What is the most effective beta-blocker for heart failure?

■ EVIDENCE-BASED ANSWER

Three beta-blockers—carvedilol, metoprolol, and bisoprolol—reduce mortality in chronic heart failure caused by left ventricular systolic dysfunction, when used in addition to diuretics and angiotensin converting enzyme (ACE) inhibitors (strength of recommendation [SOR]: **A**, based on large randomized placebo-controlled trials). No differences in mortality or patient tolerance have been demonstrated in studies comparing carvedilol and metoprolol (SOR: **B**, based on small head-to-head trials).

■ EVIDENCE SUMMARY

The **Table** shows the 5 largest trials of beta-blockers in systolic dysfunction, including patients with both ischemic and nonischemic heart disease. In all trials, the majority of subjects were taking diuretics and either an ACE inhibitor or angiotensin receptor blocker.

The Carvedilol Prospective Randomized Cumulative Survival[2] (COPERNICUS) trial, Metoprolol CR/XL Randomized Intervention Trial in Heart Failure[3] (MERIT-HF), and Cardiac Insufficiency Bisoprolol Study II[4] (CIBIS-II) all showed similar reductions in mortality in moderately ill patients with heart failure.

In contrast, the Beta-Blocker Evaluation of Survival Trial[5] (BEST) demonstrated no effect with bucindolol. This suggests there may be differences in effectiveness among beta-blockers in reducing mortality in heart failure, and that it would be unwise to assume that protection is a class effect. We found no meta-analysis that pooled data on individual drugs for comparison purposes.

The US Carvedilol trial[1] demonstrated a larger reduction in mortality than that seen in other beta-blocker trials. However, it had several methodologic problems: it was a composite of 4 smaller studies that used exercise tolerance as the primary endpoint; median duration of data collection on subjects was only 6 months; it included many minimally symptomatic patients; the actual number of deaths was small (producing a wide confidence interval); and subjects who did not survive the run-in phase were excluded from analysis.[6]

Three randomized controlled trials have compared carvedilol and metoprolol head-to-head. The largest[7] included 150 subjects with ejection fractions below 35% who were randomized to 1 of the 2 drugs and followed for more than 3 years. Symptom scores and quality of life assessments were similar in the 2 groups. A trend toward lower mortality in the carvedilol group did not

What is a Clinical Inquiry?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and individuals with particular expertise.

Questions chosen for Clinical Inquiries are those considered most important, according to results of web-based voting by family physicians across the U.S.

Answers are developed by a specific method:
• First, extensive literature searches are conducted by medical librarians.
• Clinicians then review the evidence and write the answers, which are then peer reviewed.
• Finally, a practicing family physician writes a commentary.

TABLE							
Selected trials of beta-blockers for systolic dysfunction							
Study	**Drug**	**N**	**Mortality reduction (%)**	**95% CI (%)**	**Statistically significant?**	**NNT**	**Mean duration of follow-up (months)**
US Carvedilol[1]	Carvedilol	1094	(65)	39–80	Yes	22	6.5
COPERNICUS[2]	Carvedilol	2289	(35)	19–48	Yes	14	10.4
MERIT-HF[3]	Metoprolol	3991	(34)	19–46	Yes	26	12
CIBIS II[4]	Bisoprolol	2647	(34)	19–47	Yes	18	15.6
BEST[5]	Bucindolol	2708	(9)	−0.2–22	No	—	24
CI, confidence interval; NNT, number needed to treat							

reach statistical significance. Peak oxygen uptake during exercise was greater in the metoprolol group. The carvedilol group had a statistically greater improvement in ejection fraction (+10.9 ± 11.0 vs +7.2 ± 7.7 at rest). The Carvedilol or Metoprolol European Trial (COMET), a larger head-to-head trial of carvedilol and metoprolol (N=3029), is ongoing.[8]

No large studies of older beta-blockers adequately assess mortality in heart failure. One study of propranolol (N=158) showed a 27% reduction in mortality in mild heart failure in the setting of ischemic heart disease.[9] A study of atenolol versus placebo in subjects with ejection fraction ≤25% from various causes (N=100) was halted early when atenolol produced a 50% reduction in worsening heart failure and a 71% reduction in cardiac hospitalizations.[10] A trend toward improved survival was noted but did not reach statistical significance.

■ RECOMMENDATIONS FROM OTHERS

We found no guidelines that specifically endorsed one beta-blocker over another for heart failure.

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■ CLINICAL COMMENTARY

To provide the best care, we must go beyond the conventional ACE inhibitor and diuretic therapy for congestive heart failure patients. Adding 1 of the 3 beta-blockers (carvedilol, metoprolol, or bisoprolol), as recommended above, will further improve the survival rates and decrease hospitalization rates.

Remember these pearls when using beta-blockers in congestive heart failure:

- Do not start therapy until the patient's fluid status has been stable for at least 1 month
- Avoid using in patients with bronchospastic disease, symptomatic bradycardia, or advanced heart blockage
- Start with low doses and titrate up slowly as tolerated every 2 weeks to the recommended target range of the beta-blocker chosen
- Decrease the dose if significant bradycardia or atrioventricular block occurs
- Let your patients know that it may take several months of beta-blocker therapy to obtain the protective benefits.

If you encounter difficulties with titration or don't feel comfortable initiating beta-blocker therapy, consult your cardiologist for help.

Fred Grover, Jr, MD, University of Colorado Health Sciences Center, Denver

Chronic heart failure

Complementary actions of diuretics, ACE inhibitors, and beta blockers

Evidence shows that the combination of diuretics, ACE inhibitors, and 1 of 3 beta-blockers—carvedilol, metoprolol, bisoprolol—is more effective than just diuretics plus ACE inhibitors. The clinical effect of their combined actions is reduced workload on the failing heart
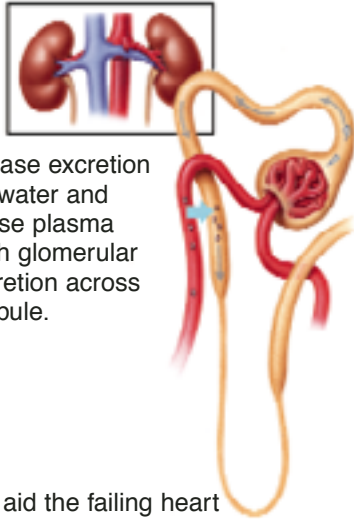
Diuretics increase excretion of sodium and water and thereby decrease plasma volume, through glomerular filtration or secretion across the proximal tubule.

Beta-blockers aid the failing heart in several ways:
- Slow the heart rate
- Reduce the myocardial contractility
- Increase vasodilation (carvedilol, metoprolol)

ILLUSTRATION BY TODD BUCK
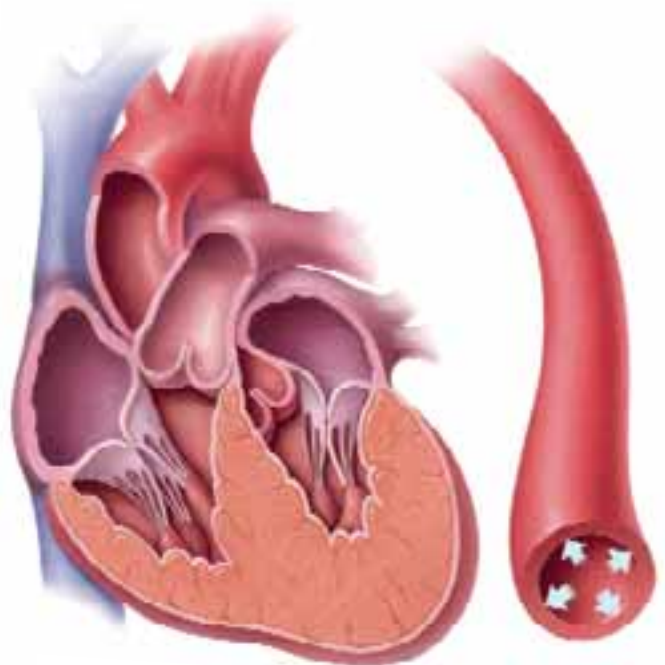
Through dilation of peripheral arteries and veins, **ACE inhibitors** enchance left ventricular function by reducing filling pressure and systemic resistance.

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Does increasing methylphenidate dose aid symptom control in ADHD?

■ EVIDENCE-BASED ANSWER

Most children with attention deficit/hyperactivity disorder (ADHD) who are started on methylphenidate will respond favorably to a dose increase if the initial dose does not sufficiently reduce symptoms. Once titrated to an effective maintenance dose, frequent follow-up is necessary to monitor for side effects and recurring symptoms. The dose of methylphenidate can then be increased further for better symptom control, which may be warranted in most cases.

In some children, methylphenidate may not achieve response even at high doses or may cause intolerable side effects. For these children, start a different stimulant medication (strength of recommendation: **B**, based on extrapolation of 1 randomized controlled trial).

■ EVIDENCE SUMMARY

Most studies of ADHD medication have lasted fewer than 4 months. The National Institute of Mental Health Collaborative Multisite Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (known as the MTA study) is the longest treatment study of children to date. This study—a 28-day, double-blind placebo-controlled trial—enrolled children aged 7 to 9 years with ADHD and compared 4 treatment strategies (including medication and behavioral interventions) over 14 months.[1–3]

Of particular interest was the dose-titration evaluation at the beginning of the study. Daily dose-switching titration of methylphenidate was used to identify the optimal starting dose for each child assigned to receive medication. In all, 289 children were randomized to receive methylphenidate, and 256 completed the titration (17 children refused to take medication, 1 moved, 4 had side effects, 4 had missing data, and 7 stopped mid-titration because of inability to follow the titration protocol).

Of the 256 children who completed titration, 198 (77%) responded favorably to 1 of the following doses: low (15 mg/day), intermediate (25 mg/day), or high (35 mg/day for children weighing less than 25 kg; or 50 mg/day for children weighing 25 kg or more). Of the remaining 23%, 32 children responded best to placebo and 26 were methylphenidate nonresponders and were subsequently placed on dextroamphetamine.

Children who responded to methylphenidate entered the 13-month maintenance phase on the optimal dose identified in the titration trial. They were monitored by monthly re-examination and review of information from parents and teachers regarding ADHD symptoms and potential drug side effects. The dose was changed if symptoms were not well controlled or if side effects were present. Subsequently, if no effective and well-tolerated dose of methylphenidate could be identified, the drug was deemed ineffective for that child and was replaced by another medication.

Of the children who responded to methylphenidate, 88% were still taking it at the end of the maintenance trial; 29% were still taking the titration-determined dose of methylphenidate, 18% took a lower dose, and 41% took a higher dose as their "optimal" dose, at which there were no clinically significant symptoms, or "no room for improvement." The mean dose increased from 31 mg/day at the start to 34 mg/day at the end of the study. Of the 430 total changes in dose made during the maintenance period, 62% were dose increases.

While commendable for its design and large study population, the MTA study had several limitations. The titration trial's complex method of determining each child's "best dose" may not be feasible in clinical practice. Furthermore, the study enrolled only children aged 7 to 9 years, while ADHD affects a much broader age range. Finally, the chronic nature of ADHD limits the generalizability of this study beyond 14 months. Additional long-term studies are needed.

■ RECOMMENDATIONS FROM OTHERS

The most common strategy for managing children taking methylphenidate is to start with a low dose and gradually adjust upward, as required by residual symptoms and as allowed by side effects. This escalating-dose titration reflects typical practice in the United States, as described in several clinical guides.[4,5] The *Physician's Desk Reference* states that the maximum total daily dose is 60 mg for methylphenidate, and experts often limit the upper range to 25 mg for a single dose.[6]

The American Academy of Child and Adolescent Psychiatry suggests using a consistent titration schedule with weekly increases in increments of 5–10 mg per dose to achieve symptom control. Alternatively, a fixed-dose titration trial similar to that found in the MTA study may be employed, in which a full set of different doses is switched on a weekly basis. If the top recommended dose does not help, a change in drug or psychosocial intervention may be more beneficial than an increase in methylphenidate dose.[6]

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■ CLINICAL COMMENTARY

It is disheartening to watch a bright child receive D's in school just because he or she cannot pay attention. Treating children with ADHD is one of the most clinically rewarding behavioral issues we can address as primary care physicians.

The escalating-dose titration and effective maintenance of methylphenidate can seem intimidating. We fear the side effects and are unsure if raising the dose of methylphenidate will have any benefits.

Clearly, it is shown that raising the methylphenidate dose brings further benefits for most children, but short-acting forms (such as Ritalin) frequently have intolerable side effects. Several long-acting forms of methylphenidate (Concerta, Metadate CD, Methylin ER, and Ritalin SR) are now on the market. This allows us to raise the dose as high as 54–60 mg/day with much less drug intolerance. For children who are benefiting from methylphenidate but cannot tolerate the side effects, consider the long-acting form.

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Are tympanostomy tubes indicated for recurrent acute otitis media?

■ EVIDENCE-BASED ANSWER

For children with recurrent acute otitis media (here defined as 3 or more episodes in 6 months, or 4 or more in a year), tympanostomy tubes are indicated if middle-ear effusion is present. Tubes reduce the frequency of recurrent acute otitis media by 2 to 3 episodes per year in these patients (strength of recommendation [SOR]: **A**; based on randomized controlled trials).

Further benefits include improved quality of life for both child and caregiver and greater parental satisfaction (SOR: **B**; based on trials

Tympanostomy tubes reduce the number of acute episodes of otitis in children with middle-ear effusion

that included patients with recurrent acute otitis media or otitis media with effusion).

Tympanostomy tubes do not decrease the number of recurrent acute otitis media episodes in children without middle-ear effusion (SOR: **A**, based on randomized controlled trials). These children run the risk of adverse outcomes of tube placement, including transient or recurrent otorrhea, tympanosclerosis, focal atrophy, perforation, and cholesteatoma (SOR: **A**; based on meta-analysis).

■ EVIDENCE SUMMARY

Several randomized controlled trials and a meta-analysis demonstrated that the children most likely to benefit from tympanostomy tubes are those more than 6 months old with middle-ear effusion who have had 3 or more episodes of acute otitis media in 6 months, or 4 or more episodes in 12 months.[1–4] Data are inadequate to determine the lowest rate of recurrence that would suggest a benefit from tube placement.

A meta-analysis of 5 randomized trials comparing no surgery with placement of tubes for recurrent acute otitis media with or without middle-ear effusion showed that the placement of tubes resulted in a mean absolute decrease in acute otitis media incidence of 1.0 per year (95% confidence interval [CI], 0.4–1.6), and a decrease in the prevalence of middle-ear effusion by 115 days per year (95% CI, 11–220).[4] The benefit of tubes for recurrent acute otitis media was demonstrated only in studies in which middle-ear effusion was present:[2,3] one found 3.01 (95% CI, 2.18–3.84) fewer acute episodes per year;[1,4] the other found 2.27 (95% CI, 1.03–3.51) fewer.[2,4]

One randomized controlled trial of 264 children, aged 7 to 35 months, with a history of recurrent acute otitis media but free of middle-ear effusion, compared tubes with medical therapy and found no difference in recurrence over 2 years.[3] The medical therapy arm received prophylaxis with either amoxicillin or placebo. The amoxicillin arm had 0.6 fewer episodes of acute otitis media per year compared with the other 2, a statistically significant 40% decrease (relative risk reduction=0.4).[3]

The average time with otitis media of any type (acute otitis media, otitis media with effusion, or ottorhea) also decreased—15.0% in the placebo group, 10.0% in the amoxicillin group, and 6.6% in the tympanostomy tube group (amoxicillin vs. placebo, P=.03; tubes vs. placebo, P<.001).[3] Higher dropout rates occurred in the amoxicillin and medical treatment groups.[3]

In prospective studies of patients receiving tubes for recurrent acute otitis media and otitis media with effusion, measures of quality of life—physical suffering, emotional distress, activity limitation, hearing loss, speech development, caregiver concern/worry, parental post-tube satisfaction,[4,5,6] and an ear symptom score[6]—improved after tube placement. Within several weeks of tube placement, 79% of children had improved quality of life, 17% had trivial change, and 4% were worse.[4]

A meta-analysis reporting sequelae of tympanostomy tubes found an absolute complication rate of 26% for transient otorrhea and 4% for chronic otorrhea.[4]

Compared with nonsurgical treatment, complication rates for tube placement were reported in 0.7% of surgically treated ears.[7] Complications included:
- tympanosclerosis (relative risk [RR]=3.5 [95% CI, 2.6–4.9])
- focal atrophy (RR=1.7 [95% CI, 1.1–2.7])
- perforation (RR=3.5 [95% CI, 1.5–7.1])
  - 2% with short-term tubes
  - 16% with long-term tubes
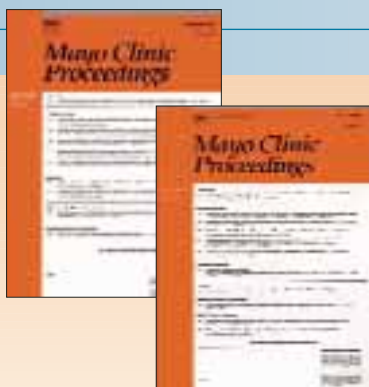- cholesteatoma (RR=2.6 [95% CI, 1.5–4.4]).
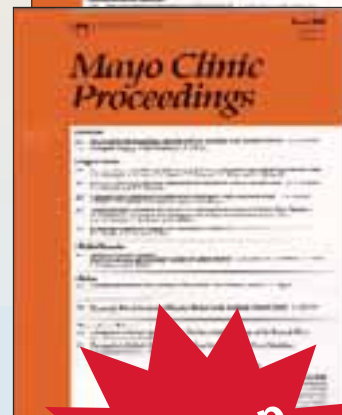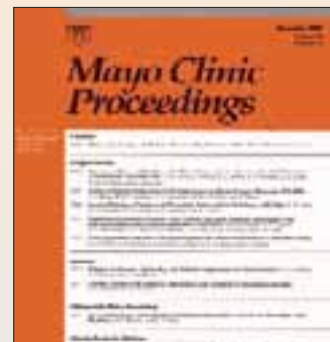
RECOMMENDATIONS FROM OTHERS

The Institute for Clinical Systems Improvement 2001 guidelines for recurrent acute otitis media treatment in children recommends initial antibiotic prophylaxis with amoxicillin (20 mg/kg/day) for 2 to 6 months (based on randomized controlled trial data). If there are 2 recurrences of acute otitis media during that time, then referral to an otorhinolaryngologist for possible tympanostomy tube placement is recommended.[8]

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CLINICAL COMMENTARY

Of the remaining challenges to the care of children with recurrent acute otitis media, 2 major issues are accurate diagnosis and the lack of information about long-term results. Diagnosis is difficult and requires pneumotoscopy and/or tympanometry. Without those techniques, a red drum (unless it is bulging) has a <40% positive predictive value for recurrent acute otitis media with effusion. On the other hand, with pneumotoscopy or tympanometry, the positive predictive value is 78% to 85%.

We don't want to refer children unnecessarily for tubes. Delaying referral up to 9 months in children aged 6 to 36 months with middle-ear effusion does not seem to hurt language acquisition at 3 years of age. At this point, I know of no long-term follow-up studies of randomized controlled trials of >4 years to assess differences in language acquisition and hearing.

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How should we manage infants at risk for group B streptococcal disease?

EVIDENCE-BASED ANSWER

Asymptomatic term infants whose mothers received adequate intrapartum antibiotic prophylaxis (defined as intravenous penicillin or ampicillin at least 4 hours before delivery) for group B streptococcal disease do not need work-up or treatment (strength of recommendation [SOR]: **B**, based on retrospective, population-based study). These infants should be observed for 48 hours, but may be discharged after 24 hours in circumstances where close follow-up is available (SOR: **D**, based on expert opinion).

Symptomatic infants, premature infants (gestational age <35 weeks) of mothers who did not receive prophylaxis, and infants whose mothers had chorioamnionitis should receive a full evaluation (complete blood count, blood culture, and chest x-ray with or without a lumbar puncture) and an initial empiric antibiotic treatment with ampicillin or penicillin and gentamycin. If a term infant is not symptomatic and maternal antibiotic prophylaxis was *not* adequate, opinions differ as to whether to perform limited evaluation with empiric treatment or close observation (SOR: **D**, based on expert opinion). See **Figure**.

FIGURE

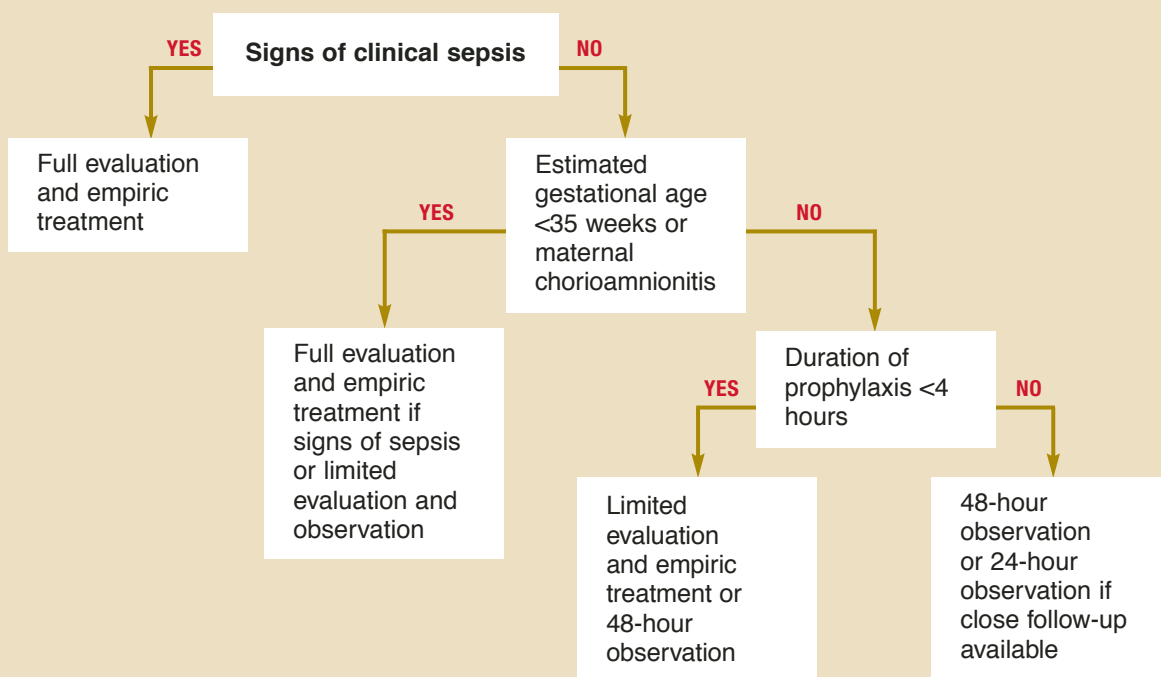## Management of infants born to mothers with group B streptococcal disease–positive cultures

Figure adapted from Schrag et al, *MMWR Recomm Rep* 2002; 51(RR-11):1–22.[1]
Limited evaluation: complete blood count and blood culture.
Full evaluation: complete blood count, blood culture, chest x-ray if respiratory symptoms, and lumbar puncture if indicated.

■ **EVIDENCE SUMMARY**

Intrapartum antibiotic prophylaxis has decreased the incidence of early-onset group B streptococcal disease by 65% in the last decade.[1] A multicenter population-based study demonstrated that basing prophylaxis on screening cultures is twice as effective as risk stratification, a previously recommended strategy.[2]

Intrapartum prophylaxis of women who had positive group B streptococcal disease screening cultures at 35 weeks will prevent 70% of early-onset disease and 89% of fatalities.[3,4] As demonstrated by multicenter retrospective studies, infants aged <35 weeks are at significantly higher risk of group B streptococcal disease than term infants (relative risk=1.5–2.07), and mortality for

premature infants with early-onset disease (25%–30%) is substantially higher than for term infants with early-onset disease (2%–8%).[2,5]

A large retrospective study demonstrated that infants who developed early-onset disease despite intrapartum prophylaxis developed the same clinical syndrome in the same time frame (78% of early-onset disease evident in first 24 hours and 96% by 48 hours) as infants whose mothers did not receive prophylaxis.[6]

The duration of adequate intrapartum antibiotic prophylaxis was initially set at 4 hours, based on a study measuring antibiotic penetration into amniotic fluid.[7] A recent randomized trial, enrolling more than 4500 women, has confirmed this finding. The vertical transmission rate of

group B streptococcal disease, as measured by neonatal colonization (as opposed to clinical illness), is 46% when antibiotic prophylaxis is started <1 hour before delivery, 2.9% when prophylaxis is given at 2 to 4 hours, and 1.2% when given at least 4 hours before delivery.[8]

Implementation of these guidelines is aided by the adoption of an institution-wide policy to support point of care decision-making.[9] A retrospective study after the release of the 1996 Centers for Disease Control (CDC) guidelines concluded that hospitals with established group B streptococcal disease policies had significantly fewer cases of early-onset disease (*P*=.038).[10]

■ RECOMMENDATIONS FROM OTHERS

The 2002 *Prevention of Perinatal Group B Streptococcal Disease Revised Guidelines* from the CDC states: "a healthy-appearing infant whose mother received >4 hours of [intrapartum antibiotic prophylaxis] before delivery may be discharged home as early as 24 hours after delivery, assuming other discharge criteria have been met and that a person able to comply fully with instructions for home observation will be present … if these conditions are not met, the infant should remain in the hospital for at least 48 hours of observation and until criteria for discharge are achieved."[1]

These guidelines strongly support universal prenatal screening and the use of intrapartum antibiotic prophylaxis. Both the American Academy of Pediatrics and the American College Obstetrics and Gynecology have endorsed the CDC's revised guidelines.

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■ CLINICAL COMMENTARY

The question of appropriate care of the infant exposed to group B streptococcal disease arises frequently in any practice caring for newborns. These clear, evidence-based recommendations are helpful in guiding that care. The evidence supports watchful waiting for appropriately covered newborns, providing reassurance for both parents and physicians.

Unfortunately, little evidence exists to guide care in a setting that seems to be quite common: the term, asymptomatic infant born to a mother who, in labor, received less-than-adequate intrapartum antibiotic prophylaxis. Further research for this subgroup is needed; in the meantime, physicians who provide maternity or newborn care should work together to develop protocols that ensure adequate intrapartum antibiotic coverage for mothers with group B streptococcal disease.

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