anatomy is also important to visualize preoperatively and can usually be determined via echocardiography.[16] Features that are challenging to discern, such as abnormal pulmonary artery anatomy (eg, in a newborn infant with a large patent ductus arteriosus [PDA]), may benefit from cross-sectional imaging such as computed tomography angiography (CTA), but this is not standard for typical TOF. CTA may also be useful in the setting of prior palliation with either a surgical shunt or a ductal stent to discern the need for any pulmonary arterioplasty. The cardiology and surgical team should review the coronary artery anatomy before any intervention where an incision across the RVOT is anticipated. On occasion, when there is ambiguity with coronary artery anatomy, CTA or other imaging modalities could prove helpful. Additional standard evaluation on echocardiography includes the location of the VSD and any features unique relative to a typical VSD in TOF, any additional VSDs (that may be challenging to visualize with a large VSD adjacent), and the status of the atrial septum. These patients may also have right aortic arches as well as vascular rings and systemic venous anomalies, which should be noted. Other more rarely associated malformations such as mitral valve dysplasia and/or left ventricular outflow tract anomalies should also be ruled out.

**For patients with TOF undergoing elective complete surgical correction, repair between ages 3 and 6 months is reasonable (Class: IIa, LOE: B-NR).**

Proponents of earlier repair tout the advantages of reducing the amount of RV hypertrophy at the time of surgical correction and its presumed short- and long-term advantages. However, a slightly older patient may allow for technical ease of the operation as well as perhaps mitigate other risks of the operation (eg, risk of cardiopulmonary bypass in a neonate vs an older infant). A number of studies have analyzed the association of patient age at the time of elective complete surgical correction with perioperative outcomes and need for reintervention. Although the results have not been uniform across studies, generally an elective repair between ages 3 and 6 months has been associated with good outcomes, although some centers may have a preference and ability to perform complete surgical correction at age younger than 3 months with similarly good outcomes.

Multiple studies exist regarding the association of outcomes with age at repair, although they are hampered by various confounding factors. Padalino and colleagues[17] performed a retrospective multi-institutional review of 720 patients with a median follow-up of 4 years and on multivariable Cox analysis found that age younger than 3 months was independently associated with postoperative complications with both a hazard ratio [HR] of 5.8 and adverse events at follow-up with an odds ratio of 2.11. Kantorova and colleagues[18] analyzed 61 patients who underwent complete repair of TOF at 2 institutions divided into age groups younger than 3 months and 3 to 6 months with a median follow-up of 4.5 years. Although there were no differences in survival, operative times, lengths of stay (LOS) or ventilation, or reoperation, there was more frequently used transannular patch (TAP) in the younger group (85% vs 61%; $P = .039$). It should be noted that all patients younger than age 3 months of age were symptomatic and hence may have had smaller pulmonary valves to begin with. Kirsch and colleagues,[19] on the other hand, analyzed 277 patients younger than age 6 months undergoing elective complete repair (all asymptomatic) and found those younger than

**Recommendations regarding the care of the symptomatic neonate with tetralogy of Fallot (TOF)**

| Neonate | COR | LOE |
|---|---|---|
| When evaluating symptomatic neonates with TOF, it is reasonable to consider those with low birth weight and/or prematurity; small or discontinuous pulmonary arteries, major genetic or extracardiac congenital anomalies; or other comorbidities such as intracranial hemorrhage, sepsis, or other end-organ compromise as "high-risk" patients. | IIa | B-NR |
| In standard-risk symptomatic neonates with TOF, both palliative procedures or complete surgical correction are reasonable at a center with demonstrated expertise. | IIa | B-NR |
| In standard-risk symptomatic neonates with TOF where the decision has been made to perform a palliative procedure, a transcatheter intervention may be preferred to a surgical intervention at a center with demonstrated expertise. | IIb | B-NR |
| In high-risk symptomatic neonates, palliative procedures may be reasonable to consider as a risk management strategy before complete surgical correction. In some circumstances, it is reasonable to consider the continued use of prostaglandin E1 as a bridge to a palliative procedure or complete surgical correction. | IIb | C-LD |
| In high-risk symptomatic neonate with TOF where the decision has been made to perform a palliative procedure, a transcatheter intervention may be preferred to a surgical intervention at a center with demonstrated expertise. | IIb | B-NR |
| For the symptomatic neonate with TOF where a decision has been made to perform a palliative surgical procedure, strategies to provide adequate pulmonary blood flow may reasonably include a systemic-to-pulmonary shunt, a right ventricular outflow tract patch, and a right ventricle-to-pulmonary artery conduit. | IIa | C-EO |

age 3 months had longer LOS and more frequently had a TAP. Younger age was not associated with increased postoperative complications, but this study does not provide midterm follow-up. Van Arsdell and colleagues[20] analyzed 277 patients and found on multivariable analysis that age younger than 3 months was associated with longer time to clear lactate, longer ventilation, and longer LOS.[20] Mouws and colleagues[21] analyzed 177 patients with a median follow-up of 7 years and found that age younger than 2 months was a risk factor for reoperation. Ooi and colleagues[22] analyzed 52 patients undergoing both elective and urgent operations with a mean follow-up of 4 years. They found those younger than age 3 months had longer ventilation times, ICU times, and LOS.[22] Monteagudo and colleagues[23] analyzed 130 patients divided into age groups of younger than 3 months and older than 3 months with a mean follow-up of 3.9 years. They found that the younger patients had longer operative times, ventilation duration, as well as ICU and hospital LOS. Complications were also substantially higher in those younger than age 3 months (70% vs 43%); however, there were no differences in mortality or need for reintervention. Ductal-dependent circulation was much more common in the younger group. In a study of Nationwide Inpatient Sample data, Yang and colleagues[24] analyzed 1112 infants and found on multivariable analysis the risk of postoperative complications was 40% lower in those aged 3 months or older compared with <30 days, as well as shorter LOS. In this study, when only elective cases were considered, complications were no longer different; LOS remained shorter for patients older than age 3 months compared with those aged 31 to 90 days or aged 30 days or younger. This study does not include midterm follow-up. The study by Dorobantu and colleagues[25] looked at the association of age on mortality at 12 years for all patients with TOF undergoing intervention, whether that be surgical or catheter-based. In the subgroup of primary complete repair, age younger than 60 days yielded worse outcomes, but again, this series included symptomatic patients and although the data were not collected, one would expect more symptomatic patients in the younger cohort.

Although these data, taken as a whole, provide some insight into the effect of timing on predominately perioperative outcomes, there are many limitations to these studies, namely the limited follow-up, that many studies include symptomatic patients and bias for symptomatic patients to be repaired earlier with a (likely) more challenging substrate, as well as institutional and surgeon bias as to timing of repair given certain clinical and anatomic scenarios. Patients with severe RVOT obstruction are more likely to undergo repair at an earlier age overall. These patients, too, are more likely to require a TAP and have a more difficult postoperative course, thus demonstrating an association rather than a causality. This age bias would be expected to be less, but still present, in a center that practices early elective repair; and such centers with more experience with that age and size may be able to provide equivalent outcomes at younger ages, which further complicates the interpretation of the data. What is needed in this regard are additional studies, ideally prospective and randomized or in a multi-institutional registry, to elucidate the ideal timing of repair for elective patients. Finally, because these studies focus on perioperative and midterm outcomes, these patients should continue to be evaluated as the long-term implications remain incompletely understood. Although some have reported excellent results of complete surgical correction at an earlier age, taken as a whole, these data indicate that, for the larger population, an elective complete correction between 3 and 6 months is reasonable and generally safe.

**When evaluating symptomatic neonates with TOF, it is reasonable to consider those with low birth weight and/or prematurity, small or discontinuous pulmonary arteries, major genetic or extracardiac congenital anomalies or other comorbidities such as intracranial hemorrhage, sepsis, or other end-organ compromise as high-risk patients (Class: IIa, LOE: B-NR).**

The heterogeneity of TOF complicates the evaluation of treatment options and outcomes. However, certain features have been identified as high-risk factors that regardless of the treatment pathway are associated with worse outcomes. Some patients may have the presence of multiple risk factors, which must be taken into consideration.

With any congenital heart defect, patient weight has been shown to be among the most important factors influencing outcomes.[26,27] When evaluating outcomes for all procedures using the Society of Thoracic Surgeons–Congenital Heart Surgery Database, weight <2.5 kg was identified as a risk factor for mortality. TOF as a subgroup showed similar survival for those <2.5 kg for primary repair or initial surgical palliation, although this was a smaller number of patients with an overall mortality of 5% to 8.5%.[27] Contrary to this, many smaller single-institution studies have identified lower weight as a risk factor for mortality and morbidity including prolonged mechanical ventilation, ICU LOS, and need for reintervention.[28-31] Further, a study from the Pediatric Cardiac Care Consortium, including more than 3000 patients, although designed to compare primary repair versus a staged approach, identified weight <2.5 kg at the time of surgery to be a risk factor for in-hospital mortality with an odds ratio of 12.5.[32] More recently, a study from the Congenital Cardiac Research Collaborative (CCRC) evaluating both treatment strategies for TOF in those patients <2.5 kg noted a high mortality, more than 15% at 5 years for either approach, although

44% of these patients had TOF/PA.[33] Others propose <2.0 kg as the new marker for lower weight; regardless, although often considered as a dichotomous variable, weight should be considered on a continuum.[34,35]

Similar to weight, and correlating with it, prematurity has been shown to be a risk factor for mortality.[26,34,36] Again, this should be considered as a continuous variable. Additionally, the presence of small, or discontinuous, PAs increases the technical complexity of a complete surgical repair, shunt procedure, or catheter-based palliation leading to higher mortality and an increased need for reintervention.[31,37-40] Genetic abnormalities are seen in about 15% of those with TOF, with 22q11.2 deletion and trisomy 21 as the most common and may be associated with hypoplastic pulmonary arteries and increase the risk of mortality.[41,42] A study from the Pediatric Cardiac Care Consortium identified genetic abnormalities as a risk factor for both early and late postoperative mortality.[32] This corroborates the results from multiple smaller single-institution studies that also noted higher mortality or morbidity associated with genetic abnormalities[42-44] and a study using the Pediatric Health Information System (PHIS) database in which the outcomes in the setting of extracardiac abnormalities are significantly worse.[36] In many of these studies, 22q11.2 deletion syndrome is a notable exception, having outcomes similar to those for children without genetic syndromes.[28,32,43] Similarly, a study using the PHIS database included 430 patients with trisomy 21; it showed that this was associated with increased morbidity, but not mortality.[44] Finally, a patient's clinical status going into either a complete surgical correction or palliative procedure is important, with the presence of intracranial hemorrhage or significant infection perhaps portending a worse prognosis, although no studies have specifically evaluated these risk factors.

As high-risk factors have been identified, important questions are raised. Should any particular factor drive the physician to pursue a different treatment strategy? Are any of these variables modifiable? Additional large multi-institutional prospective randomized clinical studies are required to allow for the specific subgroup analyses necessary to answer these questions.

**In the standard-risk symptomatic neonate with TOF, both palliative procedures or complete surgical correction are reasonable at a center with demonstrated expertise (Class: IIa, LOE: B-NR).**

Although most neonates with TOF are asymptomatic, a subgroup of patients will be symptomatic and require early intervention. These neonates have severe PS or PA and present with cyanosis, hypercyanotic episodes, or ductal-dependent pulmonary blood flow. Options for early intervention include primary, complete surgical correction, as well as palliative procedures aimed at augmenting pulmonary blood flow. Each strategy has associated risks and benefits. A primary, complete surgical correction may reduce the duration of cyanosis, limit repeat exposures to anesthesia and cardiopulmonary bypass, reduce overall morbidity and mortality by eliminating an interstage period, and improve pulmonary artery growth.[29,45,46] Initial palliation, on the other hand, may reduce exposure to anesthesia and cardiopulmonary bypass (assuming the procedure can be tolerated without bypass) during the vulnerable neonatal period, decrease early morbidity and mortality, and may reduce the need for a transannular incision by facilitating somatic growth before complete surgical correction.[25,47,48] Initial palliation may increase the technical complexity of the complete surgical correction: although this most often only requires the ligation and/or division of a PDA stent or systemic-to-pulmonary shunt, at times it may be more complicated. Additionally, palliation in the form of RVOT stenting eliminates the potential for valve preservation. Each of the above must be considered when devising the management plan using a multidisciplinary approach.

Results for initial palliation and primary complete surgical correction are largely single-institution studies that only report outcomes with 1 specific strategy, albeit excellent outcomes.[29,45,46,49] Multi-institutional analyses have been performed,[36,50] but they have relied on administrative data until the recent report from the CCRC.[51] All studies are retrospective, observational, and often their results are susceptible to confounding bias based on indication as many centers favor initial palliation in patients with high-risk features. Furthermore, most studies combine patients with PS and PA, and some include coexisting lesions. Finally, when evaluating these studies, it is important to compare the cumulative results of the staged, complete surgical correction (instead of the results of initial palliation alone) with those of primary, complete surgical correction.

Evidence supports and refutes whether mortality differs by management strategy of symptomatic neonates with TOF. Bailey and colleagues[48] demonstrated no difference in mortality between neonates who underwent complete (n = 112) or staged (n = 26) repair, but the number of patients treated may have been too few to detect a difference. Multiple investigations have used the PHIS database, an administrative database reliant on International Classification of Diseases codes for identification of patients with TOF. Ramakrishnan and colleagues[36] found no difference in mortality at hospital discharge between infants with TOF who underwent primary, complete repair (n = 554) compared with those who underwent a systemic-to-pulmonary artery shunt (n = 267) (primary repair 4% vs systemic-to-pulmonary shunt 4%; $P = 1.0$). However, they failed to account for the cumulative risks incurred with a staged approach. Savla and colleagues[50] also using the PHIS database found that primary, complete repair

(n = 1032) in neonates with TOF was associated with a greater hazard of death compared with a staged repair (n = 1331) over 2 years (HR, 1.51; 95% CI, 1.05-2.06). Goldstein and colleagues[51] pooled retrospective data from nine centers and compared primary, complete repair (n = 230) with staged repair (n = 342) in symptomatic neonates with TOF (of note approximately half of these patients had PA). Despite an earlier hazard of mortality associated with primary, complete repair compared with palliative procedures, the overall hazard of mortality over 5 years was no different (HR, 0.82; 95% CI, 0.49-1.38).

A staged repair may be associated with more reinterventions (surgical or transcatheter) than a primary, complete surgical correction. Despite excluding the complete repair as a reintervention, Goldstein and colleagues[51] found that the hazard of reintervention was greater with a staged approach compared to primary, complete surgical correction (HR, 1.55; 95% CI, 1.17-2.05), predominantly due to reinterventions during the interstage period. Sandoval and colleagues[47] similarly found that patients who underwent initial RVOT stenting had a higher incidence of reintervention on the outflow tract compared with primary, complete surgical correction before age 3 months, but the incidence of reintervention was similar once the staged repair was performed. Similarly, Bailey and colleagues[48] found that staged repair was associated with more reinterventions overall but found no difference in the rate of unexpected reinterventions (excluding the staged repair). Again, Wilder and colleagues[52] demonstrated the increased likelihood of reintervention with catheter-based palliation as part of a staged approach in a single-institution study; however, these patients had smaller branch PAs, suggesting that this may reflect the patients' underlying anatomy rather than the treatment strategy.

The 2 management strategies may differ with respect to the ability to spare the pulmonary valve at the time of complete repair, LOS, and cost. The type of palliative procedure performed will also affect the ability to spare the pulmonary valve. For example, Sandoval and colleagues[47] reported that 0% of infants palliated with an RVOT stent underwent a valve-sparing repair compared with 41% of infants who underwent primary, complete surgical correction before age 3 months. There was no difference in the incidence of pulmonary-valve-sparing repair, when neonates were palliated with a systemic-to-pulmonary artery shunt or ductal stent.[51] Although cumulative hospital LOS may not differ between management strategies at the single-center level,[48] a primary, complete surgical correction was associated with a significantly shorter hospital LOS compared with a staged repair when examined across multiple institutions: primary repair 19 days (interquartile range [IQR], 14-30 days) versus staged repair 32 days (IQR, 22-49 days) ($P < .001$).[51] Repeat interventions and longer hospital LOS may result in greater resource utilization: Multicenter analyses using the PHIS data and the CCRC data had more total costs associated with staged repair, even after adjustment for confounding by indication (although patients who undergo staged repair often have a larger comorbidity burden).[53,54]

In the standard-risk, symptomatic neonate with TOF, excellent results may be achieved with either primary, complete surgical correction, or initial palliation followed by staged, complete surgical correction. Either approach may be preferred, partially due to institutional expertise and experience. Although theoretical advantages drive institutional preferences for a given strategy, direct comparisons are observational and do not demonstrate substantial differences. As the landscape of palliative procedures shifts toward transcatheter interventions, perhaps overall risk may change; this requires future investigation. Because the hazard of mortality and reintervention plateau to similar levels late after primary or staged repair, further investigations into long-term differences in neurodevelopmental outcomes are also of interest.

**In the standard-risk symptomatic neonate with TOF where the decision has been made to perform a palliative procedure, a transcatheter intervention may be preferred to a surgical intervention at a center with demonstrated expertise (Class: IIb, LOE: B-NR).**

The data supporting this statement are based on several retrospective observational studies comparing the most commonly used surgical palliative procedures for symptomatic neonates with TOF, a systemic-pulmonary artery shunt (typically a modified BTT shunt), with the most commonly used transcatheter palliative procedure, a ductal arterial stent. A surgical shunt is the more time-tested option, with reasonable outcomes in a variety of experienced single-center reports,[55] but with unique morbidities reported in TOF[56] and a risk for significant morbidity and mortality in community-wide studies.[57,58] In the most recent Society of Thoracic Surgeons–Congenital Heart Surgery Database (from January 2015 to December 2018), 258 patients had undergone either a BTT (186) or central (72) shunt at a median age of 46 to 59 days with discharge mortality of ~3% and overall postoperative length of stay of 26 to 42 days. Approximately one-third of patients were on mechanical ventilatory support preoperatively and not an insignificant number experienced unplanned cardiac reoperation (6.5% BTT and 15.3% central), cardiac arrest (4.8% BTT and 19.4% central), and mechanical circulatory support (2.7% BTT and 15.3 central).[59]

Ductal arterial stenting has recently become more commonly used for patients with ductal-dependent pulmonary blood flow, which almost always invariably involves neonates. Direct comparisons of these 2 options (BTT shunting vs PDA stenting) are limited to a handful of large single-center[60-62] and 2 multicenter studies.[63,64] These studies demonstrated equivalency to superiority of

the less-invasive ductal arterial stenting option, with the consistent exception that ductal arterial stenting appears to be associated with a higher reintervention risk. Highlighting the 2 multicenter studies where propensity score adjustment methodology was used to mitigate bias due to confounding by indication, Glatz and colleagues[63] demonstrated equivalent freedom from mortality or unplanned reinterventions with lower complication rates and shorter LOS following ductal arterial stenting. Similarly, Bentham and colleagues[64] reported superior freedom from mortality, extracorporeal membrane oxygenation, and shorter LOS following ductal arterial stenting. These outcomes are dependent on institutional experience and expertise, as shown by the 15% failure rate for ductal stenting in one multi-institutional study. Furthermore, if the anatomy is less favorable such that stenting into the PAs would be necessary, the influence on the complete surgical correction must be considered.

The results of the above studies were supported in a subsequent review article[65] and meta-analyses[66,67]; however, several important caveats are worth mentioning. First, no studies directly compare surgical palliative procedures to transcatheter palliative procedures in symptomatic neonates with TOF. The aforementioned multicenter studies both included cohorts of infants with ductal-dependent pulmonary blood flow with a heterogenous collection of underlying anatomies, although TOF did constitute a sizable minority of the anatomic subtypes. Second, none of these studies restricted cohorts to, or performed subgroup analyses on, standard-risk neonates, although the 2 studies by Glatz and colleagues[63] and Bentham and colleagues[64] did include some elements of patient-based risk factors in their propensity score analyses. Finally, it is important to note that there are other surgical palliative options, including limited RVOT patch and use of a small right ventricle-to-pulmonary artery conduit without VSD closure. On the transcatheter side, interventions on the RVOT, including balloon pulmonary valvuloplasty[68] and RVOT stenting[47,69,70] have been used with success especially outside of the neonatal period. Inclusion of these palliative options could affect the relative risks between surgery and transcatheter options and deserve further investigation. Indeed, in symptomatic patients with TOF who do not have a PDA, RVOT stenting or balloon valvuloplasty pragmatically represents the only available catheter-based palliative option and will likely represent the more commonly observed clinical scenario. As well, in patients with particularly small pulmonary valves wherein a TAP is highly anticipated, the issue of valve preservation may be moot when considering an RVOT stent. Implementing RVOT stenting will have important implications for subsequent surgical interventions beyond the obvious inability to spare the pulmonary valve. In addition to the same possibility of needing to deal with stent protruding into the pulmonary arteries (and influence on those vessels) that can occur with patent ductus arteriosus (PDA) stenting, the surgeon will need to pay close attention to avoiding injury to the tricuspid valve apparatus and other key infundibular structures (eg, septal perforators) during extrication of stent materials (or the decision to leave some behind, including in the aorta for a PDA stent or RVOT for RVOT stents).

Currently, the best available data for catheter-based palliations versus surgical palliations stem from studies involving newborn infants with ductal-dependent pulmonary blood flow in whom PDA stent utilization predominates. Because individual patient scenarios undoubtedly create nuances that may not fit a single recommendation and given the evolving nature of therapies, a multidisciplinary discussion between cardiology and cardiac surgery should be implemented to decide on the final disposition of the various treatment options and their risks and benefits. This should be shared openly and transparently with families to allow them to participate in the decision-making process.

**In the high-risk, symptomatic neonate, palliative procedures may be reasonable to consider as a risk management strategy before complete surgical correction. In some circumstances, it is reasonable to consider the continued use of prostaglandin E1 (PGE1) as a bridge to a palliative procedure or complete surgical correction (Class: IIb, LOE: C-LD).**

Few studies directly compare palliative procedures to primary, complete surgical correction specifically in symptomatic neonates with high-risk features. The limited available data explore outcomes in low-birth-weight neonates, but the high-risk category includes a variety of other features that may interact differently with treatment type. For example, a weight of 1.6 kg likely has a different effect on outcome based on treatment than intracranial hemorrhage or hypoplastic PAs. Some components of the high-risk category are rare, but even those that occur more frequently may present with varying severities. Consequently, treatment decisions are individualized based on institution preferences and capabilities. These data are further confounded by selection bias; for example, a child with severe interventricular hemorrhage is more likely to receive a palliative intervention. This complicates the interpretation of outcomes including mortality, morbidity, and LOS. A better understanding of how individual risk factors and combinations of risk factors interact with treatment strategies is greatly needed.

Low birth weight, prematurity, and extracardiac anomalies are frequent risk factors associated with mortality in those undergoing complete repair of TOF,[36,47,71] but also palliative procedures.[36] Qureshi and colleagues[33] compared primary, complete surgical correction (n = 44) with palliative procedures (n = 76; transcatheter n = 23) in symptomatic neonates <2.5 kg among nine institutions.[33] Overall rates of mortality were much higher in this subgroup (16.7% at a median follow-up of 5.5 years) compared

with the overall cohort of symptomatic neonates in the previous study by Goldstein and colleagues[51] (between 7% and 10% at median follow-up of 4.3 years). Within this high-risk group, there was no difference in mortality (HR, 1.21; 95% CI, 0.66-2.24) based on management strategy. Although complete repair was excluded as a reintervention, there was a trend toward more reinterventions in the initial palliation group (HR, 1.69; 95% CI, 0.96-2.28), but no difference in reintervention after the definitive repair (HR, 1.21; 95% CI, 0.66-2.24). The cumulative LOS was significantly longer for those undergoing initial palliation followed by staged repair compared with those who underwent primary, complete surgical correction: staged repair, 44 days (IQR, 27-75 days) versus primary repair, 23 days (IQR, 15-34 days) ($P < .001$). Delaying complete repair with initial palliation may permit more patients to undergo a valve-sparing procedure (staged repair, 7.6% vs primary repair, 0%; $P = .06$).[33]

The interaction effect of hypoplastic pulmonary arteries with management strategy on outcomes is unknown. Pulmonary artery hypoplasia can be diffuse and bilateral, asymmetric, or focal (ie, pulmonary coarctation); however, this is not well delineated in the literature. Furthermore, distinguishing pulmonary arteries that appear hypoplastic because they are underfilled from those that are truly hypoplastic can be difficult. Palliative procedures may support pulmonary artery growth in such patients as a bridge to complete repair. The use of a BTT shunt has the potential to allow for significant branch pulmonary artery growth.[72] More recently, evaluating propensity-matched cohorts of BTT shunt versus PDA stenting, the PDA stenting group demonstrated larger and more symmetric pulmonary arteries at the time of complete surgical correction.[63] Another study showed no difference in pulmonary artery size and a similar need for pulmonary arterioplasty at the time of complete surgical correction between the 2 approaches.[64] Sandoval and colleagues[47] demonstrated that RVOT stenting in patients with hypoplastic pulmonary arteries (mean $z$ score, –6.6; range, –13.9 to –3.2) facilitated growth such that their average weight and pulmonary artery dimensions at the time of complete repair were no different from those of patients undergoing elective repair of TOF between ages 3 and 6 months.

In some circumstances, such as very low birth weight, or other severe, ideally modifiable, comorbidities, PGE1 can be used as a bridge to a palliative procedure or complete surgical correction. Indeed, nearly all patients in the multi-institution subgroup of neonates <2.5 kg were on PGE1 infusions before intervention.[33] No randomized trial exists about the use of PGE1 to maintain ductal patency because it is standard of care for the management of patients with ductal-dependent pulmonary blood flow.[73]

**In the high-risk symptomatic neonate with TOF where the decision has been made to perform a palliative procedure, a transcatheter intervention may be preferred to a surgical intervention at a center with demonstrated expertise (Class: IIb, LOE: B-NR).**

The data supporting this statement are largely extrapolated from the studies referenced above. No direct studies have compared surgical palliation with transcatheter palliation in a selected cohort of high-risk symptomatic neonates with TOF. Ductal stenting has been reported to have favorable outcomes in series of infants with commonly accepted high-risk characteristics, including low birth weight and those with hypoplastic pulmonary arteries.[74,75] An important caveat is the procedural failure rate, as discussed above, which can mandate a surgical shunt (potentially emergency) in a patient who is already at high risk.[64] This further highlights the importance of communication between cardiology and cardiac surgery about not only if a transcatheter intervention should be performed but also the timing, given the potential for PGE1 to mitigate any urgency.

**For the symptomatic neonate with TOF where a decision has been made to perform a palliative surgical procedure, strategies to provide adequate pulmonary blood flow may reasonably include a systemic-to-pulmonary shunt, an RVOT patch, and a right ventricle-to-pulmonary artery conduit (Class: IIa, LOE: C-EO).**

In symptomatic neonates with TOF, palliative procedures, either surgical or transcatheter, aim to augment pulmonary blood flow. Although the most common palliative surgical procedure is the systemic-to-pulmonary shunt (most commonly the modified BTT shunt), other palliative procedures include an RVOT patch and a right ventricle-to-pulmonary artery conduit. Mahajan and colleagues[49] use a uniform strategy whereby a systemic-to-pulmonary shunt is used to palliate symptomatic neonates and infants who require early intervention for TOF. Among 65 patients who underwent palliation, 3 died and 59 proceeded to complete repair.[49] The $z$ scores of the main and branch pulmonary arteries significantly increased, but the pulmonary valve $z$ score did not change substantially. Other centers have demonstrated equally impressive results with systemic-to-pulmonary shunt palliation, achieving mortality rates of 3% to 4%.[76]

Theoretical advantages to the RVOT patch and right ventricle-to-pulmonary artery conduit include avoiding reductions in diastolic blood pressure and decreased volume load on the left ventricle. Streaming also likely results in a higher proportion of deoxygenated blood being shunted to the lungs allowing for improved oxygen uptake. Disadvantages include the potential for overcirculation if the outflow tract is opened too widely. All procedures can be performed with acceptable outcomes, and to date, there is no direct comparison of these palliative surgical procedures. Levi and colleagues[77] palliated 22 patients with an RVOT patch, 20 of

**Recommendations regarding the complete surgical correction of tetralogy of Fallot (TOF)**

| Complete surgical correction | COR | LOE |
|---|---|---|
| For patients with TOF undergoing complete surgical correction consisting of a valve-sparing approach, a transatrial, transventricular, or a combined approach, are reasonable to perform. | IIa | B-R |
| For patients with TOF undergoing complete surgical correction, it may be preferable to minimize the size of the ventriculotomy. | IIb | B-NR |
| For patients with TOF undergoing elective complete surgical correction with a preoperative pulmonary valve annular *z* score >–2.5, it is reasonable to consider a valve-sparing approach. | IIa | B-NR |
| Techniques for repairing TOF with a borderline pulmonary valve annulus (ie, *z* score <–2.5) could reasonably include an annulus preservation or valve-sparing technique, or a limited transannular incision with or without valve reconstruction. | IIb | B-NR |
| When a transannular incision is necessary, efforts to restore pulmonary valve competency using various techniques may be reasonable to consider. | IIb | C-EO |
| When a transannular repair would otherwise be necessary, in the presence of an anomalous coronary artery crossing the right ventricular outflow tract, either a coronary artery sparing ventricular incision or a right ventricle-to-pulmonary artery conduit may be reasonable approaches based on institutional expertise. | IIb | C-EO |
| After complete repair of TOF, intraoperative anatomic and hemodynamic assessment to confirm the adequacy of repair is highly recommended. | I | C-EO |
| Significant residual fixed anatomic obstruction should prompt consideration for immediate reintervention. | IIa | B-NR |

which were performed off-pump with only 1 (4.5%) mortality. Bradley and colleagues[78] inserted right ventricle-to-pulmonary artery conduits (nonvalved) in 10 infants with biventricular hearts and inadequate pulmonary blood flow (primarily TOF with pulmonary atresia). The mortality rate was 0%, and 8 patients underwent biventricular repair by the time of publication. Jo and colleagues[79] examined their outcomes with various types of palliation, including right ventricle-to-pulmonary artery conduits (n = 14) and systemic-to-pulmonary shunts (n = 11). There were no deaths in the systemic-to-pulmonary shunt group versus 2 deaths in the right ventricle-to-pulmonary artery conduit group, and most patients underwent complete repair at approximately age 12 months. Given the available data, any of the above palliative surgical procedures appear reasonable given the surgeon's and institution's experience. As the landscape of palliative procedures shifts toward transcatheter interventions, the use of these surgical palliative procedures may change.

**For patients with TOF undergoing complete surgical correction consisting of a valve-sparing approach, a transatrial, transventricular, or a combined approach, are reasonable to perform (Class: IIa, LOE: B-R).**

**For patients with TOF undergoing complete surgical correction, it may be preferable to minimize the size of the ventriculotomy (Class: IIb, LOE: B-NR).**

For patients with TOF undergoing complete surgical correction, it is preferable to minimize the size of the ventriculotomy, whether subvalvular or transannular. The degree of infundibular hypoplasia and ability to create an unobstructed RVOT may best dictate the approach used.

The current goals in complete repair of TOF remain the same as the early experiences. The goals consist of closing the VSD, relieving RVOT obstruction at all levels and, ideally would also include achieving a competent pulmonary valve. Early experience used larger ventriculotomies for maximal exposure to facilitate rapid repair and short cardiopulmonary bypass times. Over time, advances in cardiopulmonary bypass (allowing a less hurried approach to repair) and surgical techniques have led to a focus on aspects of repair that could result in worse long-term outcomes, including the performance of a ventriculotomy, or its size. These have been described as limited or mini ventriculotomies without a precise definition, which complicates associated data interpretation.

In 1985, Kawashima and colleagues[80] reported on 90 consecutive patients with or without a minimal right ventriculotomy and compared them with conventional right ventriculotomy patients, demonstrating that a minimal or no ventriculotomy carried no increased risk, and that there was better long-term RV function and fewer ventricular arrhythmias. It has also been demonstrated, using magnetic resonance imaging, that RVOT scar size correlates with worse RV function, lower exercise tolerance, and arrhythmias.[81] Bojórquez-Ramos and colleagues[82] found in 47 patients that morbidity and mortality was higher in classical ventriculotomy group (n = 29, 62%) compared with the small infundibulectomy cohort. Talwar and colleagues[83] looked at 50 consecutive patients undergoing intracardiac repair of TOF and divided them into 2 groups: trans-right atrial (t-RA) versus trans-atrial and ventricular (t-RA/RV) approach. They concluded that both t-RA and t-RA/RV approaches provide safe repair for patients with TOF and that a limited right ventriculotomy neither leads to deleterious effects on RV function nor does it increase the incidence of arrhythmias at 2 years. While in the t-RA group, the VSD is approached via the right atrium, in the t-RV group access to the VSD is dictated by the length of the infundibular septum, which is a variable structure in TOF. It is, therefore, intuitive that the longer the infundibular septum, the longer the ventriculotomy may be (independent from the severity and location of the RVOT obstruction) to allow for proper visualization of the VSD.

Mid- and longer-term follow-up publications support minimizing the size of the right ventriculotomy. Morales and colleagues[84] demonstrated that patients who underwent RV infundibulum-sparing strategy with mini or no ventricular incision showed normal RV function for 95%, and mild dysfunction in 4.6% in 65 patients followed out to 7 years. Other investigations also support minimizing the right ventriculotomy during repair of TOF. d'Udekem and colleagues[85] looked at 191 TOF patients who underwent repair, with a mean follow-up of 22 ± 5 years. They found that right ventriculotomy patching and TAP resulted in more long-term pulmonary insufficiency and RV dilation. RV patching, whether transannular or not, was the most significant independent predictor of late adverse events. The preceding suggests the more aggressive valve-sparing approaches that require a ventriculotomy may not result in improved long-term outcomes over a TAP.[85] Inevitably, due to the nature of these single-institution, and at times single-surgeon, reports, patient selection may play a role in reported long-term outcomes rather than simply the size of the ventriculotomy and need to be taken into consideration. For example, patients with elongated RVOT often require a longer ventriculotomy to relive the obstruction. Nevertheless, the overall summation of published data suggests that minimizing the size of the ventriculotomy, even if leaving residual stenosis, will likely have beneficial effects toward preserving RV function and possibly reducing long-term pulmonary insufficiency. Alleviating RVOT obstruction and complete closure of the VSD is the primary goal of complete repair. Achieving these goals, while making the minimally necessary ventriculotomy, is reasonable and preferable.

**For patients with TOF undergoing elective complete surgical correction with a preoperative pulmonary valve annular Z-score > –2.5, it is reasonable to consider a valve-sparing approach (Class: IIa, LOE: B-NR).**

**Techniques for repairing TOF with a borderline pulmonary valve annulus (ie, *z* score <–2.5) could reasonably include an annulus preservation or valve-sparing technique, or a limited transannular incision with or without valve reconstruction (Class: IIb, LOE: B-NR).**

Multiple factors influence the likelihood of performing a successful valve-sparing approach, including the pulmonary annular size, leaflet number, leaflet mobility, thickness, or dysplasia and preoperative pulmonary insufficiency. The most commonly used factor, both clinically and in the literature, is the size of the pulmonary annulus. Some guidance as to the *z* scores for which a valve-sparing repair may be reasonably attempted can be inferred from the median, mean, and range of *z* scores reported in series demonstrating successful valve-sparing results. These *z* scores do not indicate the limits to successful valve-sparing repair (ie, do not imply that successful valve-sparing cannot be performed with a lower *z* score than reported in the study). The *z* scores that are reported are also influenced by predetermined institutional and surgeon protocols or practice patterns as well as variability in parameters that require a reintervention (eg, an RV pressure cutoff). Some studies do provide details on patients in whom a valve-sparing repair was attempted but results deemed not acceptable wherein a TAP was performed; these data are particularly valuable.

Across studies there is a wide range in the reported *z* score for valve-sparing patients, and this often overlaps with the TAP cohort within a given study (Table 1). The fact that for a given *z* score within any particular study, some patients leave the operating room with a valve-sparing repair and others with a TAP, highlights the limitations of the preoperative annular *z* score on echocardiography and that it is only 1 of several factors necessary for a successful valve-sparing repair. The annular diameter can be challenging to measure accurately and very small changes in measurement can dramatically influence the calculated *z* score. It does not account for how much this annulus can be increased intraoperatively with various techniques and does not account for cusp number, cusp dysplasia, and immobility, which also are important factors in the ability to relieve RVOT obstruction.

One key question that the surgeon faces intraoperatively is whether, after performing various techniques, the valve-sparing technique is likely to be successful longer-term or must be abandoned. Ideally this would be determined while still crossclamped. Some studies that provide guidance with regard to the *z* score to be achieved in the operating room include the study by Bove and colleagues[87] in which the valve-sparing group had a *z* score of –0.9 before repair and 0.34 after repair. Stephens and colleagues[92] found the

**TABLE 1. Transannular patch (*TAP*) versus valve-sparing *z* scores**

| Reference | TAP *z* score | Valve-sparing *z* score |
|---|---|---|
| Lee and colleagues[86] | –2.7 ± 1.4 | –0.8 ± 1.7 |
| Mahajan and colleagues[49] | –2.4 ± 0.6 | –1.9 ± 0.7 |
| Bove and colleagues[87] | TAP: –3.26 ± 0.95<br>Infundibular sparing: –2.84 ± 0.75 | –0.9 ± 1.15 (post-repair 0.34 ± 0.94) |
| Sen and colleagues[88] | –3.1 (range 0.8 to –9.0) | –1.4 (range 1.8 to –5.5) |
| Lozano-Balserio and colleagues[89] | | Balloon dilation: –2.3 (range –1.3 to –4.5) |
| Robinson and colleagues[90] | –2.8 ± 1.0 | No adjunct: –0.8 ± 1.2<br>Hegar dilation: –1.4 ± 1.1<br>Balloon dilation: –2.4 ± 1.0 |
| Hofferberth and colleagues[91] | | Balloon dilation: –2.2 (range –2.4 to –1.8) |
| Stephens and colleagues[92] | –3.1 (IQR –2.9 to –4.1) | –2.0 (IQR –2.4 to –1.8)<br>"Ideal result" –1.2 ± 1.4 |
| Hickey and colleagues[93] | –6.9 | –4.5, post-repair successful –1.5 (range –2.6 to –1.0) |
| Vida and colleagues[94] | TAP with valve reconstruction:<br>–3.35 (range –1.54 to –5.62) | Balloon dilation: –2.95 (range –0.95 to –4.06) |
| Choi and colleagues[95] | –2.5 ± 1.5 | –0.9 ± 1.3 |
| Zhao and colleagues[96] | –3.6 (range –2.6 to –5.3) | –1.5 (range –0.4 to –2.9) |
| Kasturi and colleagues[97] | –2.9 ± 1.4 | –1.1 ± 1.6 |
| Borodinova and colleagues[98] | –3.9 ± 2 | –3.0 ± 1.9 (post-repair –1.0 ± 0.9) |

*IQR*, Interquartile range.

preoperative $z$ score for the valve-sparing group to be –2.0, but those with a peak gradient <25 mm Hg and no more than mild pulmonary regurgitation on follow-up had a postrepair $z$ score of –1.2. In the study by Hickey and colleagues,[93] the $z$ scores for the valve-sparing group are markedly less than those in other studies (–4.5), but the postrepair $z$ score for the successful valve-sparing cohort was –1.5. Institutions may use different $z$ score models, which could cause differing results. In short, although these data are interesting, the minimum annular size that yields a durable result remains a question that requires further study. They do suggest that if at the end of a repair a $z$ score >–1 or so is not achieved, it is unlikely to lead to a durable result.

Other studies shed light on the limit of valve sparing in terms of $z$ scores. In the study by Awori and colleagues,[99] a regression analysis was used to analyze multiple studies and found that one-quarter of the patients with an intraoperative $z$ score postrepair of <–1.3 will have a peak gradient >30 mm Hg (which was considered unacceptable). Borodinova analyzed transesophageal echocardiograms to determine factors predictive of postoperative RVOT obstruction (defined as peak gradient of 40) found that a $z$ score of <–3.2 measured intraoperatively postrepair was predictive.[98] Zhao and colleagues[96] used receiver operator characteristic curves to analyze the optimal $z$ score cutoff for TAP and found it to be –2.1. The analysis by Sinha and colleagues[100] examining $z$ scores across 15 studies and 1100 patients found a median $z$ score of –1.7 for the valve-sparing patients across studies with a reoperation rate of 5%, and importantly no correlation between the median $z$ score and reoperation rate.

There are significant limitations to all these studies; for example, the systematic reviews, including varying surgical approaches spanning several decades, lack of uniform data points, limited follow-up, inconsistent data on catheter-based management of residual RVOT obstruction, variability in reporting pulmonary valve annulus sizes and RVOT gradients during preoperative, operative, and postoperative periods, along with disparities in the measurements of pulmonary valve $z$ scores, with a unified $z$ score utilization among others. These data provide an initial evaluation of adequacy of repair; however, longer-term clinical outcomes, including quality of life, functional data, arrhythmia burden, and exercise tolerance, are needed to make more definitive statements as to a $z$ score cutoff; they simply provide a rough guide for decision making. Finally, we do not know the long-term consequences of residual obstruction of a minor degree (ie, 20-30 mm Hg), which is not an infrequent finding with these lower limits ($z$ score –1 to –2).

Although variability is noted across studies regarding specific $z$ scores, 1 common finding is that the more aggressive annular dilation, the higher the likelihood of pulmonary insufficiency or need for reintervention. Understandably, the patients undergoing more aggressive measures are clearly the patients with smaller annular $z$ scores and therefore require more aggressive interventions.

The study by Robinson and colleagues[90] divided valve-sparing patients into those with no adjunctive dilation, those with Hegar dilation, and those with intraoperative balloon dilation; and the results were progressively worse with Hegar dilation and intraoperative balloon dilation. In this study, the $z$ score for those with no adjunctive dilation measured was –0.8, Hegar dilation was –1.4, and balloon dilation was –2.4; but the intraoperative balloon dilation group had a 20% reintervention rate at 1 year, 20% reoperation rate, and 50% had more than mild regurgitation. Further analysis from that group reported by Hofferberth of the intraoperative balloon subset found that group had progressive regurgitation and 15% required reintervention for RVOT obstruction. On multivariable analysis $z$ score <–2.45 and age younger than 3 months were risk factors for early reintervention for stenosis. Freedom from at least moderate pulmonary regurgitation was 43% at 5 years. Lazano-Baseiro and colleagues[89] in their analysis of 42 patients who underwent TOF repair with intraoperative balloon dilation with median $z$ score of –2.3 similarly reported progressive pulmonary regurgitation in >20% in a median follow-up of 45 months. In their practice, they perform commissurotomies, and then if the annulus remains 1 to 2 mm smaller than the $z$ score of 0 by Hegar, then an intraoperative balloon dilation would be performed. Vida and colleagues[94] report on their experience and in 34 patients with a median $z$ score of –2.95. At a median of 432 days of follow-up, 20% had moderate pulmonary regurgitation and 2 required reoperation for obstruction. In summary, although intuitively, attempts at valve preservation make sense, currently the optimal approach or pulmonary valve size thresholds have not been defined; and there is still insufficient evidence that valve-sparing techniques are durable in preventing pulmonary insufficiency and RV dilation in the mid- or long-term.

**When a transannular incision is necessary, efforts to restore pulmonary valve competency using various techniques may be reasonable to consider (Class: IIb, LOE: C-EO).**

Along the same lines as the rationale for valve preservation, in those where preservation cannot be accomplished, either due to size alone or due to dysplastic or nonfunctioning leaflets, many surgeons use a valve reconstructive technique, inclusive of either modifying existing native valve tissue to make it functional despite a TAP or creating a completely new valve or neovalve. In the short-term, the lack of severe pulmonary insufficiency may allow for an improved postoperative course. Over the long-term, the RV dilation and dysfunction that has become common place after TAP might be avoided, thus mitigating the need for either surgical or

**TABLE 2. Valve reconstruction techniques**

| Reference | Year | n | Technique | Outcome |
|---|---|---|---|---|
| Patukale and colleagues[101] | 2021 | 120 | Leaflet augmentation: Various materials | Freedom from moderate or greater PI of 69% at 5 y and 30% at 10 y |
| Amirghofran and colleagues[102] | 2021 | 21 | RAA | RAA valve patients had shorter hospital LOS, similar PS, and less PI at 12 mo |
| Onan and colleagues[103] | 2020 | 12 | RAA | No PI in 11 and mild in 1 at 6 mo |
| Samadi and colleagues[104]* | 2020 | 30 | Monocusp: 0.1 mm PTFE | Compared to regular TAP, less rate of severe PI with monocusp |
| Vida and colleagues[105] | 2019 | 12 | Leaflet delamination and resuspension | None/mild PI in 10 and moderate in 2 at 2.8 y follow-up |
| Singh and colleagues[106] | 2018 | 43 | Monocusp: Various materials | Less PI but no improvement in clinical outcomes |
| Aydin and colleagues[107] | 2018 | 15 | Pericardial monocusp | Less PI and overall morbidity with monocusp than only TAP |
| Kumar and colleagues[108] | 2016 | 171 | Monocusp: 0.1 mm PTFE | At 10 y only 42 required monocusp; Severe PI in <25%; severe PS in <10% |
| Jang and colleagues[109] | 2015 | 25 | Monocusp: 0.1 mm PTFE | Prolonged the development of severe PI |
| Sasson and colleagues[110] | 2012 | 74 | Monocusp: 0.4 mm PTFE | Monocusp echo results and clinical outcomes (vent d, ICU LOS, chest tube drainage) were similar to those who underwent valve preservation; both better than with TAP alone |
| Pande and colleagues[111] | 2010 | 16 | Monocusp: Pericardium | Reduced PI at 1 y without difference in clinical outcomes |
| Gil-Jaurena and colleagues[112] | 2010 | 21 | Monocusp: 0.1 mm PTFE | Low rates of PI or PS on discharge echo |
| Park and colleagues[113] | 2009 | 130 | Monocusp: various materials | No influence on early mortality or risk of reoperation |
| Quintessenza and colleagues[114] | 2009 | 126 | Bicuspid: 0.6 then 0.1 mm PTFE | Only 6 of the valves failed, all 0.6 mm type failed due to calcified leaflets |
| Anagnostopoulos and colleagues[115] | 2007 | 18 | Cusp augmentation | Cusp augmentation group had shorter ventilation and inotrope dependence, shorter ICU LOS, and less PI at discharge |
| He and colleagues[116] | 2006 | 9 | Monocusp: Pericardium | Mild PI in 5 and minimal in 4 on discharge echo |

*n*, Number of patients who underwent valve reconstructive technique; *PI*, pulmonary insufficiency; *RAA*, right atrial appendage; *LOS*, length of stay; *PS*, pulmonary stenosis; *PTFE*, polytetrafluoroethylene; *TAP*, transannular patch; *echo*, echocardiogram. *All studies are retrospective single institution studies with the exception of prospective randomized controlled trials.

catheter-based valve replacements. The ideal valve would be competent, provide no outflow obstruction, increase in size allowing for somatic growth, and be easy and quick to construct to prevent the need for increased bypass and cross-clamp time. To date, no such ideal valve reconstruction technique has been reported; otherwise the pediatric cardiac care community would have adopted it uniformly for all those patients who ultimately require a TAP or have pulmonary atresia. Many reports have touted different materials or techniques to reconstruct the pulmonary valve, the details of which are beyond the scope of this document. Of note, due to the significant overlap with the idea of valve creation in the setting of TOF with PA, some of the following data do include patients with PA.

The most commonly used and best studied technique is the monocusp valve, although significant variability exists with surgical technique and material selection even under the umbrella of a so-called monocusp valve. Many single-institution retrospective studies evaluating the use of the monocusp pulmonary outflow tract reconstruction have been published, consistently demonstrating reduced pulmonary insufficiency, at least in the short-term (Table 2).[106,107,109,110,112,116] Some also demonstrate reduced ventilation time, less chest tube drainage, and reduced ICU LOS with monocusp use.[110] Others, however, have failed to show any clinical improvements, despite echocardiographic improvement.[106,111,113] One study, notable for 171 patients over 20 years with more than 10 years of follow-up, showed that about 25% required monocusp replacement at a mean duration of 10 years, with the remaining having a mean RVOT gradient of 31 mm Hg and regurgitation that was mild in 19%, moderate in 52% and severe in 29%.[108] Another study, notable because it was a prospective randomized-controlled trial, evaluated the TAP with a monocusp reconstruction and without. Significant improvements in pulmonary

regurgitation with monocusp construction were demonstrated out to 6-month follow-up; clinical outcomes were not measured.[104] Most larger collections have failed to demonstrate benefits. A large meta-analysis of 49 studies in which a monocusp was used found survival and reintervention rate to be comparable to the overall population of TOF repairs.[41] Similarly, another meta-analysis identified 12 studies including almost 700 patients and compared the outcomes with or without monocusp after TAP, and again, found no difference in mortality.[117] Finally, 1 additional meta-analysis evaluated 8 studies and more than 500 patients and found no difference in mortality but reduced ICU LOS.[118] There is some overlap of studies included in these analyses. In summary, the entire collection of studies suggests that monocusp techniques, at least in the short-term, result in reduced pulmonary insufficiency and may improve short-term outcomes; and also centers with standardized techniques have had a better degree of long-term success (ie, longer duration to needing pulmonary valve replacement or less RV dilation). More information is needed to determine either patient-specific factors (which patients may benefit most) or technical nuances that can improve or increase the applications, if proven, to improve outcomes.

Techniques of leaflet delamination, and leaflet plasty or augmentation techniques also have been described as a mechanism to increase the number of patients who may benefit from the effects of a valve-sparing repair. Some demonstrate reasonable echocardiographic results, in terms of pulmonary insufficiency in the short-term.[101,105,119] One study using a technique of pulmonary valve leaflet augmentation, in addition to improved echocardiographic findings at discharge, showed reduced mechanical ventilation, reduced inotropic support, and a shorter ICU LOS.[115] Others have described a bicuspid valve created with polytetrafluoroethylene in 126 patients with good echocardiographic result even at midterm outcomes.[114] Finally, other small studies, have touted the right atrial appendage to be used as a neopulmonary valve with good echocardiographic results in the short-term, although without a difference in hospital course.[102,103]

Valve reconstruction likely has a learning curve and will initially result in a significantly longer bypass time.[103,106,118] Furthermore, some techniques have proven detrimental, increasing the need for reintervention.[120] Multiple meta-analyses have failed to show significant improvements in outcome,[117,118,121] although nuances in techniques are likely diluted or lost in a meta-analysis. Clearly, surgical technique is a crucial factor.[108] Although it is clear that multiple techniques can be used to reduce pulmonary regurgitation in the short-term and in some instances have shown to result in short-term clinical improvements, with rare exception, the long-term data demonstrate no difference in clinical outcome or echocardiographic function of the pulmonary valve or ventricular function. Therefore, it may be reasonable to consider 1 of these techniques for the potential short-term benefits and presumed long-term benefits, despite the lack of supportive data at this time. What cannot be ignored is the influence of attempting to overcome the challenge of creating an ideal pulmonary valve. So while attempting any of the above-described techniques (as long as it does not result in prolonged bypass or cross-clamp times or increased RVOT obstruction) is reasonable, the performance of a TAP without a reconstructive technique is also reasonable. Finally, an unknown element is whether these interventions lead to perhaps even greater sized TAP patch sizes or ventriculotomy incisions that may in turn lead to further adverse effects on the RV if their intended long-term function proves ineffective.

**When a transannular repair would otherwise be necessary, in the presence of an anomalous coronary artery crossing the RVOT, either a coronary artery sparing ventricular incision or an RV to pulmonary artery conduit may be reasonable approaches based on institutional expertise (Class: IIb, LOE: C-EO).**

An anomalous coronary artery crossing the infundibulum is still considered a risk factor by many.[122,123] Although some have reported equivalent outcomes, it requires important surgical consideration.[124,125] A coronary artery coursing across the infundibulum can be a large conal branch or an left anterior descending (LAD) from the right coronary artery (RCA), accessory LAD from the RCA, or rarely RCA from the LAD, circumflex from the RCA, RCA from the left coronary artery or left coronary artery from the RCA. Although an enlarged conal branch may not technically represent an anatomical variant, it is considered with anomalous coronary arteries as a vessel that ideally should be spared (especially if large; however, strict definitions of size have not been published but pragmatically a size that approaches at least 50% of primary coronary artery arising from the aorta), as it is in this document. When large conal branches are included, anomalous coronary arteries coursing over the RVOT occur in approximately 10%.[126-129]

A description of the various techniques to relieve RVOT obstruction in the setting of an anomalous coronary artery is beyond the scope of this document; but it may include a deviation of the ventriculotomy incisions (most common approach described among the following) when such is deemed necessary, undermining and elevating the crossing coronary artery for short distances to allow a limited incision or patch, thinning of the endocardium under the coronary artery via a transatrial approach, use of separate patches for the infundibulum and pulmonary artery leaving an island of intact infundibulum, and creation of a double outflow by using the anterior wall of the pulmonary artery

folded over the coronary artery and sutured to a right ventriculotomy.[124,125,130,131] Alternatively, an RV to pulmonary artery conduit can be placed. An RV to pulmonary artery conduit (ether in parallel with native valve or as a complete substitute) provides complete relief of the RVOT obstruction and can provide a functioning valve, even if only for the short-term and may extend the overall longevity of the conduit from stenosis perspective if used in parallel configuration (because there is less dependence on the conduit as the sole source of pulmonary blood flow). Use of any conduit necessitates future reinterventions. So while the risk of injury to a coronary artery may be minimized by conduit placement, the cumulative risk of the required future interventions must also be considered. Not surprisingly, reports have shown the use of an RV to pulmonary artery conduit to be an independent risk factor for reoperation.[125] It is worth noting that the proximity of a conduit to a crossing coronary artery may make future catheter-based interventions on a dysfunctional conduit difficult given the risk of coronary artery compression. Other approaches are not without risk, including the potential to damage a coronary artery or even complete coronary artery transection. Myocardial ischemia can occur even in the absence of transection, due to coronary artery distortion by a suture line placed too close to a coronary artery and requires awareness in the perioperative period. For these reasons, some suggest leaving at least 1 cm of myocardium between suture line and coronary artery.[132] Further, a sufficient margin from the coronary artery to allow for eventual valve or conduit placement should be kept in mind. In this latter context, there may be benefit to marking the path of the anomalous coronary artery with marking stitches or clips to allow for easy of visualization during subsequent surgical- or catheter-based interventions.

Few reports have been published comparing the differing approaches on the relief of the RVOT obstruction in the setting of a coronary artery coursing across the RVOT. However, it has been demonstrated that complete TOF repair without need for a conduit can be performed in the setting of an anomalous coronary artery without damaging the coronary artery.[124] Furthermore, in a single-institution retrospective review including 76 patients with an anomalous coronary artery, the RVOT obstruction was adequately relieved without the need for an RV to pulmonary artery conduit in 96%.[122] Finally, in a single-center retrospective review of 72 patients, 3 approaches were evaluated: tailored right ventriculotomy with RVOT patch, RV to pulmonary artery conduit, and transatrial-transpulmonary. The transatrial-transpulmonary approach was found to be superior as all had similar survival, but the transatrial-transpulmonary approach resulted in lower risk from RVOT obstruction and need for reoperation.[125]

In summary, no data have definitively shown that a specific approach to RVOT obstruction relief in the setting of an anomalous coronary artery is clearly superior. The approach may be individualized based on the location and size of the coronary artery, as well as the preference and expertise of the surgeon.

**After complete repair of TOF, intraoperative anatomic and hemodynamic assessment to confirm the adequacy of repair is highly recommended (Class: I, LOE: C-EO).**

As with any operation, at the conclusion of the procedure, the adequacy of repair must be evaluated. In the case of TOF, the post-bypass evaluation may include pressure measurement of the RV with respect to the left ventricle/aortic pressure in addition to transesophageal or on occasion epicardial echocardiography. Acceptable repairs are generally considered to have an RV pressure <70% to 80% of the aortic pressure, and details about that are included in the following section. During intraoperative postrepair echocardiography, evaluation for any residual lesions will primarily be focused on adequacy of VSD closure (as well as ensuring no injury to the aortic or tricuspid valves) and on any residual RVOT obstruction. The degree and location(s) of residual RVOT obstruction should be carefully delineated. Dynamic subvalvar obstruction caused by muscle bundles can improve with adequate filling of the ventricle, minimizing inotropes, and a slower heart rate. This type of dynamic obstruction often can also improve over time because the hypertrophied RV remodels once the primary obstruction has been improved. If there is a question about the location and degree of residual obstruction, direct needle measurement can be used to clarify. The specifics of what degree of obstruction warrants reintervention are discussed in the next section but are case-specific. The degree of pulmonary regurgitation is also evaluated.

Intraoperative assessment is also made for residual VSDs or any additional muscular VSDs that may not have been seen on initial imaging due to the large malalignment VSD. Residual VSDs considered hemodynamically significant include those >3 mm and/or with a Qp:Qs >1.5, the latter assessed by sampling blood simultaneously from the superior vena cava and the main PA while on minimal oxygen supplementation (eg, <40% inspired oxygen fraction). It is important to remember that the shunt calculation in a patient with TOF with an atrial-level shunt will also reflect this atrial-level shunt in addition to the residual VSD.[133] Small muscular VSDs commonly spontaneously close and do not necessarily require additional interventions. Other portions of the transesophageal echocardiogram that deserve attention include the direction of the shunt across the atrial septum (commonly a patent foramen ovale is left to aid perioperative recovery), as well as degree of tricuspid regurgitation. Significant tricuspid regurgitation in the setting of concomitant significant pulmonary

regurgitation (whether that be after a TAP or a valve-sparing repair) is generally poorly tolerated in an infant with TOF, and tricuspid valve repair should be considered.

**Significant residual fixed anatomic obstruction should prompt consideration for immediate reintervention (Class: IIa, LOE: B-NR).**

Among the goals of complete repair of TOF is adequate relief of RVOT obstruction. The determination of what constitutes adequate relief or a significant fixed residual obstruction is not clear. Various institutions and surgeons often have thresholds in their practice for which they would re-intervene (commonly by performing a TAP if the issue is fixed obstruction at the level of the pulmonary valve annulus). Although such thresholds are frequently reported in the methods portions of various articles, the evidence supporting such practices is limited. In the study by Hennein and colleagues,[134] multiple risk factors for reintervention were identified including intraoperative RV-to-left ventricle pressure ratio >0.75, left pulmonary artery stenosis of 15 mm Hg, and RVOT obstruction of 40 mm Hg at discharge. Examples of studies specifying parameters include Bove and colleagues[87] who considered RV-to-left ventricle pressure ratio <0.80 acceptable and reported otherwise to be associated with reoperation. In the study of Lozano-Balseiro and colleagues,[89] a gradient >30 mm Hg in the RVOT was used as a threshold for going back on bypass and performing a TAP. The threshold for going back on pump and performing a TAP in the study of Choi and colleagues[95] was RV-to-left ventricle pressure ratio >0.80 or a maximum instantaneous RVOT gradient of 40 mm Hg. In the study of Borodinova and colleagues[98] repair was considered adequate if RV pressure was less than left ventricle pressure and $z$ score >–3. The analysis by Boni and colleagues[135] included patients with RV pressure >70% of LV pressure postrepair and found that the ratio of RV pressure relative to left ventricle pressure decreased by 28% for those with RV pressure >70% of left ventricle pressure, whereas those with RV pressure <70% decreased by 12% after a median of 33 months.[135]

Although these studies provide a cutoff of what constitutes a need for reintervention in the operating room and an indication of unlikely significant resolution or improvement postoperatively, the pressure ratios of 70% to 80% may not represent what would be considered an ideal TOF repair. Many of the authors, as well as reviewers, believed in general that RV pressures of less-than-or-equal-to half systemic and an RVOT gradient <30 to 40 mm Hg are often attainable and desirable; but this must be considered in the context of the individual case and what is surgically attainable. For example, a persistent obstruction from a residual muscle bundle may be worth reintervention despite an RV-to-left-ventricle pressure ratio <70%, whereas in other instances with a hyperdynamic RVOT and acceptable anatomic result, modification of intraoperative hemodynamic parameters may be all that is necessary. The presence of a significant collateral burden should be considered that may elevate the RV-to-left-ventricle pressure ratio. Direct pressure measurements may be useful to quantify any residual obstruction and guide the need for reintervention. The preceding are predicated on individual case scenarios and assessment of specific anatomic factors in the context of intraoperative hemodynamic parameters. Other studies focused on this as a clinical question, rather than a predetermined value used to guide the need for reintervention, that may help to improve decision making and avoid a TAP when unnecessary or the need for reintervention to relieve recurrent RVOT obstruction when a TAP should have been performed originally.

### Atrial Septal Communication

A number of other potential surgical considerations in the patient with TOF are beyond the broader strokes considered within the scope of this work. For instance, it has been suggested that in patients with associated deficiency of infundibular septum, wherein the VSD is subarterial or doubly committed, there is a higher risk for postoperative RVOT obstruction and hence, a lower threshold to consider TAP.[136] Other studies have discussed the importance of dividing the PDA or ligamentum arteriosum in patients requiring a TAP to avoid future distortion of RVOT and possible kinking of the left pulmonary artery over time.[137] There are currently insufficient data for these potentially important topics to be able to make definitive statements.

Perhaps the most common additional consideration pertains to the associated atrial septal defect(s). Keeping an interatrial communication potentially allows for maintenance of cardiac output at the expense of desaturation. A small defect will likely close on its own with time. A larger defect will require closure, either complete or with a fenestration, to minimize the need for reintervention and perhaps reduce the risk of reoperative surgery. The most common practice is to keep an interatrial communication for any symptomatic neonate because they are likely to have the most severely restrictive RV physiology. In a patient who presents asymptomatic for elective repair, any interatrial connection can generally be closed. Because this practice pattern is quite pervasive, very little literature exist about this topic. In a retrospective single-institution study, no difference was noted in those patients where the atrial communication was kept compared with when it was completely closed. In that study, although the authors performed propensity matching, there likely remains a potential for selection bias.[138] The lack of data does not allow for a statement, rather just to report the most common practice as it is performed by the experts on this panel. That said, there was

not enough support, or certainty to allow this to rise to a recommendation with C-EO level of evidence or even a Best Practices Statement.

### Future Directions

Despite decades of experience in treating patients with TOF, controversy about optimal management approaches persists, with substantial practice variations and many opportunities for further investigation to improve care. As noted throughout this article, most data on the influence of surgical strategy emerge from single-institution, retrospective analyses that are often based on small patient populations, which makes it difficult to translate to the general TOF population. Even existing registry data published by Society of Thoracic Surgeons or other similar entities often omit many crucial surgical and clinical variables that can potentially influence outcomes; hopefully, this situation will be mitigated with ongoing database upgrades. Ultimately, only with dedicated multicenter and multidisciplinary collaborations will many questions be addressed. Additionally, longer-term studies are needed to not only understand the influence of various treatment algorithms on cardiovascular outcomes and performance, but also other key health measures such as neurocognitive development (eg, effect of 1 vs 2 exposures to volatile anesthetics and the influence of relative hypoxia during infancy), as well as influence on the inevitable adult congenital heart disease experience of the patients and their long-term quality of life. Advances in cardiac surgery, cardiology, critical care, and radiology are having, and will continue to have, tremendous influence on the future of patients with TOF and will undoubtedly inform their future care as well as research insights. We anticipate catheter-based interventions will gain greater and broader popularity and application, and perhaps many of the lessons learned during the BTT shunt era will also bear on these interventions (eg, risks of overcirculation with too large of a PDA stent and risks of thrombosis). With increased utility of RVOT stenting, beyond influence on valve preservation (not feasible), the surgeon will have to become more comfortable working around the stent materials, avoiding possible injury to the TV apparatus, the underlying septal perforator, and the native pulmonary artery as well as technical modifications to deal with the altered pulmonary artery or residual stent materials. Surgeons need to continue to evaluate the criteria for when a valve-sparing approach is most likely to be successful, the ideal pulmonary valve reconstructive technique (and material), and how all of these influence outcomes long-term.

## CONCLUSIONS

Our work provides an expert consensus document for the management of TOF. It should serve as a basic framework about the approach to the majority of patients with TOF. When applied to individual patients, due to the heterogeneous nature of the defect and institutional experience and expertise, some treatment strategies may seem inconsistent with this document but exist well within the standard of care. Future large, long-term, multi-institutional, collaborative studies will help guide treatment strategies.

### Webcast

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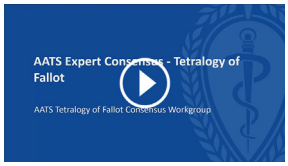


### Conflict of Interest Statement

The authors disclose relationships with industry and other entities in Appendix 1 and 2.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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**Key Words:** tetralogy of Fallot, guidelines, management, treatment, high-risk, surgical approach, palliation, PDA stent, RVOT stent, complete repair, annulus preservation, pulmonary valve reconstruction, postoperative assessment

## APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES

| Witing Group Memeber | Primary Affiliation | Location | Grants or contracts | Consulting fees | Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events | Payment for expert testimony | Support for attending meetings and/or travel | Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid | Stock or stock options | All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution. |
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| David L.S. Morales, MD | Cincinnati Children's Hospital | Cincinnati, OH, USA | x | x | x | x | x | | | All unrelated to subject of manuscript. RO 1: I am the PI I am a consultant for below companies Abbott, Inc Berlin Heart Inc Syncardia Xeltis Cormatrix Masa Valve |
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| Jonathan Chen | Children's Hospital of Philadelphia | Philadelphia, PA, USA | | x | | | | | | Medtronic, WL Gore |

## APPENDIX 3.

A librarian used a mix of controlled vocabulary terms and free text terms to create individual search hedges for each of the following concepts; aortopulmonary connection, balloon pulmonary valvuloplasty, complete repair surgery, elective surgery, high risk infants, long-term outcomes, neonate/infant, tetralogy of Fallot (TOF)-related outcomes, palliative intervention/procedure, patent ductus arteriosus (PDA) stent, pulmonary artery size, pulmonary stenosis, pulmonary valve preservation, RVOT stent/patch, Right ventricle-to-pulmonary artery conduit (RV-PA) conduit, standard risk, surgical palliation, symptoms of TOF, systemic pulmonary shunt, systemic-pulmonary arterial connection Blalock-Taussig (BT) shunt, TOF, timing/time to treat, trans atrial/pulmonary versus trans ventricular, transannular patch, valve sparing, and young child. These concept hedges were then combined and searched in Embase to answer pertinent research questions about TOF and the results were used in this article.

Here is an example question and the resulting literature search for 1 of the focused research questions:

*What literature is available on TOF AND ('palliative procedure' transcatheter palliation, PDA stent, RVOT stent) OR surgical palliation OR (systemic-pulmonary shunt, limited RVOT patch OR RV-PA conduit without VSD closure) AND outcomes?*

*('fallot tetralogy'/exp OR ((tetralogy NEAR/4 fallot):ti,ab,kw) OR 'tetralogy of fallot surgery'/exp OR 'tetralogy of fallot complications'/exp OR 'tetralogy of fallot case reports'/exp OR 'tetralogy of fallot diagnosis'/exp OR 'tetralogy of fallot pathology'/exp) AND ('palliative therapy'/exp OR palliative:ti,ab,kw OR palliation:ti,ab,kw OR ('stent'/exp AND 'patent ductus arteriosus'/exp) OR 'patent ductus arteriosus stent*':ti,ab,kw OR 'pda stent*':ti,ab,kw OR 'patent ductus arteriosis stent*':ti,ab,kw OR 'persistent ductus arteriosus stent*':ti,ab,kw OR ('heart right ventricle outflow tract'/exp AND 'stent'/exp) OR ((('heart right ventricle outflow tract' OR rvot OR 'arterial cone' OR 'artery cone' OR 'cardiac infundibulum' OR 'heart infundibulum' OR 'right heart ventricle outflow tract' OR 'right outflow tract' OR 'right ventricle infundibulum' OR 'right ventricular infundibulum' OR 'right ventricular outflow tract') NEAR/2 stent*):ti,ab,kw) OR 'surgical palliation':ti,ab,kw OR 'palliative surger*':ti,ab,kw OR 'systemic pulmonary shunt'/exp OR 'blalock taussig shunt'/exp OR ((('systemic pulmonary' OR 'systemic to pulmonary' OR 'systemico-pulmonary' OR blalock OR taussig OR 'subclavian pulmonary') NEAR/3 (shunt* OR anastomoses OR anastomosis OR operation* OR procedure)):ti,ab,kw) OR 'right ventricle to pulmonary artery conduit'/exp OR (('right ventricle to pulmonary artery' NEAR/2 (bypass OR conduit* OR connection* OR shunt*)):ti,ab,kw) OR (('rv-pa' NEAR/2 (bypass OR conduit* OR connection* OR shunt*)):ti,ab,kw) OR (('right ventricle pulmonary artery' NEAR/2 (bypass OR conduit* OR connection* OR shunt*)):ti,ab,kw) OR ((sano NEAR/2 (operation* OR procedure* OR shunt*)):ti,ab,kw)) AND ('survival'/exp OR 'survival rate'/exp OR survival:ti,ab,kw OR 'mortality'/exp OR mortality:ti,ab,kw OR ((('pulmonary artery' OR 'pulmonary valve') NEAR/3 (size OR growth)):ti,ab,kw) OR 'z score'/exp OR 'z-score':ti,ab,kw OR 'z score':ti,ab,kw OR (((reintervantion OR reoperation) NEAR/3 rate*):ti,ab,kw) OR 'quality of life'/exp OR 'quality of life':ti,ab,kw OR hrqol:ti,ab,kw OR qol:ti,ab,kw OR 'outcomes'/exp) AND.2006–2021/py AND ('article'/it NOT 'review'/it)*