Aortic Stenosis: New Thoughts on a Cardiac Disease of Older People

Felix J. Rogers, DO

We have entered a new era in understanding degenerative aortic stenosis in elderly patients. With the aging of the US population and the progressive decrease in coronary heart disease prevalence in the past 50 years, aortic stenosis has become a major cardiac concern. New perspectives of the disease now lead us to see the condition in terms of the response of the left ventricle and of systemic features, rather than just in terms of the valve area itself. A new classification of aortic stenosis recognizes 4 categories based on flow state (normal or low) and valve gradient (high or low). “Paradoxical” low-flow, low-gradient stenosis has a dismal prognosis in spite of a normal left ventricular ejection fraction. New measures of aortic flow and the response of the left ventricle provide new insights into the treatment of patients with this condition.

J Am Osteopath Assoc. 2013;113(11):820-828
doi:10.7556/jaoa.2013.057

Aortic stenosis (AS) is the most common cardiac valve disease in the United States.1 Over the past decade, the number of aortic valve replacement operations has doubled and, because of the anticipated growth of the older adult population, it is predicted to double again over the next 20 years.1,2 Increasingly, AS is the focus of interventional cardiologists who are typically performing fewer coronary angioplasty procedures and more percutaneous aortic valve replacement procedures.

Because AS plays such a prominent role in cardiovascular care, there is a renewed interest in several aspects of the disease, including understanding the pathophysiologic processes, predicting adverse cardiac events accurately, diagnosing severe disease, and indicating cardiac surgical procedures. We are in a new era in which the timing of a surgical procedure is determined not just by the patient’s symptoms, but also by the severity of the valve narrowing and the response of the left ventricle to valve stenosis.

Pathophysiologic Processes

The incidence of rheumatic heart disease has dropped so much in North America that, in my experience, rheumatic AS is rarely seen. With a nod to tradition, it should be noted that there are 3 forms of AS from the perspective of congenital heart disease. The first presentation of AS occurs because of a unicommissural aortic valve and typically presents in the first decade of life. The second presentation of AS occurs...
because of a bicuspid aortic valve and typically presents in the fifth or sixth decade of life. The third presentation—the most common presentation—occurs because of calcific degeneration of an otherwise normal trileaflet aortic valve and typically presents in the seventh or eighth decade of life.

The pathophysiologic process of degenerative AS begins with endothelial damage. As with atherosclerosis, this damage results from increased mechanical stress and decreased shear stress. The noncoronary cusp has the greatest involvement. With the bicuspid aortic valve, the eccentric leaflet configuration leads to increased mechanical stress and clinical presentation occurs 2 decades earlier than that of degenerative trileaflet AS. The bicuspid aortic valve is also associated with an aortopathy, in which ascending aortic root dilatation or aneurysm occurs, further complicating this clinical condition.

Inflammation plays a role in the early phases of AS. Traditional cardiac risk factors (eg, smoking, hypertension, obesity), metabolic syndrome, and diabetes lead to incorporation of low-density lipoprotein cholesterol and highly cytotoxic lipoprotein(a) particles into the valve. The result is aortic sclerosis. It is unclear why a small percentage of patients with aortic sclerosis will undergo an accelerated process of valve leaflet calcification. Logically, it would seem that management of these risk factors would reduce the progression of aortic valve disease. However, a large randomized controlled trial showed no benefit to lipid lowering with a statin agent.

A recent, large international study of genome-wide risks for AS identified a single nucleotide polymorphism that established lipoprotein(a) as a causative factor in the development of aortic calcification. It has been suggested that the reason management of lipids did not demonstrate a beneficial effect is that the frequency of this risk allele is low 5 or 6 per 100 persons. Valvular calcification is also related to factors such as osteoporosis and renal failure. The evidence in favor of bisphosphonates in the management of aortic calcification is scant.

The response of the left ventricle (LV) is now viewed as a key element in the progression of asymptomatic AS

**KEY POINTS**

- Improved understanding of the pathophysiologic process of aortic stenosis has ushered in a new era in which disease severity is considered in terms of systemic conditions and the ventricular response to stenosis instead of just in terms of the aortic valve surface area.
- Traditional cardiac risk factors are part of the predisposing conditions that lead to aortic sclerosis. A small percentage of these patients will progress to calcific aortic stenosis.
- Presently, the guidelines for the treatment of patients with aortic stenosis recommend surgical treatment for only symptomatic patients. Although there is clinical evidence that many asymptomatic patients will benefit from surgical treatment, the guidelines have not yet caught up to that evidence.
- If there is doubt about whether the patient is truly asymptomatic, exercise stress testing can be of benefit.
- Longitudinal shortening, measured by excursion of the mitral valve annulus or by strain imaging, is useful in detecting left ventricular systolic dysfunction in patients with normal left ventricular ejection fraction.
- The valvuloarterial impedance (Zva) is a simple Doppler echocardiography measurement that incorporates information about the systolic demand on the valve with an assessment of left ventricular performance. It is superior to the measurement of aortic valve area in predicting clinical outcomes.

The response of the left ventricle is key to understanding the progression to severe, symptomatic aortic stenosis.
to severe, symptomatic AS. There is considerable variation in the degree and pattern of LV hypertrophy. The progression from hypertrophy to heart failure involves myocyte-programmed cell death (apoptosis) and fibrosis. In particular, fibrosis involves the subendocardial fibers, which are oriented longitudinally in the LV.

**Bedside Approach**

There are 3 cardinal symptoms of AS: chest discomfort, syncope, and dyspnea (or other symptoms of heart failure). In most patients, however, AS is identified well before patients have symptoms because of its characteristic heart murmur. By convention, physicians are accustomed to describing a murmur by its intensity (eg, grade II systolic murmur). In this context, it is helpful to recall the other characteristics of a heart murmur: pitch, quality, timing, configuration, and location. The murmur of severe AS can be mimicked by the sound of vigorously clearing your throat. It is harsh, rasping, and crescendo-decrescendo. In severe AS, the murmur peaks in the last half of the systole, and the second heart sound is muffled.

Other bedside findings of AS such as delayed carotid upstroke are relegated to severe disease; therefore, it would be unusual that these symptoms alone would lead to the diagnosis.

Electrocardiogram may show characteristic LV hypertrophy with secondary ST and T wave changes (strain pattern) or LV hypertrophy by voltage criteria alone. A large number of patients with severe AS will have normal electrocardiograms. Left bundle branch block occurs in a small proportion of patients. A chest radiograph is likely to show a LV contour to the cardiac silhouette. Prominence of the ascending aorta is more frequently found in bicuspid aortic valves than in trileaflet valves because of the commonly associated aortopathy. The demonstration of calcium in the vicinity of the aortic valve on a lateral chest radiograph is an ominous finding of severe disease and may predict the need for surgical treatment.

**Definition of Severe AS**

In 2006, the joint American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on the management of valvular heart disease described the characteristics of severe AS: an estimated aortic valve area that is less than 1.0 cm$^2$, a peak aortic velocity as measured by Doppler echocardiography that is greater than 4 m/s (peak valve gradient >64 mm Hg), and a mean aortic valve gradient that is greater than 40 mm Hg. The guidelines of the European Society of Cardiology add another measure: a ratio of the LV outflow velocity to the velocity at the aortic valve (dimensionless velocity index) that is less than 0.25. These parameters are all routinely measured at the time Doppler echocardiography is performed. Cardiac catheterization for hemodynamic measurements is not recommended for assessing the severity of AS when noninvasive tests are adequate and concordant with clinical findings. With cardiac catheterization and Doppler echocardiography, multiple measurements must be taken and averaged because the irregular heart rate in patients with atrial fibrillation creates considerable beat-to-beat variation. The ACC/AHA guidelines further state that surgical treatment is indicated only when the patient with severe stenosis develops symptoms. The exception to this guideline is when the patient is scheduled for another major open-heart surgical procedure such as coronary artery bypass grafting, in which case aortic valve replacement can be performed at the same time.

It has long been recognized that severe AS may occur in the setting of LV systolic dysfunction. In that situation, LV dysfunction renders the LV chamber weak, and it cannot generate high flow across the valve to produce a high peak systolic velocity or a high mean valve gradient. Echocardiographers estimate the aortic valve area using the continuity equation, which uses the LV outflow tract diameter and the flow velocity at that...
location along with the aortic valve velocity to solve for aortic valve surface area.

If the results in patients with depressed LV function are borderline or uncertain for the diagnosis of severe AS, dobutamine stress Doppler echocardiography is used to measure the response of the aortic valve gradient to the increase in contractility caused by the inotropic effect of dobutamine. When the valve is severely stenotic with low resting gradient, the valve gradient increases but the calculated aortic valve area does not change. With “pseudo-stenosis,” the increase in contractility causes the valve to open more fully, so the estimated aortic valve area increases and little change occurs in the aortic valve gradient. Calcium scoring using computed tomography is also helpful to distinguish these 2 conditions. A calcium score greater than 1650 Agatston units is almost always indicative of critical AS.

Recently, a “paradoxical” situation has been identified in which patients with severe AS have a low gradient across the aortic valve with associated low flow states but have a normal LV ejection fraction. This low flow state is related to a decrease in stroke volume due to diminished LV cavity size. These patients have been shown to have a poor prognosis in spite of an asymptomatic presentation. The low flow state has been attributed to restrictive physiologic effects due to LV myocardial fibrosis and myocyte apoptosis. It represents a situation analogous to diastolic heart failure with a preserved ejection fraction. Like patients with diastolic heart failure and a preserved ejection fraction, patients with a low flow state and a normal LV ejection fraction are typically older, are female, and have concomitant systemic arterial hypertension. Features include concentric remodeling with myocardial fibrosis. There is a marked reduction in intrinsic LV function in terms of longitudinal shortening because of the predominant involvement of the subendocardial layer with fibrosis. The ejection fraction and systolic wall thickening remain normal. Patients may have normal blood pressure in spite of a decrease in systemic arterial compliance, an increase in systemic vascular resistance, or both. The Figure shows the spectrum of LV function in a normal person, a person with aortic

Figure.
Depictions of the left ventricle (LV) in (A) a normal, healthy individual, (B) a patient with aortic stenosis and normal myocardial function, and (C) a patient with advanced aortic stenosis and LV systolic dysfunction. The LV hypertrophy results in a greater contribution of wall thickening to endocardial inward displacement. The LV ejection fraction (EF) and percentage of wall thickening are normal in each situation, despite intrinsic LV systolic dysfunction, which is only manifest by the reduced longitudinal shortening. The change in longitudinal shortening can be easily measured by LV strain imaging or by M mode echocardiographic assessment of mitral annular excursion. Left ventricle longitudinal shortening is an additional measure of LV performance, which is superior to LV EF. Reprinted from Pibarot and Dumesnil with permission from Elsevier.
stenosis and preserved LV systolic function, and a patient with severe AS and a reduced stroke volume due to LV systolic dysfunction. Each of these patients has a normal ejection fraction and normal wall thickening.

The observation of adverse prognosis in patients with “paradoxical” low-flow, low-gradient AS with normal ejection fraction has led to a new classification that includes 4 categories of severe AS (Table 1). This classification involves 2 conditions with normal flow (1 with high valve gradient and 1 with low valve gradient) and 2 conditions with low flow (1 with high valve gradient and 1 with low valve gradient).

A prospective study of 150 asymptomatic patients with aortic valve area <1.0 cm² defined several important clinical characteristics. In the most common form of severe asymptomatic AS, the patient had normal flow across the valve and high valve gradient. This form accounted for 52% of patients and led to the standard definitions of the ACC/AHA. The mean valve gradient was greater than 40 mm Hg, and the 2-year cardiac event–free rate was about 44%.

In the second most common form of severe asymptomatic AS, the patient had normal flow across the valve and low valve gradient. Approximately 31% of patients with severe AS had this form. These patients had the best prognosis with a 2-year cardiac event–free rate of 83%. They had preserved longitudinal myocardial function and lower levels of brain natriuretic peptide (BNP).

The form in which the patient had low flow across the valve and high valve gradient accounted for 10% of patients. These patients had a decrease in cardiac output manifested by a stroke volume index of less than 35 mL/m² in spite of a normal LV ejection fraction. They had a decrease in longitudinal contraction of the ventricle and very elevated levels of BNP.

In the least common form of severe asymptomatic AS, the patient had low flow across the valve and low valve gradient. This form accounted for 7% of asymptomatic patients with severe AS. In these patients, the mean valve gradient was less than 40 mm Hg and the stroke volume index was less than 35 mL/m² in the setting of preserved ejection fraction. The valve area was less than 1.0 cm². These patients had more pronounced LV concentric remodeling, a smaller LV cavity, intrinsic myocardial dysfunction, an increase in global LV afterload, and a dismal prognosis.

### Table 1.
**Proposed New Grading Classification** for Severe Asymptomatic Aortic Stenosis With Normal Left Ventricular Ejection Fraction (N = 150)

<table>
<thead>
<tr>
<th>Flow State</th>
<th>Valve Gradient</th>
<th>Event-Free Survival, %, mean (SD)</th>
<th>Median BNP, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Low</td>
<td>83 (6)</td>
<td>22</td>
</tr>
<tr>
<td>Normal</td>
<td>High</td>
<td>44 (6)</td>
<td>47.5</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>30 (12)</td>
<td>114</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>27 (13)</td>
<td>78</td>
</tr>
</tbody>
</table>

The proposed classification divides patients with severe aortic stenosis (valve area <1.0 cm²) into 4 categories on the basis of normal vs low flow and high vs low valve gradient.

The 2-year, event-free survival is the outcome without cardiovascular death, need for valve replacement because of symptoms, or left ventricular systolic dysfunction (left ventricular ejection fraction <50%).

Low-flow, low-gradient aortic stenosis was an independent predictor of markedly reduced cardiac event–free survival compared with low-flow, high-gradient aortic stenosis (hazard ratio 5.4; 95% confidence interval, 1.03-28.6; \( P = .046 \)).

**Abbreviations:** BNP, B-type natriuretic peptide level; SD, standard deviation.

### Other Considerations in Assessing Aortic Stenosis Severity

The guidelines of the ACC/AHA and the European Society of Cardiology are clear cut for patients with symptomatic severe AS, with or without LV systolic dysfunction. These patients have better outcomes with aortic valve replacement surgery. Likewise, if a concomitant heart surgical procedure is to be performed, such as coronary artery bypass grafting, aortic valve replacement should be performed in patients with moderate to severe AS, even if it is not believed to be causing symptoms. Data suggest that asymptomatic patients with severe AS who undergo surgical treatment have a better prognosis than patients who receive medical therapy and a “wait until symptoms occur” treatment approach. For this reason, primary care physicians should refer asymptomatic patients for specialty evaluation when the...
patients have moderate or severe AS on the basis of clinical findings.

Because physicians need to take a comprehensive approach to treating a patient with AS, it is helpful to have an organized perspective. The definitive work of Pibarot and Dumesnil is valuable and forms the basis of the considerations in the following sections. In the best case situation, the decision to recommend or not recommend that an asymptomatic patient undergo a surgical treatment will be a result of the combined evaluation of the specialist and the primary care physician.

Is the Patient Truly Asymptomatic?
It is important for physicians to determine if a patient with AS is truly asymptomatic. Because AS is typically found in elderly individuals, comorbid conditions may prevent a determination of exertional limitations. For example, the natural decline in activity levels that occurs with age may mask disease progression. In addition, patients may subconsciously limit their activities. One way physicians can determine if symptoms are being masked is to perform exercise stress testing. The patient is considered to be asymptomatic if the exercise stress test shows a normal exercise duration, a normal blood pressure response to stress, and no evidence of exercise-induced ventricular arrhythmias. The ST segment response to stress is not useful, and nuclear imaging is not needed. Because severe AS is historically considered to be a contraindication to exercise stress testing, the primary care physician is likely to defer the request for this test to the clinical cardiologist, who will perform the test in a setting where there is considerable experience with exercise stress testing.

Account for Body Size
The body surface area determines the cardiac output requirements. Therefore, AS severity may be overestimated in patients with small body surface areas and underestimated in patients with large body surface areas. To accurately determine AS severity, physicians should divide the valve area by the body surface area to generate the valve area index. In this situation, the definition of severe AS—1.0 cm²—correlates with an indexed valve area of 0.6 cm²/m². In patients with severe obesity, indexing for body surface area may result in overestimating the severity of stenosis.

Account for Vascular Load Symptoms
The symptoms of AS develop at a lower degree of stenosis severity in patients who have coexisting hypertension, because the LV has to work against a higher pressure. Therefore, careful measurements of blood pressure at the time of echocardiography and calculations of the systemic arterial compliance and stroke volume index provide useful additional information. Serial evaluations are helpful. Clinical follow-up and management of elevated blood pressure are useful.

The aortic valve impedance is superior to aortic valve gradient and estimated valve area in predicting clinical outcomes.

Assess for Global Left Ventricular Hemodynamic Load
The valvuloarterial impedance (Zva) is a simple echocardiographic measure that takes into account the systolic blood pressure load on the left ventricle and the contractile performance of the ventricle itself. It should be clear that all patients with a transvalvular gradient of 64 mm Hg (ie, the threshold of severe AS) do not have the same load placed on the LV. For example, a patient with a brachial systolic blood pressure of 160 mm Hg has an additional 40 mm Hg of systolic load compared with a patient with a brachial systolic blood pressure of 120 mm Hg. Likewise, a left ventricle that is sufficiently impaired that it cannot generate at least 40 mL of blood flow per square meter of body surface area for each stroke volume is not meeting the demand placed on that heart. The valvuloarterial impedance represents the systolic blood pressure plus the mean valve gradient divided by the stroke volume index determined by echocardiography findings. Values greater
Assess LV Geometry

The pattern of LV hypertrophy in response to AS is heterogeneous. There may be concentric remodeling, concentric hypertrophy, and eccentric hypertrophy. With more severe concentric remodeling, there is worse LV function, an increase in cardiovascular events, and an increase in operative and late mortality. The pattern of LV remodeling is determined by AS severity, patient age, sex, obesity, metabolic syndrome, and diabetes.

Assess Intrinsic LV Function

Because the subendocardial layers are involved in the longitudinal motion of the ventricle, and because fibrosis caused by AS preferentially affects the subendocardium, measurements of ventricular longitudinal shortening are sensitive indicators for adverse ventricular responses to AS. The longitudinal shortening is measured by strain rate imaging, an echocardiography technique that has some technical variability and is only now available as a standard parameter in some echocardiography laboratories. Longitudinal shortening can also be estimated by measuring mitral annular motion with an M-mode cursor from the apical transducer.

than 3.5 mm Hg/mL/m² represent moderately severe AS, and values greater than 4.5 mm Hg/mL/m² represent severe AS. The Zva helps to explain the patient population with low-flow, low-gradient AS and normal LV ejection fraction. In addition, it represents a prognostic marker that is modifiable, because abnormally high blood pressure can be managed to lower the patient’s risk.

The Zva is proven to be superior to the aortic valve gradient and estimated valve orifice area in predicting the clinical outcomes and the development of LV dysfunction (Table 2). Further, patients with an abnormally high Zva do better with surgical intervention than with medical management, even if they are asymptomatic.

For patients with a moderate increase in Zva (3.5 mm Hg/mL/m² < Z < 4.5 mm Hg/mL/m²), the mean (standard deviation) percentage of those with a 4-year survival was 74 (4%) for patients treated medically compared with 89 (5%) for patients treated surgically. For patients with a high Zva (>4.5 mm Hg/mL/m²), mean (standard deviation) percentage of those with a 4-year survival was 42 (9%) for those treated medically compared with 87 (5%) for those treated surgically.

Table 2. Outcome Data in 544 Asymptomatic Men and Women With at Least Moderate Aortic Stenosis

<table>
<thead>
<tr>
<th>Zva Category</th>
<th>Age, y</th>
<th>AVA, cm²</th>
<th>EF, %</th>
<th>Deaths, No. (%)</th>
<th>4-Year Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low⁠</td>
<td>66 (15)</td>
<td>1.2 (0.2)</td>
<td>67 (7)</td>
<td>15 (9)</td>
<td>88 (3)</td>
</tr>
<tr>
<td>Moderate⁠</td>
<td>70 (12)</td>
<td>1.0 (0.3)</td>
<td>66 (7)</td>
<td>36 (19)</td>
<td>78 (4)</td>
</tr>
<tr>
<td>High⁠</td>
<td>73 (13)</td>
<td>0.8 (0.2)</td>
<td>65 (5)</td>
<td>40 (22)</td>
<td>65 (5)</td>
</tr>
</tbody>
</table>

a Moderate aortic stenosis was defined as peak aortic jet velocity of >2.5 m/s. Patients were enrolled prospectively but analyzed retrospectively and were stratified by valvuloarterial impedance.
b Data are presented as mean (standard deviation [SD]) except for deaths, which are presented as No. (%).
c Normal in all groups.
d The hazard ratio (HR) for an increase in Zva was a stronger predictor of death than aortic valve area (AVA): HR AVA <1.0 cm², 1.67; HR moderate Zva, 2.24; HR high Zva, 2.95.
e Greater age and more severe reduction in AVA was associated with worse 4-year survival.
f Low Zva defined as <3.5 mm Hg/mL/m² (n=172).
g Moderate Zva defined as 3.5-4.5 mm Hg/mL/m² (n=192).
h High Zva defined as >4.5 mm Hg/mL/m² (n=180).

Abbreviation: EF, ejection fraction.
position. This simple measurement can be performed in any echocardiography laboratory.

**Identify Myocardial Damage**

There are 2 markers of myocardial damage: fibrosis and elevated BNP levels. Fibrosis is easily identified by cardiac magnetic resonance imaging. However, the cost of this procedure makes it prohibitive for screening purposes. Brain natriuretic peptide is better than the usual parameters in terms of predicting myocardial damage and the subsequent clinical course for patients with AS. It also reflects the concomitant presence of coronary artery disease or cardiomyopathy. Most importantly, it reflects the total burden of disease on the left ventricle. It varies by age and sex, and it should be measured routinely. However, unless the result is unequivocal (>500 µg/dL), the other variables described previously need to be considered with the BNP value as part of the definitive approach.

**TAKE-HOME POINTS**

- The primary care physician will usually establish the diagnosis of aortic stenosis at physical examination before the patient becomes symptomatic.
- Guidelines for aortic stenosis recommend surgical treatment when the patient becomes symptomatic. The symptoms are chest discomfort, syncope, and dyspnea.
- The primary care physician should arrange cardiac evaluation for patients who appear to have moderate or severe stenosis before they develop symptoms.
- The left ventricular ejection fraction may be a misleading measurement of left ventricular systolic function in severe aortic stenosis. Brain natriuretic peptide should be measured routinely.
- The final decision about the appropriateness of surgical treatment in patients with aortic stenosis will require the input of the primary care physician because of the advanced age of these patients and their multiple comorbidities.

**Summary**

The initial diagnosis of AS is usually established by the primary care physician on a clinical basis. The next step is to stage the disease in terms of aortic valve stenosis severity, in terms of the response of the left ventricle to the stenosis burden, and in terms of systemic issues. These systemic issues include those conditions directly related to the pathophysiologic process of valve stenosis and those comorbid conditions that would affect decision making, such as cognitive impairment, chronic obstructive lung disease, and limiting degenerative joint disease. Because of the advanced age of many of these patients, the appropriateness of a cardiac surgical procedure for a patient with AS should be determined by the primary care team, the cardiologist, and the cardiac surgeon working together.

The new classification of severe AS in terms of high or low flow and high or low valve gradient is a useful way to further categorize patients in terms that have direct relevance to prognosis and management decisions. If there is concern about whether the patient is truly asymptomatic, an exercise stress test can be useful.

If the patient with severe AS has any of the cardinal symptoms of angina, syncope, or heart failure, the guidelines are clear in the recommendation that the patient will benefit from aortic valve replacement, if clinically appropriate for his or her overall health status. If the patient has severe AS but is asymptomatic, there is evidence that many of these patients will do better with surgical treatment, but the guidelines have not caught up to this evidence base. In these cases, the physician or general cardiologist may choose to have the decision for a surgical procedure validated by a medical center with a structural heart disease program. These centers are likely to have programs for percutaneous valve replacement, a procedure that has been applied with increasing success in an expanding number of patient settings.

**Conclusion**

The management of severe AS calls for a coordinated approach that includes the primary care physician, the cardiologist, and the specialist who performs aortic valve replacement. New methods of management involve an
assessment of the valve itself and the response of the ventricle to the stenosis. Management also involves an evaluation of the patient’s overall condition because AS tends to occur in elderly patients who often have multiple comorbid conditions.

References


