Diagnosis and Management of Valvular Heart Disease

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KEYWORDS
\begin{itemize}
  \item Valvular heart disease
  \item Aortic stenosis
  \item Aortic regurgitation
  \item Mitral stenosis
  \item Mitral regurgitation
  \item Right-sided valvular disease
  \item Endocarditis prophylaxis
\end{itemize}

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Patients with known or suspected valvular heart disease should be carefully questioned to assess for the presence of symptoms such as heart failure, angina, syncope, or exercise limitations.
2. Careful auscultation should be performed to identify murmurs and other findings that may point toward a particular valvular disorder.
3. The primary diagnostic imaging modality for valvular heart disease is transthoracic echocardiography.
4. Echocardiography should assess the severity of the valvular disease based on defined criteria for each type of valvular disease.
5. Indications for surgical intervention vary depending on the valve involved, but in general any patient with severe valvular disease on echocardiography or symptoms related to their valvular disease should be referred for cardiology and/or surgical evaluation.
6. Transcatheter aortic valve replacement and percutaneous mitral valve repair are now available as minimally invasive strategies, and can be considered for patients thought to be at high surgical risk.

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7. Right-sided valvular disease is often congenital, rheumatic, or secondary to another process. Less clear guidelines are available for the management of right-sided lesions.
8. Endocarditis prophylaxis for valvular disease is now only recommended for patients with prosthetic material related to valve replacement/repair or a prior history of infective endocarditis.

When should an echocardiogram be ordered in a patient with a murmur?

Cardiac murmurs are a relatively common finding on physical examination. Although many are benign and warrant no further evaluation, others can be important clues to the patient’s condition and require further evaluation. Assessment of a murmur begins with a thorough history and physical examination. Symptoms of heart failure, syncope, or angina should be elicited. Signs and symptoms of endocarditis should also be pursued. Examination of the murmur should assess timing in the cardiac cycle, location, radiation, intensity, and configuration (crescendo, decrescendo, and so forth).

According to the American College of Cardiology/American Heart Association (ACC/AHA), Class I indications for echocardiography include:

1. Diastolic, continuous, holosystolic, and late systolic murmurs
2. Murmurs associated with ejection clicks
3. Murmurs that radiate to the neck or back
4. Grade 3 or louder midpeaking systolic murmurs
5. Signs of symptoms of heart failure, myocardial ischemia, syncope, thromboembolism, endocarditis, or other structural heart disease

What are the stages of valvular heart disease?

The 2014 ACC/AHA update introduced a new classification scheme to outline the progression of patients with valvular heart disease. These criteria are related to, but distinct from echocardiographic criteria for severity of the valve disorder.

Stage A: Patients at risk for the development of valvular heart disease
Stage B: Patients with valvular heart disease that is not yet symptomatic or severe. Severity of valvular heart disease depends on a variety of parameters specific to the valve in question
Stage C: Patients meet criteria for severe valvular heart disease but are asymptomatic
Stage D: Patients with symptoms from valvular heart disease

Depending on the valve in question, each stage may have subcategories (C1, C2, D1, D2, and so forth).

Aortic Stenosis

What are the causes of valvular aortic stenosis?

Most cases of aortic stenosis (AS) in Western countries are due to calcific valvular disease, accounting for more than 90% of cases in patients older than 75 years. In younger patients, AS is related to calcification of congenitally abnormal valves,
including bicuspid and unicuspid valves, or rheumatic heart disease. Although the prevalence of bicuspid aortic valves is less than 1%, they make up half of the aortic valve replacements (AVRs) performed. Worldwide, rheumatic heart disease is the most common cause of AS, but is very rare in Western countries.

**What are the important signs and symptoms in a patient with known or suspected AS?**

The most significant manifestations include angina, syncope, and heart failure, for which surgical intervention is indicated. Physical examination will frequently demonstrate a harsh, crescendo-decrescendo systolic murmur at the cardiac base, with radiation to the carotids. Paradoxic splitting of the second heart sound may be present, owing to delayed aortic valve closure. Examination of the carotid pulsation may demonstrate a slow and delayed carotid upstroke, called pulsus parvus et tardus (Table 1).

**What are the diagnostic methods of evaluation for AS?**

Doppler echocardiography remains the major imaging modality for the diagnosis and evaluation of AS. Aortic valve area (AVA), peak and mean gradients, and peak aortic jet velocity can be measured to categorize the severity of the stenotic valve. Gross valvular opening, leaflet function, and the degree of calcification can also be assessed, along with left ventricular (LV) wall thickness and ejection fraction (EF).

If there are discrepancies in measurements, other modalities are available for clarification or confirmation. Multidetector electrocardiogram-gated computed tomography is more accurate than echocardiography in estimating the degree of calcification, but is considered second line because of radiation and the need for intravenous contrast. Cardiac magnetic resonance (CMR) imaging is superior to echocardiography in the assessment of systolic function and ventricular volume, and can visualize myocardial fibrosis, but is not readily available. Left heart catheterization is indicated when there is discordance between noninvasive testing and clinical assessment. Concurrent evaluation for coronary artery disease can also be performed.

Exercise testing can be used in asymptomatic patients with severe AS to confirm the absence of symptoms, but should be avoided in symptomatic patients.

**How is severity of AS defined by echocardiography?**

The 2014 guidelines provide definitions for mild, moderate, severe, and very severe AS. Echocardiography measurements of maximum aortic velocity, AVA, and mean pressure gradient across the valve help define the severity of AS:

1. **Mild:** Mean pressure gradient less than 20 mm Hg, or maximum aortic velocity 2 to 2.9 m/s
2. **Moderate:** Mean pressure gradient 20 to 39 mm Hg, maximum aortic velocity 3 to 3.9 m/s
3. **Severe:** Valve area 1 cm² or less, mean pressure gradient 40 mm Hg or greater, maximum aortic velocity 4 m/s or greater
4. **Very severe:** Mean pressure gradient 60 mm Hg or greater, maximum aortic velocity 5 m/s or greater

In addition, low-flow/low-gradient AS is defined as an AVA 1 cm² or less with maximum aortic velocity less than 4 m/s or mean pressure gradient less than 40 mm Hg.
When should a patient be referred for surgical intervention?

The decision to pursue surgery for AS should be interdisciplinary, with the input of cardiologists and surgeons. The major indication for AVR is the development of symptomatic severe AS (Table 2). Development of angina, syncope, or heart failure portends 50% mortality at 5, 3, and 2 years, respectively. The other evidence-based indications for valve replacement include those patients with severe AS who will be undergoing coronary artery bypass graft (CABG) surgery, aortic or other
The following are Class I indications for surgical intervention:

1. Severe high-gradient AS with symptoms based on history or with exercise testing
2. Severe AS with LVEF less than 50% in asymptomatic patients
3. Presence of severe AS in patients undergoing cardiac surgery for other reasons

Table 2

<table>
<thead>
<tr>
<th>Class I indications for valvotomy, replacement, or repair</th>
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<tbody>
<tr>
<td>Aortic stenosis (replacement only)***</td>
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<tr>
<td>1. Symptomatic patients with severe AS (LOE B)</td>
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<tr>
<td>2. Severe AS undergoing other cardiac surgery (LOE B)</td>
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<tr>
<td>3. Asymptomatic patients with severe AS and LVEF &lt;50% (LOE B)</td>
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<td>Surgical replacement</td>
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<td>1. Patients who meet indication for AVR and have low or intermediate surgical risk (LOE A)</td>
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<td>TAVR</td>
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<tr>
<td>1. Patients who meet indication for AVR but have prohibitive risk for surgery and predicted survival &gt;12 mo (LOE B)</td>
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<td>Aortic regurgitation (replacement or repair)</td>
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<td>1. Symptomatic patients with severe AR (LOE B)</td>
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<tr>
<td>2. Chronic severe AR and LVEF &lt;50% (LOE B)</td>
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<tr>
<td>3. Chronic severe AR and undergoing other cardiac surgery (LOE C)</td>
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<td>Mitral stenosis (percutaneous balloon valvotomy)***</td>
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<tr>
<td>1. Symptomatic patients with severe MS (LOE A)</td>
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<tr>
<td>Mitral stenosis (repair if possible)</td>
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<td>1. Symptomatic patient with moderate or severe MS when percutaneous balloon valvotomy is not available or contraindicated (LOE B)</td>
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<td>2. Moderate to severe MS with concomitant moderate to severe MR (LOE C)</td>
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<tr>
<td>Mitral regurgitation (chronic primary) (repair if possible)</td>
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<tr>
<td>1. Symptomatic patient with chronic severe primary MR and LVEF &gt;30% (LOE B)</td>
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<tr>
<td>2. Asymptomatic patients with LVEF 30%–60% and/or LV end-systolic dimension 40 mm or greater (LOE B)</td>
</tr>
<tr>
<td>3. Patients with severe MR undergoing cardiac surgery for other indications (LOE B)</td>
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Abbreviations: AS, aortic stenosis; AVR, aortic valve replacement; LOE, level of evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; TAVR, transcatheter aortic valve replacement.

*a* Aortic balloon valvotomy does not have Class I indications.

*b* Percutaneous mitral balloon valvotomy requires favorable valve morphology for the intervention and absence of left atrial thrombus or moderate to severe mitral regurgitation.


Valvular surgery, and those with severe AS with an EF of less than 50%, even in the absence of symptoms.\(^1,6\)

In asymptomatic patients with severe AS, there is significant controversy as to the benefit of AVR. Exercise stress testing can identify those patients at highest risk for the development of symptomatic AS. Dyspnea, chest pain, or dizziness during exercise stress testing predicts the development of symptomatic severe AS within 12 months.\(^8\)

As such, the 2012 European Society of Cardiology guidelines include symptoms attributable to valvular abnormality during exercise testing as a Class I indication for valve replacement, whereas the ACC/AHA guidelines label this a Class IIb indication\(^1,6\).

To summarize, the following are Class I indications for surgical intervention\(^2\):

1. Severe high-gradient AS with symptoms based on history or with exercise testing
2. Severe AS with LVEF less than 50% in asymptomatic patients
3. Presence of severe AS in patients undergoing cardiac surgery for other reasons
Several Class II recommendations also exist, and can be found in Table 7 of the 2014 ACC/AHA guidelines.2

How are patients with low-flow, low-gradient severe AS managed?

Low-flow, low-gradient (LF-LG) AS refers to 2 groups of patients. The first includes individuals with severe AS, but with LF-LG resulting from a depressed EF.9 True severe AS can be distinguished from pseudosevere AS with low-dose dobutamine stress echocardiography (DSE). Patients with true severe AS will show a minimal change in aortic valve area of less than 0.2 cm$^2$ but with a significant increase in mean gradient to more than 40 mm Hg,10 whereas those with pseudosevere AS will have a more significant increase in AVA ($\geq 0.3$ cm$^2$) but with a mean gradient remaining less than 40 mm Hg.9

DSE testing is also useful for prognosticating operative risk of surgical valve replacement. Patients who undergo DSE who have an increase in stroke volume less than 20% are labeled as having no LV flow reserve9 and have an operative mortality 4 to 5 times higher than those with LV flow reserve. Because operative mortality is high in patients without LV flow reserve, transcatheter AVR may be a more appropriate option.

The second type of LF-LG severe AS occurs in individuals with a preserved EF, and is thought to result from the development of restrictive LV physiology in the setting of marked thickening of the LV wall leading to a smaller cavity, reduced LV compliance and filling, and a decreased stroke volume.9 Those patients with this “paradoxical” LF-LG severe AS with preserved EF who undergo AVR have a 50% survival nearly twice as long as patients treated medically.9 Based on this, AVR is a Class IIa recommendation for paradoxical LF-LG severe AS even with preserved LVEF, if the stroke volume index is less than 35 mL/m$^2$ and the valve area index is 0.6 cm$^2$/m$^2$ or less.

Which medical treatment options are available for AS?

There is no medical therapy that has been proved to slow the progression of AS. Although the process of calcific AS mimics atherosclerosis, statin therapy has not been shown to slow progression.6

Concomitant hypertension should be carefully treated. Optimal agents are not known because of a lack of evidence; however small studies of angiotensin-converting enzyme (ACE) inhibitors suggest that this class is safe and effective in patients with mild to moderate AS.11 Diuretics for hypertension management are generally avoided owing to concerns that a noncompliant left ventricle is preload dependent. No guidelines exist regarding the ideal regimen for the management of hypertension in AS.

If heart failure is present then standard heart failure medications can be used, but should be cautiously initiated. There may be a precipitous drop in blood pressure in the setting of vasodilator therapy, owing to the inability to generate increased stroke volume.6

Echocardiography should be repeated every 3 to 5 years in mild disease, 1 to 2 years in moderate AS, and every 6 to 12 months in severe disease.2

What are the surgical treatment options available for symptomatic severe AS?

Surgical AVR is the definitive treatment for symptomatic severe AS. There are several valve replacement options. Bioprosthesis valves do not require indefinite postoperative anticoagulation; however, they do not have the longevity of mechanical valves. Of
note, bioprosthetic valve longevity is longer in older patients (10–20 years), making it an ideal option for patients older than 60 years without another long-term indication for warfarin. Mechanical valves have better durability, and are thus generally preferred in patients younger than 60 or in patients already requiring long-term anticoagulation. Transcatheter AVR (TAVR) is a minimally invasive option available for those patients deemed at high risk for surgery, estimated to be more than 30% of patients with symptomatic severe AS. The procedure is completed via transfemoral or transapical approaches (Fig. 1). Major clinical contraindications to TAVR include an estimated life expectancy of less than 1 year, additional significant valvular disease, and a quality of life that is unlikely to improve because of other comorbidities. In high-risk surgical patients that do not have contraindications, TAVR is superior to standard medical therapy, with a 2-year survival of 56.7% versus 32%. One-year survival after TAVR ranges between 60% and 80%. At present there are no longer-term outcomes data available for patients who have received TAVR.

Fig. 1. Severe, calcific aortic stenosis in a 63-year-old woman with peripheral vascular disease undergoing transcatheter aortic valve replacement (TAVR). (A) Two-dimensional (2D) transesophageal echocardiography with biplane views across the aortic valve, showing a severely stenotic tricuspid aortic valve (arrow). Aortic valve area was calculated to be 0.44 cm² with a mean gradient of 49 mm Hg. (B) Three-dimensional (3D) transesophageal echocardiography showing the narrowed orifice of the aortic valve (arrow) with heavily calcified leaflets. (C) Deployment of a 26-mm Sapien transcatheter aortic valve (Edwards Lifesciences, Irvine, CA) across the aortic valve. The radiopaque stainless-steel frame of the valve is seen (thick arrow) with expansion of the valvuloplasty balloon (thin arrow). (D) 3D Transesophageal echocardiography showing the 26-mm Sapien valve post TAVR (arrow). The resultant aortic valve area was 1.72 cm² with a mean gradient of 9 mm Hg. AoV, aortic valve; LA, left atrium; LCC, left coronary cusp; NCC, noncoronary cusp; RCC, right coronary cusp; RV, right ventricle.
Based on this knowledge, guidelines recommend TAVR in patients with prohibitive surgical risk and a life expectancy greater than 12 months or with high surgical risk. In patients deemed low to intermediate surgical risk, surgical AVR is recommended.²

**How should AS be managed in the preoperative evaluation of patients for noncardiac surgery?**

Preoperative evaluation is beyond the scope of this article, but AS deserves special mention because severe AS poses the greatest risk for complications among the different types of valvular heart disease. In one study of 108 patients with moderate or severe AS, the incidence of perioperative mortality or nonfatal myocardial infarction was 7 times greater than in controls.¹⁴ For this reason, severe or symptomatic AS should be addressed with AVR if the surgery can be safely delayed. In patients who are not candidates for valve replacement, percutaneous balloon valvuloplasty can be considered.¹⁵

**AORTIC REGURGITATION**

**What are the commonest causes of aortic valve regurgitation?**

There are several common causes of aortic regurgitation (AR): idiopathic dilatation of the aortic root, congenital abnormalities of the aortic valve (such as bicuspid valves [Fig. 2]), calcific degeneration, rheumatic disease, infective endocarditis, systemic hypertension, myxomatous degeneration, dissection of the ascending aorta, and Marfan syndrome. Less common causes include traumatic injuries to the aortic valve, ankylosing spondylitis, syphilitic aortitis, rheumatoid arthritis, osteogenesis imperfecta, giant-cell aortitis, Ehlers-Danlos syndrome, Reiter syndrome, discrete subaortic stenosis, and ventricular septal defects with prolapse of an aortic cusp. Anorectic drugs have also been reported recently to cause AR.

Most of these causes result in a long asymptomatic phase lasting many years with chronic dilatation of the left ventricle. Others, such as aortic dissection, infective endocarditis, and trauma, can cause sudden elevations of LV pressure, pulmonary edema, and cardiogenic shock.

**Fig. 2.** Transesophageal echocardiography findings of bicuspid aortic valve with eccentric moderate aortic regurgitation. (A) Short-axis view across the aortic valve. Two commissures are identified in systole (arrows), which identify the aortic valve as having bicuspid morphology. (B) Three-chamber view showing very eccentric moderate aortic regurgitation aimed directly toward the anterior mitral valve leaflet (arrow). AoV, aortic valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve.
**What are the clinical manifestations of chronic AR?**

Chronic severe AR imposes a volume load on the left ventricle, resulting in an enlarged end-diastolic volume and eccentric hypertrophy. Initially, when LV compliance remains normal, the excessive volume is accommodated without an increase in filling pressures. In most patients, this eventually leads to impaired LV contractility, and patients often develop dyspnea. Owing to a diminished coronary flow reserve in the hypertrophied myocardium, patients may also experience exertional angina. It is possible for patients to remain asymptomatic until severe LV dysfunction has developed. In fact, because left atrial pressure increases late in the course of the disease, symptoms (including dyspnea and angina) usually develop slowly.\(^16\)

The variables associated with higher risk of future symptoms, death, or LV dysfunction are age, LV end-systolic and end-diastolic dimension (or volume), and the change in LVEF during exercise.

**What are the principal clinical examination findings in AR?**

The diagnosis of chronic severe AR can usually be made on the grounds an early decrescendo diastolic murmur, displaced LV impulse, wide pulse pressure, and characteristic peripheral findings that reflect wide pulse pressure (described below). A third heart sound (S3) is often heard as a manifestation of the volume load, and is not necessarily an indication of heart failure. An Austin-Flint murmur is a mid-diastolic rumble that is thought to be the result of mitral valve leaflet displacement in tandem with turbulent mixing of antegrade mitral flow and retrograde aortic flow, and is a specific finding for severe AR (see Table 1).\(^17,18\)

In many patients with more mild to moderate AR, the physical examination will identify the regurgitant lesion but will be less accurate in determining its severity. When the diastolic murmur of AR is louder in the third and fourth right intercostal spaces than in the third and fourth left intercostal spaces, the AR likely results from aortic root dilatation rather than a deformity of the leaflets alone.\(^19\)

The various peripheral hemodynamic signs traditionally associated with AR\(^20\) include the de Musset head-bobbing sign, a wide pulse pressure greater than 50 mm Hg, the brachial-popliteal pulse gradient (Hill sign), Duroziez femoral murmur, the femoral pistol-shot murmur, and Corrigan water hammer pulse. Other, less well studied peripheral hemodynamic signs include the Mayne sign (a decrease in diastolic blood pressure of 15 mm Hg when the arm is held above the head compared with when the arm is held at the level of the heart), Quinke capillary pulsation, Muller pulsatile uvula, and Rosenbach liver pulsation. The reader is referred to an excellent review of the clinical examination findings in patients with AR published elsewhere.\(^20\)

**What is the role of echocardiography/imaging in patients with suspected AR?**

The following are all deemed Class I indications for the use of echocardiography in AR\(^1\):

1. To confirm the presence and severity of acute or chronic AR (level of evidence: B)
2. For diagnosis and assessment of the cause of chronic AR, including valve morphology and aortic root size and morphology, and for assessment of LV hypertrophy, dimension (or volume), and systolic function (level of evidence: B)
3. In patients with an enlarged aortic root, to assess regurgitation and the severity of aortic dilatation (level of evidence: B)
4. For the periodic reevaluation of LV size and function in asymptomatic patients with severe AR (level of evidence: B)
5. To reevaluate mild, moderate, or severe AR in patients with new or changing symptoms (level of evidence: B)

If the echocardiogram is suboptimal in assessing LV function, radionuclide angiography or CMR imaging should be used in asymptomatic patients to measure LVEF and LV volumes at rest.

If the echocardiogram is suboptimal in assessing LV function or severity of AR in patients who are symptomatic on initial evaluation, it is reasonable to proceed directly to transesophageal echocardiography or cardiac catheterization and angiography.

In addition to accurate assessment of LV volume, mass, wall thickness, and systolic function, CMR imaging may be used to quantify the severity of valvular regurgitation.

Serial exercise treadmill testing is not recommended routinely in asymptomatic patients with preserved systolic function; however, exercise testing may be useful to assess functional capacity and symptomatic responses in patients with equivocal changes in symptomatic status.

**How often should echocardiography be repeated in patients with various AR severities?**

After an initial echo consistent with moderate to severe AR, a repeat physical examination and echocardiography should be performed within 2 to 3 months to ensure that a rapidly progressive subacute process is not present.

Repeat echocardiograms are recommended in 3 clinical scenarios:

1. When the patient has onset of symptoms
2. When there is an equivocal history of changing symptoms or exercise tolerance
3. When clinical findings suggest worsening regurgitation or progressive LV dilatation

In general the following guidelines can be used:

1. Mild: Patients should be seen annually with echocardiograms every 3 to 5 years
2. Moderate: Patients should be seen every 1 to 2 months
3. Severe: If patients are stable and remain asymptomatic with LVEF greater than 50% and normal LV dimensions (LV end-diastolic dimension <60 mm, LV end-systolic dimension <45 mm), physical examination and echocardiograms should be repeated every 6 to 12 months. If the left ventricle shows signs of dilating, echocardiography should be performed more frequently.

**How is AR graded on echocardiography?**

Several Doppler ultrasonography indexes have been developed for the assessment of valvular regurgitation including color, pulsed-wave (PW), and continuous-wave (CW) Doppler.

Color Doppler provides near real-time visualization of aortic valve regurgitant jet related to LV outflow tract (LVOT), width of vena contracta, regurgitant volume (RVol), regurgitant fraction (RF), and effective regurgitant orifice (ERO) area. Each of these variables has independent diagnostic utility for quantifying underlying regurgitation severity.

Several commonly used methods for AR assessment have been developed, including PISA (proximal isovelocity surface area), continuity equation, and spectral Doppler signals (CW and PW). Hemodynamic factors such as systemic blood pressure, heart rate, and intravascular volume may alter the aforementioned measurements and AR severity, and should be taken into account on serial examinations.
Some of the key parameters defining mild, moderate, and severe AR are:

1. Mild: Jet width less than 25% of LVOT, width of vena contracta less than 0.3 cm, RVol less than 30 mL/beat, RF less than 30%, ERO area less than 0.10 cm²
2. Moderate: Jet width 25% to 64% of LVOT, width of vena contracta 0.3 to 0.6 cm, RVol 30 to 59 mL/beat, RF 30% to 49%, ERO area 0.10 to 0.29 cm²
3. Severe: Jet width greater than 65% of LVOT, width of vena contracta greater than 0.6 cm, RVol greater than 60 mL/beat, RF 50% or greater, ERO area 0.3 cm² or greater

What constitutes contemporary medical therapy for AR?

Mild or moderate AR is usually managed conservatively, unless dilatation of the ascending aorta justifies surgery. Severe AR can be managed conservatively if the patient remains asymptomatic, and has normal LV dimensions and normal systolic function (LVEF>50%).

Controlled trials indicate that vasodilators such as hydralazine, nifedipine, and ACE inhibitors reduce LV wall stress and volumes. In the 2014 guidelines, a Class I recommendation (level of evidence B) is made for treatment of hypertension (systolic blood pressure>140 mm Hg) for patients with chronic AR (stages B and C), preferably with dihydropyridine calcium-channel blockers or ACE inhibitors/angiotensin-receptor blockers (ARBs).

A Class IIa recommendation is made for ACE inhibitors/ARBs and β-blockers, and these are considered reasonable in patients with severe AR who have symptoms and/or LV dysfunction (stages C2 and D) when surgery is not performed because of comorbidities.

There are no data to support the long-term use of digoxin, diuretics, nitrates, or positive inotropic agents in asymptomatic patients, and no data with regard to any drug in patients with mild or moderate AR.

Which clinical settings warrant vasodilator therapy for severe AR?

There are 3 potential clinical scenarios for the use of vasodilatory agents in chronic severe AR:

- Long-term treatment of patients with severe AR who have symptoms and/or LV dysfunction who are considered at very high surgical risk, or candidates who are inoperable because of additional cardiac or noncardiac factors
- Improvement in the hemodynamic profile of patients with symptoms of severe heart failure and severe LV dysfunction with short-term vasodilator therapy before proceeding with AVR; vasodilatory agents with negative inotropic effects should be avoided
- Prolongation of the compensated phase of asymptomatic patients who have volume-loaded left ventricles but normal systolic function

Vasodilator therapy is not recommended for asymptomatic patients with mild or moderate AR and normal LV function in the absence of systemic hypertension, because these patients have an excellent outcome even without therapy.

When should patients undergo AVR?

Patients who are treated medically may subsequently require surgery because of progression of aortic regurgitation (which occurs at a rate of 5% to 6% per year among
patients with initially severe but asymptomatic aortic regurgitation). In patients with chronic AR, AVR should be considered only when AR is severe (see Table 2).

Class I indications for AVR include:

1. Symptomatic patients with severe AR irrespective of LV systolic function (level of evidence: B)
2. Asymptomatic patients with chronic severe AR and LV systolic dysfunction (EF<0.50) at rest (level of evidence: B).
3. Patients with chronic severe AR while undergoing CABG or surgery on the aorta or other heart valves (level of evidence: C).

A single Class IIa indication exists:

1. AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (EF>0.50) but with severe LV dilatation (end-diastolic dimension >75 mm or end-systolic dimension >55 mm) (level of evidence: B).

MITRAL STENOSIS

What are the major causes of mitral stenosis?

The major causes of mitral stenosis (MS) are rheumatic fever and calcific or degenerative disease. Degenerative MS has been associated with elderly patients and dialysis patients, and typically manifests as annular calcification. Mitral annular calcification (MAC), which can lead to hemodynamically significant MS, is associated with advanced age, chronic renal disease, diabetes, female gender, hypertension, and coronary artery disease.

Another cause of MS is radiation exposure, particularly in patients exposed to mediastinal radiation, which can affect 6% to 15% of patients exposed to mediastinal radiotherapy; on average, valve lesions are diagnosed 11.5 years after radiation therapy.

Other rare causes of MS can include left atrial tumors causing mitral obstruction (ie, myxoma), endocarditis, or mucopolysaccharidosis.

What imaging should be done to diagnose and assess MS?

Echocardiography should be performed to assess the severity of MS and determine the mechanism of stenosis, and to evaluate for other causes of MS (ie, left atrial myxoma, congenital causes, severe calcific disease, and so forth). Transthoracic echocardiography with Doppler can measure mitral valve area, transmural gradient, and pulmonary artery pressures (Fig. 3). Severity of calcific MS may be more difficult to assess, and may require more detailed 3-dimensional planimetry assessment (Fig. 4).

Transeosophageal echocardiography is indicated to assess for the presence of left atrial thrombus and to further evaluate the severity of mitral regurgitation (MR) in patients being considered for percutaneous mitral valvuloplasty (Class I). It should also be considered to evaluate mitral valve morphology and hemodynamics when transdiagnostic echocardiography provides suboptimal data (Class I).

What are the definitions of severity for MS?

With the 2014 AHA/ACC Valvular Heart Disease guidelines the severity of MS was updated, replacing “mild” with “progressive” MS, and defining “severe” MS as
hemodynamic severity at which symptoms can occur and where intervention can improve symptoms.2

1. Progressive MS: Normal pulmonary pressures at rest and a mitral valve area (MVA) of greater than 1.5 cm² (by planimetric assessment of pressure half-time calculations on echocardiography)

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Fig. 3. Transesophageal echocardiography in a 78-year-old man with a history of rheumatic mitral stenosis and past surgical commissurotomy. (A) 2D Transesophageal echocardiography with concurrent color Doppler flow assessment showing the hockeystick appearance of the anterior mitral valve, and the thickened leaflet tips (arrows) and commissural fusion characteristic of rheumatic valve disease. The mean transmitral gradient was measured at approximately 15 mm Hg with severe left atrial enlargement and moderate mitral regurgitation, which did not make the patient a candidate for percutaneous mitral valvuloplasty. (B) 3D Transesophageal echocardiography of the mitral valve from the view of the left atrium. AoV, aorta; LA, left atrium; LV, left ventricle.
2. Severe MS: PA systolic pressure of greater than 30 mm Hg and an MVA of 1.5 cm² or less
3. Very severe MS: MVA 1.0 cm² or less

What are the physical examination findings consistent with MS?

The characteristic finding of MS is a prominent, loud first heart sound attributable to the increased force of mitral valve closure, although in severe calcification with limited mobility it may be diminished (see Table 1). An opening snap is a high-pitched sound that can be heard after the aortic (A2) component of the second heart sound (S2), which is due to the forceful opening of the mitral valve. As MS progresses in severity, left atrial pressure rises, resulting in the opening snap occurring earlier in diastole. A mid-diastolic rumbling murmur with presystolic accentuation, during
atrial contraction, is best heard at the apical region. It is low-pitched in nature and can be amplified with the bell portion of a stethoscope. Moving the patient to a left lateral decubitus position and isometric exercise can also make the murmur louder. The intensity of the murmur can also decrease if flow across the mitral valve is reduced owing to coexisting conditions such as heart failure, AS, or pulmonary hypertension.

**How often should asymptomatic patients with MS be serially followed?**

In patients with progressive MS (MVA > 1.5 cm²), a yearly follow-up, history and physical examination, chest radiograph, electrocardiogram, and a baseline 2-dimensional transthoracic echocardiogram should be performed. Echocardiography should be performed in asymptomatic patients with stable clinical findings and preserved LV systolic function to assess pulmonary artery pressures: yearly for patients with very severe MS, every 1 to 2 years for severe MS, and every 3 to 5 years with progressive MS.

**What are the indications for invasive hemodynamic evaluation for MS?**

Direct measurements of left atrial pressure (through transseptal access) and LV pressure can determine the transmitral gradient, which is a reflection of the severity of MS. Pulmonary artery pressure tracings can be used as a surrogate, but can overestimate the transmitral gradient.

Invasive cardiac catheterization is indicated when noninvasive tests are inconclusive or if there is a discrepancy between noninvasive tests and clinical findings (Class I). Exercise testing with Doppler measurement and/or invasive testing can also be indicated to assess hemodynamic response to exercise when symptoms and resting hemodynamics are inconsistent (Class I).

**Which pharmacologic agents are available to control the physiologic effects of MS?**

Negative chronotropic agents, such as β-blockers and calcium-channel blockers, may help patients who have symptoms at high heart rates. Restriction of salt intake and diuretics are useful in the setting of pulmonary edema. Digoxin is not known to be beneficial in MS patients in sinus rhythm unless LV or right ventricular (RV) dysfunction is present.

**Which surgical interventions are available for MS?**

Percutaneous mitral balloon valvotomy/valvuloplasty (PBMV) consists of a transcatheter approach whereby 1 or more valvuloplasty balloons are inflated across the mitral valve, thus opening the fused commissures (Fig. 5). Typically patients with noncalcified, pliable valves achieve the best immediate and long-term results. Compared with surgical commissurotomy, PBMV has had similar immediate results, with 50% to 60% reduction in the transmitral gradient and success rates ranging from 80% to 95%.

The most common acute complications that can occur include severe MR and residual atrial septal defect from transseptal puncture. Embolic events, myocardial infarction, and LV perforation are rare. Long-term follow-up of 3 to 7 years shows favorable symptomatic and hemodynamic results with PBMV when compared with closed commissurotomy, making it the preferred approach in patients with favorable mitral anatomy.
Patients with calcific MS are unlikely to benefit from PBMV given that the mechanism of stenosis originates from the base of the mitral leaflets as opposed to commissural fusion, and typically surgical repair/replacement is indicated for these patients.

Class I recommendations for PBMV include severe MS (MVA ≤ 1.5 cm²) with symptoms. Contraindications include the presence of a left atrial thrombus or moderate to severe MR. In these circumstances, surgical repair/replacement should be considered instead of PBMV (see Table 2). Class II indications are also outlined in the ACC/AHA 2014 guidelines.

**When is anticoagulation indicated for MS?**

Approximately 30% to 40% of patients with symptomatic MS can develop atrial fibrillation. Because of the high risk of systemic embolization, atrial fibrillation in the presence of MS is a Class I indication for anticoagulation, independent of other risk factors. A prior embolic event, even if in sinus rhythm, and presence of a left atrial thrombus also are Class I indications for anticoagulation.

Treatment with heparin and/or coumadin has been traditionally used. The efficacy of newer agents (ie, dabigatran, rivaroxaban, apixaban) has not been studied in the context of MS-related atrial fibrillation.
MITRAL REGURGITATION

What are the different mechanisms of MR?

Broadly, the mechanism of MR can be divided into primary (intrinsic) and secondary (functional). Primary MR is an intrinsic valvular problem (degenerative, perforation, and so forth), whereas in secondary MR the valve itself is structurally normal and the dysfunction is caused by myocardial infarctions or cardiomyopathy.

What are the causes of mitral regurgitation?

The most common cause of primary MR is mitral valve prolapse (MVP). Other causes include endocarditis, congenital malformations, inflammatory disorders, MAC, radiation, and drugs (ergotamine, cabergoline, and others). Rheumatic heart disease continues to be a major cause in underdeveloped countries, but constitutes only 2% to 5% of cases in developed countries.51

Secondary MR is most commonly caused by ischemia or other causes of LV systolic dysfunction.

What is mitral valve prolapse?

MVP is caused by bulging of the valve leaflets into the left atrium during systole (Fig. 6). In severe cases, the entire leaflet may become dislodged and protrude into the left atrium in a condition known as flail MVP.

Myxomatous degeneration is the most common cause of MVP, and is most commonly due to a genetic predisposition. MVP is also seen in Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta.52 Acquired causes include rheumatic, endocarditis, trauma, and ischemia. Although the mitral valve is most commonly affected, other valves may also be involved, with tricuspid valve prolapse occurring in up to 40% of patients.1

Some patients may present with mitral prolapse syndrome, a constellation of symptoms that is not explained by echocardiogram or telemetry recordings. Symptoms include palpitations, atypical chest pain, fatigue, and panic attacks. True arrhythmias can occur; therefore, careful evaluation should be undertaken in these patients and positive findings managed accordingly.

What are the signs and symptoms in a patient with mitral regurgitation?

The history in a patient with MR should focus on symptoms typical for heart failure, as the presence of symptoms is an indication for surgical evaluation. The murmur classically associated with MR is a holosystolic murmur at the apex with radiation to the axilla. The murmur in MR is increased with isometric strain, owing to increased afterload causing increased regurgitant flow. The murmur intensity decreases with Valsalva (see Table 1).

Which imaging modalities should be used in the evaluation of MR?

Echocardiography should be obtained for baseline evaluation and serially, depending on severity and symptoms. Echocardiography measures the LV size and EF, estimated regurgitant volume and fraction, ERO area, dimensions of the LA and LV chambers, and width of vena contracta, defined as the narrowest cross section of the regurgitant stream.
Transesophageal echocardiography should only be used when transthoracic images are inadequate, for the evaluation of endocarditis, or intraoperatively during mitral valve repair. CMR imaging can provide excellent assessment of mitral valve morphology and function as well as quantitative measurements of severity. It has excellent reproducibility, and should be used when echocardiography provides inadequate or inconsistent results. (Figs. 7 and 8).
How is MR defined by echocardiography?

Progressive MR is defined as:
1. Width of vena contracta less than 0.7 cm
2. RVol less than 60 mL

Fig. 7. Mitral regurgitation from ruptured papillary muscle. 2D Transesophageal echocardiography (A) with simultaneous color Doppler flow assessment (B) of the mitral valve in a 56-year-old man who presented with an inferolateral ST-elevation myocardial infarction and sudden onset of hypotension and cardiogenic shock. A flail scallop of the anterior mitral leaflet (thick arrow) is seen with resultant severe, eccentric, posteriorly directed mitral regurgitation (thin arrows) that extends to the back of the left atrium. (C) 3D Transesophageal echocardiography of prior figure of the mitral valve from the view of the left atrium, showing a flail anterior leaflet in systole with a ruptured anterolateral papillary muscle (thick arrow) and attached chordae (thin arrow). (D) Gross surgical specimen of the anterolateral papillary muscle (thick arrow) with attached chordae and a portion of the anterior mitral valve leaflet after undergoing mitral valve replacement. Note the twisted nature of the chordae (thin arrow) caused by the continual rotational movement of the papillary muscle with severe mitral regurgitation. Ao, aorta; LA, left atrium; LV, left ventricle.
Echocardiographic criteria of severe primary MR include:

1. Width of vena contracta greater than or equal to 0.7 cm
2. RVol greater than or equal to 60 mL per beat
3. RF greater than or equal to 50%
4. ERO area of 0.40 cm² or greater

Progressive primary MR is defined as:

1. ERO area less than 0.2 cm²
2. RVol less than 30 mL
3. RF less than 50%

Severe secondary MR is defined as:

1. ERO area of 0.2 cm² or greater
2. RVol greater than or equal to 30 mL
3. RF greater than or equal to 50%

Other elements that are found in severe MR include LVEF less than 60% and systolic flow reversal in the pulmonary veins.

**When should a patient be referred for surgical intervention, and what issues should be considered before surgical intervention?**

In general, the key elements that inform the indication for a mitral valve operation are presence of symptoms, severe MR on imaging, and degree of LV dysfunction. Earlier repair for severe MR leads to better outcomes, as a successful operation will...
preserve LV function. Thus referral to cardiology and surgery should not wait for the development of symptoms or LV dysfunction in the patient with symptomatic severe MR.

Class I indications for surgical intervention in severe primary MR include presence of symptoms and LVEF greater than 30%, or asymptomatic patients with LVEF of 30% to 60% or end-systolic dimension 40 mm or greater (see Table 2). Patients with chronic severe primary MR who are planned for cardiac surgery because of other indications also meet Class I indications for mitral valve surgery. Asymptomatic patients with severe MR and normal LV function should be considered for surgery if pulmonary hypertension or new-onset atrial fibrillation is found, or if the likelihood of repair is greater than 90%.

Repair is preferred over replacement whenever possible (Class I), as studies have shown decreased operative risk with repair (1% vs >4%), although it should be noted that no randomized controlled trial exists that directly compares the 2 approaches. The experience of the surgical center is an important consideration, as this may affect whether repair or replacement is performed, in addition to operative mortality.

What is percutaneous mitral valve repair?

A percutaneous mitral valve clip (endovascular edge-to-edge repair) is now available in the United States and Europe, with European guidelines recommending this technique in patients with symptomatic severe primary MR who are inoperable or at high surgical risk (Class IIb). The new 2014 ACC/AHA guidelines also give a Class IIb recommendation for transcatheter mitral valve repair in patients with chronic severe primary MR who are severely symptomatic despite optimal medical therapy and are deemed poor surgical candidates. Such patients must have anatomy that is likely to be successful for the transcatheter approach.

In this procedure, the mitral valve is accessed through the interatrial septum via access in the femoral vein. A clip is placed to attach the anterior leaflet to the posterior leaflet. In the EVEREST II trial, 20% of the percutaneous intervention group required surgery for mitral valve dysfunction, compared with 2.2% in the surgical group at 12 months’ follow-up. Improvement in MR was significant in both groups but was greater in the surgery group. A composite end point of major adverse events in 30 days was less in the percutaneous repair group. At 4 years’ follow-up, the need for surgery was 24.8% in the percutaneous group and 5.5% in the surgical arm. There was no significant difference in mortality or rate of severe/moderately severe MR.

How are patients with primary mitral regurgitation medically managed? How often should patients be seen for surveillance and follow-up imaging?

Heart failure should be managed with diuretics, but resolution of symptoms with medical management should not delay referral for surgery. Systemic embolization is more common in patients with mitral regurgitation. Therefore, warfarin therapy with a goal international normalized ratio (INR) of 2 to 3 is indicated in patients with a history of systemic embolization or with atrial fibrillation.

In general, clinical evaluation and echocardiography should be performed in a patient with known MR if there is any change in clinical symptoms or findings. Patients with mild MR without evidence of heart failure, chamber enlargement, or pulmonary hypertension can be seen yearly without the need for echocardiography. Moderate MR should be seen annually with echocardiography to assess for change in function.
Asymptomatic patients with severe MR should be carefully followed every 6 months with echocardiography and clinical evaluation.1

**How should the risk of stroke be managed in patients with MVP?**

A detailed history of stroke and transient ischemic attack (TIA) in patients with MVP should be obtained, and if present managed with anticoagulation. Current guidelines recommend aspirin for the following indications in a patient with MVP:

1. TIA in a patient with sinus rhythm and no evidence of atrial thrombi (Class I)
2. Atrial fibrillation with age younger than 65 and no history of MR, hypertension, or heart failure (Class I)
3. History of stroke without atrial fibrillation, left atrial thrombus, or 5 mm or greater redundancy of valve leaflets (Class II)

Warfarin should be used with a goal INR of 2 to 3 in patients with atrial fibrillation and other risk factors, history of prior stroke, or TIAs while on aspirin therapy.1

**How is secondary MR managed medically and surgically?**

The underlying cause of secondary MR should be diagnosed and managed appropriately. Standard heart-failure therapy should be initiated for patients with secondary MR and decreased LVEF. Cardiac resynchronization therapy can also be considered for such patients. Mitral valve surgery receives a Class IIa recommendation in patients with symptomatic, chronic severe secondary MR who are undergoing other cardiac surgery such as AVR or CABG. A Class IIb recommendation is given for patients with severe symptoms despite optimal medical therapy.2

**RIGHT-SIDED VALVULAR HEART DISEASE**

**What should be considered in the evaluation and management of tricuspid regurgitation?**

Tricuspid regurgitation (TR) most commonly occurs as a secondary process, so the signs and symptoms will be related to the primary cause. Examples include left-sided valvular disease and pulmonary hypertension. Primary TR can occur as a congenital or acquired process (endocarditis, rheumatic heart disease, carcinoid).58

The murmur in TR is classically holosystolic along the sternal border. Inspiration causes increased venous return, which can augment the intensity of the murmur. Severe TR is defined as a vena contracta width greater than 0.7 cm, central jet area greater than 10 cm², and systolic flow reversal in the hepatic veins.1,2 In addition, echocardiography should evaluate RV systolic pressure, RV and right atrial dimensions, LV function, and left-sided valvular function.

Management should focus on treating the underlying cause. Guidelines for surgical intervention are not as well established as for mitral regurgitation, but should be considered in the following patients1,2,6:

1. Severe TR in patients undergoing left-sided valvular surgery
2. Symptomatic, severe primary TR
3. Mild to moderate functional TR with either a dilated annulus or evidence of right heart failure in patients undergoing left-sided valvular surgery.
4. Moderate functional TR and pulmonary artery hypertension at the time of left-sided valvular surgery.

Other Class IIb indications can be found in the 2014 ACC/AHA guidelines for valvular heart disease. In general, repair with annuloplasty is preferred to replacement when possible.

**What should be considered in the evaluation and management of tricuspid stenosis?**

Tricuspid stenosis (TS) is a rare condition that is almost always due to rheumatic heart disease and usually presents along with other valves involved. Findings on auscultation could include a prominent a-wave with slow y-descent and an opening snap with a diastolic, rumbling murmur. In severe TS, RV failure can occur with findings of right atrial pressure overload such as jugular venous distension, edema, ascites, and hepatomegaly.\(^1,5^8\)

Echocardiography should be performed to diagnose TS and determine the severity. A valve area of less than or equal to 1 cm\(^2\) is consistent with severe TS. As TS is usually present in the setting of left-sided lesions, surgical intervention for severe TS is usually carried out at the time of left-sided surgery (Class I).\(^2\) Surgery is also given a Class I recommendation in patients with isolated severe symptomatic TS.\(^2\) Balloon valvuloplasty is an option in patients, but is not well studied and can result in severe TR. Replacement is therefore the preferred option in most cases.\(^1,6^\)

**What should be considered in the evaluation and management of pulmonary stenosis?**

Pulmonary stenosis is most often due to a congenital or genetic disorder, which is beyond the scope of this article. Rheumatic heart disease can also rarely cause pulmonary stenosis.\(^1\) Symptoms include edema, ascites, fatigue, syncope, and angina. Examination may reveal signs of RV failure as well as a pulmonary ejection click, an RV heave, and wide splitting of S2. A systolic murmur will be audible at the left sternal border, and can radiate into the neck.

Echocardiography should be performed to evaluate the right-sided chamber sizes and pulmonary valve anatomy, screen for left-sided lesions, and assess severity of the stenosis. A peak instantaneous gradient greater than 64 mm Hg or a maximal velocity greater than 4 m/s is diagnostic for severe PS.\(^2\)

Treatment is generally performed using balloon valvotomy in symptomatic patients with a gradient greater than 30 mm Hg and for asymptomatic patients with a gradient greater than 40 mm Hg (Class I). It can also be considered in asymptomatic patients with a gradient of 30 to 39 mm Hg. Postprocedure regurgitation is common but rarely clinically significant.\(^1^\)

**What should be considered in the evaluation and management of pulmonary regurgitation?**

Pulmonary regurgitation (PR) typically occurs secondarily to interventions for congenital heart disorders. Less commonly, primary PR can occur in the setting of carcinoid or rheumatic heart disease, or secondary to pulmonary hypertension.\(^5^8\)

Signs and symptoms include a soft diastolic decrescendo murmur, parasternal lift, and signs of RV failure. Severe PR can cause RV dilation, which increases the risk of ventricular arrhythmias and sudden cardiac death.

Indications for valve replacement are not clearly defined but, according to ACC/AHA guidelines from 2008, it is reasonable to intervene in patients with severe PR and symptoms of New York Heart Association Class II or III.\(^5^9\) Indications for
asymptomatic patients are not clear, but there may be benefit to intervening before the development of RV dysfunction.

**Which patients with valvular heart disease will benefit from bacterial endocarditis prophylaxis?**

The guidelines surrounding the use of antibiotic prophylaxis to prevent bacterial endocarditis have changed in the past 5 years. The ACC/AHA put forth a focused update on this topic in 2008, in which they removed all Class I recommendations, and recommended antibiotic prophylaxis as a Class IIa indication for patients with prosthetic material related to valve replacement or repair, or a prior history of infective endocarditis for more involved dental procedures with higher rates of transient bacteremia. Other Class II indications include cardiac transplant patients with valve regurgitation from a structurally abnormal valve, and patients with congenital heart disease that is either unrepaired or repaired with residual prosthetic material. If the congenital defect is completely repaired, prophylaxis is recommended only during the first 6 months after the procedure.

**When should a patient with native valve endocarditis be referred for surgical evaluation?**

Several indications exist for surgical management of native valve endocarditis. When performed, repair is preferable over replacement because of the risk of infection of the foreign material.

Class I indications according to ACC/AHA guidelines include:

1. Heart failure resulting from infective endocarditis
2. AR or MR with elevated LV end-diastolic or left atrial pressures
3. Organism is highly resistant, fungal, or persists despite 5 to 7 days of appropriate antibiotics
4. Complications including heart block, destructive lesions, or abscess

Recurrent embolus despite antibiotic therapy is a Class IIa recommendation.

**REFERENCES**


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