When should patients with mitral valve prolapse get endocarditis prophylaxis?

**EVIDENCE-BASED ANSWER**

Patients with suspected mitral valve prolapse (MVP) should undergo echocardiography before any procedure that may place them at risk for bacteremia. Patients with MVP and documented absence of mitral regurgitation or valvular thickening likely do not need antibiotic prophylaxis against subacute bacterial endocarditis (SBE). Patients with MVP with documented mitral regurgitation, valvular thickening, or an unknown degree of valvular dysfunction may benefit from antibiotics during procedures that often lead to bacteremia (strength of recommendation: C).  

**EVIDENCE SUMMARY**

Only disease-oriented evidence and expert opinion address prevention for endocarditis. A randomized trial would require an estimated 6000 patients to demonstrate benefit.  

Endocarditis occurs in MVP at a rate of 0.1 cases/100 patient-years. However, MVP is the most common predisposing/precipitating cause of native valve endocarditis. In animal models, antibiotics prevent endocarditis following experimental bacteremia. The antibiotic can be administered either just before or up to 2 hours after the bacteremic event. It is worth noting that most bacteremia is not associated with medical procedures. Since endocarditis is often fatal, recommendations have been developed based on these animal models. Estimates of effectiveness of prophylaxis from case-control studies in humans (not limited to patients with MVP) estimate effectiveness from 49% to 91%. For patients with MVP who do not have evidence of mitral regurgitation on physical examination or echocardiography, the risk of
Mitral valve prolapse involves the degeneration of the mitral valve, dilation of the mitral annulus, abnormal chordal insertions, redundant mitral leaflet tissue that bulges into the left atrium during systole, and elongated chordae. Stethoscopic exam will reveal a mid-systolic click followed by a regurgitation murmur. A completely degenerated valve leads to mitral regurgitation.

**TABLE 1**

**Recommended prophylactic regimens for mitral valve prolapse**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental, oral, respiratory, esophageal procedures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard prophylaxis</td>
<td>Amoxicillin</td>
<td>Adult: 2 g</td>
</tr>
<tr>
<td>Allergy to penicillin</td>
<td>Clindamycin</td>
<td>Child: 50 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Cephalexin</td>
<td>Adult: 600 mg</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Child: 20 mg/kg</td>
</tr>
<tr>
<td>Moderate-risk patients</td>
<td>Amoxicillin</td>
<td>Adult: 2 g</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>Child: 20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Cephalexin</td>
<td>Adult: 2 g</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Child: 50 mg/kg</td>
</tr>
<tr>
<td></td>
<td>1 hour before procedure</td>
<td></td>
</tr>
<tr>
<td>High-risk patients</td>
<td>Clindamycin</td>
<td>Adult: 2 g</td>
</tr>
<tr>
<td>Moderate-risk patients allergic to penicillin</td>
<td>Vancomycin</td>
<td>Child: 20 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>1 g IV</td>
<td>Administrator over 1-2 hrs; complete 30 minutes before procedure</td>
</tr>
<tr>
<td></td>
<td>1 hour before procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Add gentamicin to amoxicillin or vancomycin</td>
<td>1.5 mg/kg (up to 120 mg) IV to be completed 30 minutes before procedure. If not allergic to penicillin, give penicillin give penicillin, give amoxicillin 1 g 6 hours after</td>
</tr>
</tbody>
</table>

Modified from Dajani 1997.
morbidity may be greater from antibiotic therapy than the risk of endocarditis. Prophylaxis for these patients is not recommended. Patients with MVP associated with regurgitation are at moderate risk and may benefit from antibiotic prophylaxis.

**RECOMMENDATIONS FROM OTHERS**
The American Heart Association has published recommendations in 1985,6 1990,7 and 1997.1 The 1997 recommendations are summarized in Figure 2. The Swiss Working Group for Endocarditis Prophylaxis published similar recommendations in 2000.8 Recommended prophylactic regimens appear in Table 1. Table 2 shows a modified list of procedures for which prophylaxis is recommended.

**REFERENCES**
Guidelines assist decision-making regarding who needs SBE prophylaxis

It is unfortunate, but not surprising, that the evidence for SBE prophylaxis for patients with MVP is disease-oriented evidence and expert opinion. Too often, the easy thing to do in a busy practice is not necessarily in the best interest of either the patient or the public. However—despite the low incidence of SBE—the high mortality of the disease and community standard of care often drive clinicians to write that prescription for antibiotics.

With the improved resolution and sensitivity of newer generations of echocardiograms, clinicians often face the dilemma of the patient with MVP and “trivial” or “minimal” mitral regurgitation. Unfortunately, no guidelines assist us in our decision-making regarding these patients.

Another consideration for the clinician is the American Heart Association’s recommendation for SBE prophylaxis for patients with MVP and thickened leaflets, regardless of whether there is associated mitral valve regurgitation.

One significant change that should lessen the frequency of unnecessary antibiotic prescribing was published recently. The echocardiographic criteria for diagnosing MVP were changed in the 2003 updated guidelines from the American College of Cardiology, American Heart Association, and American Society of Echocardiography. Valve prolapse of 2 mm or more above the mitral annulus is required for diagnosis. This change has effectively lowered the prevalence of MVP from 4% to 8% of the general population down to 2% to 3%.

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What is the best macrolide for atypical pneumonia?

**EVIDENCE-BASED ANSWER**

Erythromycin, clarithromycin, and azithromycin are equally effective in treating pneumonia caused by *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* (formerly *Chlamydia psittaci*) (strength of recommendation [SOR]: B, small head-to-head trials). Macrolide choice can be based on other considerations—cost, side effects, and effectiveness against other suspected pathogens (SOR: C, expert opinion).

**EVIDENCE SUMMARY**

*M. pneumoniae* and *C. pneumoniae* account for about 30% of community-acquired pneumonia (CAP), making them the most common “atypicals.” Clinically they are indistinguishable from other causes of pneumonia; most studies use cultures to identify cases among populations with CAP.

Azithromycin and erythromycin were compared in 3 studies of children with CAP.\(^1\)-\(^3\) Together, they identified 69 cases due to *M. pneumoniae* or *C. pneumoniae*. Only 3 patients did not respond to either antibiotic. In the largest of the 3 studies,\(^3\) side effects were noted in 10% of CAP patients on azithromycin and 20% on erythromycin (\(P<.05\)).

Another study looked at patients aged 12 to 80 years with pneumonia due to *M. pneumoniae* (75 cases) or *Chlamydia psittaci* (formerly *Chlamydia psittaci*, 16 cases).\(^4\) All patients responded to treatment. Clarithromycin and erythromycin were compared in children aged 3 to 12 years with CAP.\(^5\) *M. pneumoniae* or *C. pneumoniae* was identified in 42 cases. Two of 18 patients did not respond to erythromycin; 3 of 27 patients did not respond to clarithromycin.

Another study compared these antibiotics for patients with CAP aged 12 to 93 years.\(^6\) Subgroup analysis of those with *M. pneumoniae* or *C. pneumoniae* (\(n=27\)) showed similar efficacy. Pooling all 268 patients with CAP, side effects were seen in 31% of patients on clarithromycin and 59% on erythromycin (\(P<.001\)).

A comparison study of newer macrolides in 40 adults with CAP identified 13 with *M. pneumoniae* or *C. pneumoniae* (Table).\(^7\) One patient did not respond of the 8 treated with clarithromycin; none among the 5 treated with azithromycin. There was 1 adverse event (from clarithromycin).

**RECOMMENDATIONS FROM OTHERS**

The Infectious Diseases Society of America\(^8\) recommends a macrolide for adults with pneumonia caused by *M. pneumoniae* or *C. pneumoniae*, and does not promote one over another. The British Thoracic Society\(^9\) recommends any of the macrolides for pneumonia caused by these pathogens in children.

Since CAP is often caused by “atypical organisms,” macrolides are sometimes recommended as empiric outpatient therapy. In this setting, the American Thoracic Society\(^10\) discourages using erythromycin, citing a higher side-effect rate and poorer effectiveness against *Haemophilus influenzae*. However, the Canadian Infectious Disease Society\(^11\) supports the use of any of the 3 macrolides in mild CAP except for patients with chronic obstructive pulmonary disease, who are more likely to harbor *H. influenzae*.

**REFERENCES**


Does warfarin prevent deep venous thrombosis in high-risk patients?

**EVIDENCE-BASED ANSWER**
Warfarin (Coumadin) is effective in preventing deep venous thrombosis (DVT) among patients with a history of DVT. Conventional dosing and longer durations are the most effective, but the ideal length of therapy is unknown (strength of recommendation [SOR]: A, based on large randomized controlled trials and meta-analysis).

Warfarin is useful in preventing DVT in patients with cancer, specifically those treated with chemotherapy (SOR: B, based on small randomized Controlled Trials).
controlled trials). Warfarin may be effective in preventing DVT in immobilized patients such as those with trauma, spinal cord injury, or stroke (SOR: B, based on an underpowered randomized controlled trial and uncontrolled studies).

**EVIDENCE SUMMARY**

Warfarin, at both low and conventional doses, has been shown to be effective in preventing recurrence of DVT. A large, 4-year placebo-controlled randomized controlled trial showed that long-term low-dose warfarin (international normalized ratio [INR], 1.5–1.9) was more effective than placebo for prevention of DVT (hazard ratio=0.36; 95% confidence interval [CI], 0.19–0.67).^1^ A double-blind randomized controlled trial of 738 patients demonstrated that conventional-intensity warfarin therapy (INR=2.0–3.0) was more effective than low-intensity therapy (INR=1.5–1.9) in prevention of recurrent DVT. There were 1.9 vs 0.7 DVTs per 100 person-years in the low-intensity vs conventional-intensity therapy groups (hazard ratio=2.8; 95% CI, 1.1–7.0; number needed to treat [NNT]=37). No significant difference was seen in the frequency of bleeding complications between the groups. This and other studies suggest that low-intensity warfarin therapy reduces the relative risk of thrombosis by about 75%, and conventional-intensity therapy reduces this risk by over 90%.^2^

Several studies have examined the duration of warfarin therapy. A meta-analysis found treatment with warfarin for 12 to 24 weeks decreased DVT recurrence compared with 2- to 6-week regimens (relative risk [RR]=0.60; 95% CI, 0.45–0.79; NNT=21).^3^ A multicenter randomized controlled trial found extending warfarin treatment for 12 months vs 3 months resulted in a 95% relative risk reduction (RRR) in risk of DVT recurrence (95% CI, 63–99; NNT=5).^4^ A multicenter randomized trial showed similar results, but risk for recurrence was the same after treatment was stopped, regardless of the length of treatment.^^5^ In patients with cancer, warfarin was shown to be more effective than placebo in prevention of DVT. In a trial of 311 breast cancer patients receiving chemotherapy, treatment with very-low-dose warfarin (INR=1.3–1.9) decreased thrombotic events compared with placebo, with no increase in bleeding complications (RRR=85%; P=0.031; NNT=27).^6^ A later cost analysis showed that very-low-dose warfarin can be used in prevention of DVT in breast cancer patients on chemotherapy without an increase in health care costs.^^7^ Although immobilized patients are at high risk for DVT, no randomized controlled trials exist for the use of warfarin in these patients. A few small studies suggest that warfarin reduces DVT rates in spinal-cord-injured patients.^^8^ A small trial randomized stroke patients undergoing rehabilitation to placebo or fixed 1- or 2-mg doses of warfarin. This underpowered study showed a nonsignificant decrease in the risk of development of DVT (RR=0.39; 95% CI, 0.13–1.37).^^8^

**RECOMMENDATIONS FROM OTHERS**

The 6th American College of Chest Physicians Consensus Conference on Antithrombotic Therapy makes these recommendations:

- **Prior DVT**: Oral anticoagulation therapy (INR=2.0–3.0) is indicated for at least 3 months for patients with proximal DVT or for at least 6 months in those with idiopathic proximal vein thrombosis or recurrent venous thrombosis. Indefinite anticoagulation is indicated for patients with more than 1 episode of idiopathic proximal vein thrombosis or pulmonary embolus.

- **Malignancy**: Indefinite anticoagulation (INR=2.0–3.0) is indicated for patients with thrombosis complicating malignancy. Prophylaxis with low-intensity warfarin in ambulatory patients with cancer to prevent initial DVT warrants further study.

- **Acute spinal cord injuries**: Low-molecular-weight heparin or switch to full-dose oral anticoagulation (INR=2.0–3.0) for the duration of the rehabilitation phase.

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CLINICAL COMMENTARY

Routine prophylaxis dramatically reduces DVT cases

I can clearly recall the dramatic reduction in the number of our patients who developed DVT when our orthopedic colleagues embraced routine prophylaxis for the high-risk surgical patients with hip surgery and knee replacements. This answer indicates that we may also be able to reduce the risk of DVT in our high-risk nonsurgical patients with previous DVT or breast cancer. Note that much of the evidence is based on the use of low-dose and very-low-dose warfarin. This may help mitigate our fear of substituting bleeding complications for the prevention of clots.

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REFERENCES


Do antibiotics improve outcomes in chronic rhinosinusitis?

EVIDENCE-BASED ANSWER

For children, antibiotics do not appear to improve short-term (3–6 weeks) or long-term (3 months) outcomes of chronic rhinosinusitis (strength of recommendation [SOR]: A, randomized controlled trials). No adequate placebo-controlled trials have been performed in adults. Two consensus statements report that 10 to 21 days of antibiotics active against organisms producing beta-lactamase might be beneficial in some cases (SOR: C).

EVIDENCE SUMMARY

The American Academy of Otolaryngology–Head and Neck Surgery defines chronic rhinosinusitis as the persistence of 2 major or 1 major and 2 minor criteria lasting at least 12 weeks (Table). The other categories of rhinosinusitis are acute (symptoms lasting <3 weeks) and subacute (symptoms lasting 3–12 weeks).

Two placebo-controlled trials have evaluated antibiotic treatment of chronic rhinosinusitis in children. In 1 study, 141 children with chronic rhinosinusitis were randomly assigned to 1 of 4 treatment arms: saline nose drops; xylometazoline (Otrivin) drops with oral amoxicillin 3 times daily; surgical drainage; or surgical drainage, amoxicillin 3 times daily and xylometazoline drops. Outcomes were resolution of purulent rhinitis, no purulent drainage on exam, and no abnormalities of maxillary sinus on x-ray. The absence of all 3 findings constituted cure. At 6 weeks there was a non-statistically significant higher resolution in the fourth group, but by 26 weeks the groups were indistinguishable. At 6 weeks, 53%, 50%, 55%, and 79% of each group, respectively, were cured. These results increased to 69%, 74%, 69%, and 64% at 26 weeks.

Another study randomized 79 children with chronic sinusitis to treatment with cefaclor vs placebo following antral washout. Measured
At 6 weeks, 12.3% more patients in the antibiotic group achieved cure than the placebo group (64.8% vs 52.5%), but this difference was not statistically significant (P= .28). At 12 weeks, no differences in improvement were seen between the 2 groups (89% vs 89.5%).

No studies (since 1966) have evaluated antibiotic use compared with placebo in adults. We did not review the numerous studies comparing different antibiotics without placebo.

**RECOMMENDATIONS FROM OTHERS**

The American Academy of Otolaryngology–Head and Neck Surgery, in conjunction with the American Academy of Rhinology and the American Academy of Otolaryngic Allergy, state that the use of antibiotics active against beta-lactamase producing organisms might be beneficial in some cases. A consensus statement from a panel convened in Belgium in 1996 stated antibiotics should be given for 5 to 7 days with repeat treatments if the child does not respond initially.

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**TABLE 2**

**Diagnostic criteria for rhinosinusitis**

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial pain/pressure*</td>
</tr>
<tr>
<td>Facial congestion/fullness</td>
</tr>
<tr>
<td>Nasal obstruction/blockage</td>
</tr>
<tr>
<td>Nasal discharge/purulence/discolored drainage</td>
</tr>
<tr>
<td>Hyposmia/anosmia</td>
</tr>
<tr>
<td>Purulence in nasal cavity on examination</td>
</tr>
<tr>
<td>Fever (acute only)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Fever (all nonacute)</td>
</tr>
<tr>
<td>Halitosis</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Dental pain</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Ear pain/pressure/fullness</td>
</tr>
</tbody>
</table>

*Symptom alone does not constitute a major sign in the absence of another major nasal symptom. Adapted from Lanza DC, 1997.

For chronic sinusitis, I start by emphasizing nonantibiotic treatments, such as decongestants, nasal steroids, antihistamines, smoking cessation, and avoidance of passive smoke, allergens, and other irritants. With education and experience, patients realize that antibiotics provide only short-term relief, not long-term answers. Having learned this, patients can better participate in antibiotic treatment decisions. Most are able to weigh the short-term, symptomatic benefits against potential medication side effects and the cost. I believe that 2 or 3 courses of antibiotics per year are not excessive, but I try not to exceed that limit.

Finally, I don’t always choose a beta-lactamase–resistant antibiotic. Given that antibiotics do not alter the long-term prognosis, I worry less about resistance and more about minimizing cost and side-effect potential. Therefore, I occasionally treat with amoxicillin or Pen Vee K. Patients seem to appreciate my flexibility and collaborative approach to decision-making.

**REFERENCES**

What is the best approach for patients with ASCUS detected on Pap smear?

■ EVIDENCE-BASED ANSWER
DNA testing for human papillomavirus (HPV), especially if the sample can be obtained at the same time as the Papanicolaou (Pap) smear, can guide the management of women whose test result shows atypical squamous cells of undetermined significance (ASCUS). Those who test positive for high-risk types of HPV should be referred for colposcopy (strength of recommendation [SOR]: B), and those with a negative test result may resume regular Pap testing in 12 months (SOR: B). If HPV testing is unavailable, an alternative strategy is to repeat the Pap smear at 4- to 6-month intervals. After 2 negative Pap smears are obtained, usual screening may resume. But if either of the repeat Pap smears results in ASCUS or worse, the woman should be referred for colposcopy (SOR: B).

■ EVIDENCE SUMMARY
Although only 5% to 10% of women with the result of ASCUS on a Pap smear have a high-grade squamous intraepithelial lesion (HSIL), estimates suggest that more than one third of these lesions are identified during follow-up to ASCUS Pap smears.¹

The recent ASCUS-LSIL Triage Study (ALTS), a multicenter randomized trial, directly addressed the appropriate evaluation of ASCUS.² The trial compared 3 management strategies for ASCUS Pap smears: reflex HPV-DNA testing (the initial Pap sample is tested for HPV only if the results are ASCUS), immediate referral for colposcopy, and repeat Pap smears. Reflex HPV testing had a sensitivity of 96% for detecting HSIL and a negative predictive value of 98%. The 44% of women with ASCUS who tested negative for high-risk HPV were able to avoid colposcopy. A single repeat Pap smear within 4 to 6 months, with referral for colposcopy if abnormal, had a sensitivity of 85% (sensitivity might be expected to improve with a second repeat test) and a similar colposcopy referral rate.³

A cost-effectiveness analysis that modeled data from the trial found that reflex HPV testing was most cost-effective.⁴ For women aged 29 years or older, HPV testing resulted in a much lower colposcopy referral rate, 31% vs 65% for younger women, without sacrificing sensitivity.⁴

■ RECOMMENDATIONS FROM OTHERS
Evidenced-based guidelines were developed at a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology in September 2001.⁵ Recommendations were also made for women with ASCUS in special circumstances. Pregnant women should be managed the same way as nonpregnant women; immunosuppressed women should be referred for colposcopy; and postmenopausal women, who are at a lower risk for HSIL, may try a 3- to 6-week course of intravaginal estrogen followed by repeat Pap smears 1 week after estrogen treatment and again 4 to 6 months later.

If either repeat test is reported as ASCUS or greater, the woman should be referred for colposcopy. Any woman with a Pap smear reported as ASCH (atypical squamous cells, cannot exclude HSIL) should be referred for colposcopy.⁵

The US Preventive Services Task Force recently concluded that evidence is insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer, but they did not address the management of abnormal Pap smears.⁶
Thin-prep Pap smears can make workup of ASCUS easier for physician and patient

The management of ASCUS Pap smears has often confused primary care doctors. This is confounded by the fact that it is often a challenge to ensure that patients follow our recommendations. How could we blame them—after all, who wants to undergo 4 Pap smears instead of 1? The advent of thin-prep Pap smears, with reflex HPV testing on the same specimen, has simplified our lives. By obtaining routine thin-prep Pap smears and then reflex HPV testing for only high-risk HPV types, fewer Pap smears and colposcopic exams are needed, without reducing the detection of HSIL. Best of all, fewer women are overtreated or lost to follow-up.

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REFERENCES
The mortality benefit with ARBs has not been as consistent as that shown with ACE inhibitors.

nephropathy defined by a urinary albumin excretion rate >200 µg/min that is at least 30% higher than the baseline rate. This trial showed that irbesartan delayed progression to nephropathy independent of its effect on blood pressure compared with conventional therapy (NNT=16 at the 150-mg dose and NNT=11 at the 300-mg dose).

A third double-blind, placebo-controlled trial—IDNT (Irbesartan Diabetic Nephropathy Trial)—randomized 1715 patients to irbesartan, amlodipine (Norvasc), or placebo for a median follow-up of 2.6 years. Each group could also use other conventional antihypertensive therapy (but again excluding ACE inhibitors, ARBs, and calcium-channel blockers). Irbesartan reduced progression of nephropathy (defined by doubling of the serum creatinine) and the onset of end-stage renal disease more effectively than amlodipine (NNT=12) or placebo (NNT=16). Irbesartan did not decrease cardiovascular mortality, nonfatal myocardial infarction, heart failure resulting in hospitalization, neurologic deficit caused by a cerebrovascular event, or above-ankle lower-limb amputation.

The mortality benefit with ARBs has not been as consistent as that shown with ACE inhibitors. Both classes of drugs conferred reduced mortality as seen with ramipril in the HOPE (Heart Outcomes Prevention Evaluation) trial and losartan in the LIFE (Losartan Intervention For Life) trial. However, a survival benefit was not seen with irbesartan in the RENAAL and IDNT trials.

■ RECOMMENDATION FROM OTHERS

The American Diabetes Association recommends both ACE inhibitors and ARBs for the treatment of early nephropathy in hypertension to delay the progression of microalbuminuria to macroalbuminuria and overt nephropathy.

**REFERENCES**


**DRUG BRAND NAMES**

Amlodipine • Norvasc
Amoxicillin • Amoxil, Biomox, Polymox, Trimox, Wymox
Azithromycin • Zithromax
Cefaclor • Cefclor
Cephallexin • Biocif, Keflex
Clarithromycin • Biaxin
Clindamycin • Cleocin, Dalacin
Irbesartan • Avapro
Losartan • Cozaar
Ramipril • Altace
Vancomycin • Vancocin
Warfarin • Coumadin
Xylometazoline • Otrivin