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TERAZOSIN VS FINASTERIDE FOR BPH

Reference Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. N Engl J Med 1996; 335:533-9.

Clinical question **How do terazosin, finasteride, and combination therapy compare in the treatment of benign prostatic hypertrophy (BPH)?**

Background A variety of therapeutic options are available for the treatment of BPH. These include prostatectomy, medical treatment with alpha-1-adrenergic antagonists such as terazosin or 5-alpha-reductase inhibitors such as finasteride, and no treatment. The comparative efficacy of medical therapies has not been assessed.

Population studied Men aged 45 to 80 with symptomatic benign prostatic hyperplasia who were seen in Veterans Affairs outpatient clinics were enrolled. No specified level of prostatic enlargement was required. Exclusion criteria included concurrent treatment with alpha-adrenergic agonists, cholenergic agonists or antagonists, topical beta-adrenergic antagonists; antihypertensive medications other than diuretics and ACE inhibitors; hormone therapy; cardiac, cerebrovascular, or other prostatic disease; diabetes mellitus; orthostatic hypotension; renal or hepatic impairment; and elevation of prostate specific antigen.

Study design and validity This was a four-armed, randomized, placebo-controlled trial lasting 1 year that compared placebo, terazosin, finasteride, and a combination of the two drugs. Patients in the study were similar in age, prostatic volume, American Urological Association symptom score, peak urinary flow, and prostate-specific antigen level. Withdrawal rates were significantly higher in the treatment arms compared with the placebo group; however, statistical analysis was appropriately done on an intention-to-treat basis.

Outcomes measured The primary outcome was the American Urological Association symptom score. Secondary outcomes included the peak urinary flow, prostatic volume, prostatic specific antigen level, and occurence of side effects.

Results Of the 1229 men who entered the study, 1007 (82%) completed the study. Among these, the average symptom score decreased by 2.6 in the placebo group, 3.2 in the finasteride group, 6.1 in the terazosin group, and 6.2 in the combination-therapy group. Peak urinary flow rate increased by 1.4, 1.6, 2.7, and 3.2 mL per second, respectively ($P<.001$ for the comparisons of terazosin and combination therapy with finasteride and placebo). Most importantly, finasteride did not differ significantly from placebo in either the decrease in symptom score or the change in peak urinary flow rate. The rate of withdrawal from the study because of side effects was not significantly different among the active treatment groups, but in all three cases was significantly higher than the withdrawal rate for the placebo group.

Recommendations for clinical practice **This study showed that terazosin, but not finasteride, resulted in an improvement in symptoms compared with placebo, a finding of both statistical and clinical significance. The study differs from prior studies of finasteride alone that showed efficacy.[1,2] The associated editorial[3] suggests that the difference between these studies may lie in the inclusion criteria. While the present study had no restrictions as to prostatic size, studies showing efficacy of finasteride enrolled patients with prostatic hypertrophy. BPH may be a heterogeneous disorder with differential responses to therapy depending on the presence of glandular enlargement. Thus, for patients without palpable hypertrophy, alpha-1-adrenergic antagonists may be the initial medical treatment of choice. For patients with prostatic hypertrophy, finasteride may be an alternative treatment.**

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Vascular Events During Antihypertensive Treatment

Reference Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. JAMA 1996; 276:785-91.

Clinical question **Is there an increased risk of morbidity and mortality in hypertensive patients treated with the calcium channel blocker isradipine as compared with patients treated with hydrochlorothiazide?**

Background Several large randomized trials have shown that treatment of hypertension with diuretics and beta-blockers reduces the risk of fatal and nonfatal coronary artery disease and stroke. Although long-term outcomes of treating hypertension with calcium channel blockers are not known, these agents are currently prescribed for hypertension as frequently as diuretics and more frequently than beta-blockers.

Population studied Hypertensive patients were recruited from nine university-based clinics. Of 18,800 subjects initially identified, 883 met all inclusion criteria and were enrolled in the study. Hypertension was defined as an average diastolic pressure of 90 to 115 mm Hg, measured twice in the sitting position on three consecutive visits. Exclusion criteria included elevated total cholesterol (> 240 mg/dL) or low-density lipid level (> 160 mg/dL); elevated blood glucose, creatinine, or liver enzymes; recent history (within 3 months) of stroke, myocardial infarction, coronary bypass surgery, or angioplasty; contraindication to either study medication; and a history of carotid endarterectomy, insulin-dependent diabetes, or secondary hypertension.

Study design and validity Patients were randomized in a double-blind fashion to receive either isradipine (2.5 to 5.0 mg twice daily) or hydrochlorothiazide (HCTZ; 12.5 to 25 mg twice daily), with follow-up every 2 to 3 months for 3 years. Doses of the medications were titrated during the first 4 months to achieve a target reduction in diastolic blood pressure of at least 10 mm Hg. Patients who failed to reach this goal with the highest dose of study medication were prescribed enalapril.

There were no significant differences between the groups with respect to demographic criteria or cardiovascular risk factors. The percentage of patients in each group requiring the addition of enalapril to reach the target blood pressure was not significantly different. There was also no significant difference in the percentage of patients discontinuing their medication because of noncompliance or adverse reactions (9.3% for isradipine vs 8.2% for HCTZ). All subjects were included in the final analysis according to intention-to-treat and no patients were lost to follow-up.

Outcomes measured The primary outcome measured was the rate of progression of mean maximum intimal-medial thickness (IMT) in carotid arteries as measured by quantitative B-mode ultrasonography. Secondary outcomes measured included the incidence of major and nonmajor vascular events that resulted in hospitalization or a return to a physician's office.

Results In the first 6 months of the study, the mean maximum IMT increased more in the HCTZ group. After this period, the rate of progression of IMT did not differ significantly between the two groups. With respect to patient-oriented clinical events, there were more major vascular events (stroke, myocardial infarction, angina, congestive heart failure, or sudden death) in the isradipine group (25 vs 14, P=.07). There were also significantly more nonmajor vascular events (transient ischemic attack, aortic valve replacement, or arterial bypass graft placement) in the isradipine group (40 vs 23, P=.02). All-cause mortality was not significantly different between the two groups.

Recommendations for clinical practice **Calcium channel blockers should not be used as first-line therapy for hypertension. Because of their established efficacy in the prevention of stroke and myocardial infarctions, diuretics and beta-blockers are still the drugs of choice. Several recent studies have raised concern about the risk of cardiovascular complications associated with short-acting dihydropyridine calcium channel blockers, and other studies have linked calcium channel blockers with increased perioperative bleeding, increased gastrointestinal hemorrhage, and an increased risk of cancer. Large-scale randomized trials are currently underway to compare long-term effects on morbidity and mortality of different antihypertensive agents, including calcium channel blockers.**

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Effect of Primary Care on Hospitalization

Reference Weinberger M, Oddone EZ, Henderson WG. Does increased access to primary care reduce hospital readmissions? N Engl J Med 1996; 334:1441-7.

Clinical question **Does providing increased access to primary care following hospital discharge decrease subsequent hospitalization?**

Background The changing health care climate has led to increased scrutiny of primary care and its effect on patient outcomes. This trial studied the effect of enriching the primary care available to seriously ill veterans.

Population studied Hospitalized patients from nine Veterans Affairs medical centers with diabetes, congestive heart failure, or chronic obstructive pulmonary disease (COPD) and without continuous primary care were identified. Almost all were male, the mean age was 63 years, and most were severely ill. Half of those with heart failure were New York Heart Association (NYHA) class III or IV, and one third of the COPD patients required home oxygen or long-term treatment with steroids. The generalizability of the results from this population is further limited by the system of care, characterized by relatively low patient satisfaction (average score of 3, with scores ranging from 1, least satisfied, to 5, most satisfied) and high hospital utilization (17,600 hospital days/1000 patients/year).

Study design and validity This was a multicenter, randomized controlled trial. Consenting patients (n = 1396) were randomized to customary post-discharge care or "intensive" primary care. The intervention group received visits from a nurse and a primary care clinician in the hospital, and then had a scheduled visit with the physician and a telephone follow-up. Of these, 82% kept their first post-discharge appointment. Follow-up was for 6 months, data analysis was on an intention-to-treat basis, and potential confounders were controlled with multivariate techniques. Statistical power was adequate.

Although the overall design was appropriate, the intervention was quite modest, focusing on *access* to care rather than *coordination* of care with a relatively short follow-up period. Moreover, the training and orientation of the "primary care physicians" is unclear, since over a quarter were not board-certified internists or family physicians, and the subspecialty training of the internists was not specified.

Outcomes measured Primary outcomes were rates of hospital readmission and total number of days of hospitalization, with data collected from Veterans Affairs databases and the hospitals and physicians identified by the patients. Other outcomes were emergency department and clinic visits as well as quality-of-life and patient satisfaction, measured using standardized, well-validated questionnaires.

Results Study and control groups were similar at baseline. The study group had a higher monthly readmission rate (19% vs 14%, P=.005) and more days of rehospitalization (10.2 vs 8.8, P=.041). When the results were adjusted for the patients' severity of illness and assessed risk of readmission, the difference in number of days of hospitalization was no longer significant. Quality-of-life scores did not change in either group, but the patients in the intervention group reported increased satisfaction with their care that was clinically and statistically significant (P>.0001).

Recommendations for clinical practice **The primary care intervention increased rather than decreased the rate of rehospitalization, although patients in the study group were more satisfied with their care. Reports in the popular press have touted this study as evidence that organizing health care around primary care is ineffective. This trial was a serious effort to address the special needs of a sick population. Given how small the intervention was, the increase in patient satisfaction is remarkable.**

Leaving aside the issue of what rate of hospitalization is right for this sick population, the actual result of this study was modest: a minimal intervention geared at access only has minimal effect. Primary care includes much more than just meeting a primary care physician; it must also include an evidence-based practice, intensive coordination of care, and collaboration with different kinds of providers. These kinds of interventions are now being put together under the rubric of "disease state management." This study is another clear reminder for family physicians that our performance will in part be evaluated by how effectively we care for our highest risk patients.

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Efficacy of Right Heart Catheterization

Reference Conners AF, Speroff T, Dawson NV, Thomas C, Herrell FE, Wagner D, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996; 276:889-96.

Clinical question **How does right heart catheterization in critically ill patients affect survival and utilization of medical resources?**

Background Right heart catheterization (RHC) is commonly used to guide therapy in critically ill patients. Despite the expense and widespread acceptance of this procedure, it has never been shown to improve outcomes. Prior observational studies have found that

patients managed with RHC actually have worse outcomes, but these studies did not control adequately for variables that affect treatment selection.

Population studied Study subjects included 5735 patients in the intensive care unit (ICU) at one of five geographically diverse academic medical centers participating in SUPPORT (the Study to Understand Prognoses and Preferences of Outcomes and Risk of Treatment). Eligible subjects had to be 18 years of age or older, meet defined criteria for one or more of nine disease categories including acute respiratory failure, congestive heart failure, and multiorgan system failure, and have an estimated 6-month survival rate of 50%.

Study design and validity This is a prospective cohort study using case controls. To minimize the impact of a treatment selection bias, researchers developed a "propensity score" to assist in case matching. This score is the probability of a patient having RHC based on a number of demographic, clinical, and physiologic factors. Eligible ICU patients were enrolled and nurse reviewers performed chart abstractions and interviews. Admission diagnosis and comorbid conditions were noted. Physiological status and the intensity of care were assessed using standard scales. Additional information was collected to assess functional status. Ten percent of all charts were randomly selected for reabstraction by a second abstractor. Overall reliability of agreement between the two abstractors was over 80%.

Investigators matched patients who had RHC to those who had not undergone RHC, using disease category and propensity score. Patients were followed for 6 months to accumulate data on mortality, cost, and length of stay. Comparisons of the two groups were made using a series of statistical analyses.

Outcomes measured Primary outcomes included patient survival time, length of stay in the ICU, intensity of care, and cost of care.

Results Right heart catheterization was performed in 2184 of the study patients within the initial 24 hours of the ICU stay. Of these patients, 1008 were case-matched as described above. The majority of the diagnoses (91%) included acute respiratory failure, congestive heart failure, and multiorgan system failure. There were no differences detected between the cases and controls in the variables used to define severity of illness.

The patients with RHC had an increased 30-day mortality (OR 1.24; 95% CI, 1.03 to 1.49). Similar results were obtained when assessing mortality at 60 and 180 days. The intensity of care and mean length of stay in the ICU was increased in the group with RHC (14.8 days vs 13.0 days). Patients managed with RHC had increased mean hospital costs ($49,000 vs $35,700). There was no single group of patients for whom the relative risk of death was reduced by using RHC. Patients with the highest predicted probability of survival on study entry tended to have an increased risk of death when RHC was used.

Recommendations for clinical practice **In this study, RHC was associated with an increased risk of mortality and increased resource use, despite adjustment for treatment selection bias and for a variety of risk factors. Family physicians involved in the care of critically ill patients in the ICU setting should encourage judicious use of RHC, especially in patients with mild to moderate severity of illness (>50% probability of 60-day survival). Until we know with more certainty whether some patients, if any, are benefited by this procedure, we should encourage our patients, their families, and our local experts to enroll in a randomized controlled trial, when available, to look more closely at this important issue.**

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RIBAVIRIN FOR RSV LOWER RESPIRATORY TRACT INFECTION

Reference Randolph AG, Wang EEL. Ribavirin for respiratory syncitial virus lower respiratory infection: A systematic overview. Arch Pediatr Adolesc Med 1996;150:942-7.

Clinical question **Does aerosolized ribavirin offer clinically significant benefits for high-risk infants with lower respiratory tract infection caused by respiratory syncitial virus (RSV)?**

Background Initial evaluation of the expensive antiviral drug ribavirin in RSV infection suggested significant benefit. In 1993 the American Academy of Pediatrics Committee on Infectious Diseases recommended 3 to 7 days of aerosolized ribavirin in all infants with confirmed or suspected RSV infection who were severely ill or mechanically ventilated, and in all infants who had underlying conditions that put them at risk for RSV-associated complications.[1] The recent publication of several studies demonstrating no significant benefit of ribavirin in these clinical settings led this same committee in 1996 to change the wording of its recommendation to reflect that ribavirin "may be considered" in these circumstances rather than "should be used."[2]

Population studied Infants with RSV infection who were the subjects of 8 randomized, controlled trials of ribavirin.

Study design and validity This study was a meta-analysis of randomized, controlled trials of ribavirin in lower respiratory tract infection caused by RSV. The authors located 8 studies on a total of 250 infants that met their predefined inclusion criteria. Appropriate meta-analytic methods for data synthesis were used.

Outcomes measured The principal study outcomes were the relative risks for mortality or respiratory deterioration for infants treated with ribavirin as opposed to placebo; these outcomes could be compared for a total of only 99 infants in 3 of the 8 trials meeting inclusion criteria. Secondary outcome measures included length of hospitalization, ventilation, and oxygen dependence; these outcomes could be compared in a total of only 69 infants in 2 of the 8 trials meeting inclusion criteria.

Results The relative risk of mortality due to respiratory failure and respiratory deterioration in the ribavirin groups approached, but did not reach, statistical significance after data synthesis (RR=.42, 95% CI=0.13 to 1.44 for mortality and RR=.42, 95% CI=0.16 to 1.34 for deterioration). Both of these confidence intervals include 1, suggesting no benefit from ribavirin on these outcomes. Similar results demonstrating favorable trends or barely statistically significant benefits of ribavirin were seen for the secondary outcome measures.

Recommendations for clinical practice **This study shows no statistically significant benefit of ribavirin in preventing death or respiratory deterioration in high-risk infants with RSV infection. Viewed in isolation, this result would not be especially compelling; the consistently favorable trends in both the primary and secondary outcome measures need to be interpreted within the context of the small sample size. Proponents of ribavirin use could easily argue that larger trials would make these trends both statistically and clinically significant. But a number of other trials of varying methodologies with substantial statistical power have demonstrated no benefit from ribavirin therapy. One recent retrospective study of 768 infants with RSV infection treated at a single children's hospital from 1986 through 1992 showed that patients who received ribavirin stayed in the hospital longer than those who did not, even after carefully controlling for confounding variables.[1] Another historical cohort study compared two hospitals, one of which used ribavirin and the other of which did not; no significant benefit of ribavirin use was demonstrated.[1] These findings have reinforced the skepticism about ribavirin efficacy within the pediatric critical care community.**

The reason for the apparent inconsistency between the beneficial trends seen in the randomized trials and the disappointing results in observational studies is not entirely clear. One possibility is that the placebo in some of the trials (sterile water) had deleterious effects. Another possibility is that overall improvements in pediatric critical care over the past decade have obscured any specific therapeutic advantage of ribavirin. Given its high cost ($1320 a day for the drug alone) and its questionable efficacy, the routine use of ribavirin even in high-risk infants[1,2] cannot be supported. A large, randomized, controlled, multi-institutional trial would be desirable to put this issue to rest once and for all. Until such a trial is completed, physicians caring for children with RSV infection can withhold ribavirin without fear of violating the standard of care.

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A Scoring System for Streptococcal Pharyngitis

Reference Dobbs F. A scoring system for predicting group A streptococcal throat infection. Br J Gen Pract 1996; 46:461-4.

Clinical question **Can a clinical scoring system based on Bayes' theorem assist clinicians in the management of group A beta-hemolytic streptococcal (GABHS) throat infection?**

Background Previous scoring systems to predict the likelihood of GABHS based on patient presentation have had limited portability from one practice to another. This study sought to create one that can adjust for the differing likelihood of GABHS in differ-

ent populations.

Population studied The study enrollment comprised 206 patients who presented to a semi-rural general practice in Ireland over a 3-year period with a main symptom of sore throat. Patients younger than 4 years old and those who had taken antibiotics in the previous 2 weeks were excluded. Physicians in different settings would have to determine the prevalence of GABHS in their patient population before utilizing this scoring system.

Study design and validity This was a cross-sectional study. Physicians recorded information about a variety of signs and symptoms, together with a presumptive diagnosis and whether antibiotics were prescribed; a throat culture was sent on each patient. Occurrence rates for each data item were compared in culture-positive vs culture-negative patients, and whenever a statistically significant difference existed, a Bayesian probability score (B-score) was calculated. Bayes' is a method that estimates the likelihood of disease by taking into account not only the sensitivity and specificity of a sign or symptom, but also the prevalence of the disease in that population. Multiple logistic regression was used to determine which signs and symptoms were independently associated with GABHS.

This ability to adjust for differences in the prevalence of GABHS between populations makes the Bayesian method an improvement over previous scoring systems, and increases its portability from one practice to another. Unfortunately, such prevalence data is not readily available to most clinicians. In addition, the method of calculating the B-score is mathematically cumbersome. For these reasons, the Bayesian scoring system is not easily generalizable to other settings.

Outcomes measured The sensitivity and specificity of the Bayesian scoring system in predicting positive throat culture were compared with the sensitivity and specificity of study clinicians' predictions.

Results Thirty-five percent (n=72) of the patients had GABHS. Comparison of occurrence rates found that the following factors significantly favored positive throat culture: autumn season; age <11 years; duration <3 days; very sore throat; sore to swallow; bad smell from breath; absence of sore ears and cough; fever; myalgia; flushed; very enlarged or tender glands; exudate; and mouth red or ulcerated. Because many of these items are correlated with each other, this scoring system would tend to overestimate the likelihood of infection. The following items showed independent positive correlation with GABHS: age <11 years ($P<.005$), myalgia ($P<.025$), and tender or very large glands ($P<.005$). Independent negative correlation was found with cough ($P<.0001$) and ear pain ($P<.005$). The Bayesian scoring system had a sensitivity of 71% and specificity of 71% in predicting positive throat culture. This was a mild improvement over the sensitivity and specificity of the general practitioner's opinion: 61% and 65%, respectively.

Recommendations for clinical practice **Scoring systems assist clinicians by providing an objective way to predict who may harbor streptococcal pharyngitis. This can greatly decrease unnecessary antibiotics and throat cultures, while improving our ability to diagnose GABHS. The Bayesian method improves on previous scoring systems by providing a formal way to utilize it in practices with a different prevalence of the disease. Patients with a very low likelihood of GABHS based on the scoring system can be treated symptomatically, while those with a very high likelihood should be treated empirically without further testing. For patients with an intermediate likelihood of GABHS, physicians should consider rapid antigen testing to guide therapy. Partly because of Clinical Laboratory Improvement Act (CLIA) regulations, however, the latter is currently underutilized; all but one of the commercially available rapid streptococcal kits require a moderate complexity laboratory under the CLIA.**

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Trial of Labor After Cesarean Section

Reference McMahon MJ, Luther ER, Bowes WA, Olshan AF. Comparison of a trial of labor with an elective second cesarean section. N Engl J Med 1996; 335:689-95.

Clinical question **Is a trial of labor (TOL) a safe alternative for pregnant women with a history of one low transverse cesarean section as compared with an elective repeat cesarean section?**

Background In an effort to reduce cesarean section rates, clinicians providing maternity care are encouraged to offer a TOL to women with a prior cesarean section. The morbidity for women who have a successful vaginal birth after a cesarean delivery is lower than those choosing an elective repeat cesarean section. Another relevant issue affecting the decision process,

however, is the morbidity and mortality associated with an actual trial of labor.

Population studied Study data were obtained from the perinatal records of 82,488 pregnant women registered in the Nova Scotia Atlee Perinatal Database for the years 1986 through 1992. Of the 6457 women who had undergone one prior cesarean section, 319 were excluded because of factors that would necessitate a repeat cesarean delivery, leaving 6138 women eligible for a TOL. Of these, 3249 women (53%) attempted vaginal delivery and 2889 (47%) underwent elective cesarean section. The decision process regarding how an option was chosen (TOL vs elective cesarean section) was not studied, though women undergoing TOL were apparently agreeable to that option.

Study design and validity Inherent in this nonrandomized study design is the possibility of selection bias. The groups did have some obvious differences. Specifically, there was an overrepresentation in the TOL group of women less than 20 years of age and over 30 years of age, women with a prior successful vaginal delivery, women who had attended prenatal classes, infants with birth weights less than 2500 g and greater than 4000 g, and births occurring at tertiary care hospitals. Labor management was not controlled and reflected local practice patterns of the clinicians caring for these patients.

Outcomes measured Delivery complications were classified as major or minor. Major complications included hysterectomy, uterine rupture, and significant surgical injury. Minor complications included transfusion, puerperal fever, and abdominal wound infection. Women with multiple complications were counted only once and were recorded with major complications if both major and minor complications occurred.

Results In aggregate, there were 53 major complications in the TOL group (1.6%) and 24 in the repeat cesarean group (0.8%). Uterine rupture (defined as a defect involving the entire wall of the uterus requiring operative intervention) was reported 10 times in the TOL group for a rate of 0.3%. The repeat cesarean group did not labor and uterine rupture did not occur. Two perinatal deaths occurred after uterine rupture. Surgical injuries were approximately twice as frequent in the TOL group (1.3% vs 0.6%). Given this difference, 143 repeat cesarean sections would need to be performed to prevent one surgical injury. There was no difference between groups in hysterectomy rates and there were no maternal deaths.

Minor complications occurred more frequently in the elective cesarean group (7.6% vs 6.3%), including more episodes of puerperal fever and abdominal wall infections. Although not statistically significant, the perinatal mortality rate was 9 per 1000 live births in the TOL group and 5 per 1000 in the elective cesarean section group (P=.09).

Major and minor complications were most likely to occur in women who underwent a cesarean section after a failed TOL. Women with one prior vaginal delivery were over three times as likely to have a successful vaginal birth, and women with two or more prior vaginal deliveries were five times as likely to succeed.

Recommendations for clinical practice **Women with a prior cesarean section and at least one successful vaginal birth are most likely to choose and succeed with a vaginal birth after cesarean section. The current study did find increased, although infrequent, risks involved with undergoing a trial of labor, especially among those women who failed and required a cesarean section. Current studies are underway in the hope of predicting which subgroups of women will be successful at delivering their babies vaginally. Meanwhile, women should be encouraged to consider a trial of labor after a prior low transverse cesarean section.**

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Acyclovir or Prednisone for Treating Herpes Zoster

Reference Whitely RJ, Weiss H, Gnann JW, et al, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Acyclovir with and without prednisone for the treatment of herpes zoster: a randomized controlled trial. Ann Intern Med 1996; 125:376-83.

Clinical question **Does treatment with acyclovir or prednisone improve pain relief, quality of life, or lesion healing for patients with herpes zoster?**

Background In immunocompetent adults, both antiviral therapy and corticosteroids can decrease the pain of acute episodes of herpes zoster. The changes are small, and of questionable clinical significance when measured against the costs and potential side effects of treatment.[1,2] Corticosteroids have never been shown to affect the duration of postherpetic neuralgia, and the effectiveness of acyclovir for this condition is controversial. This article evaluates the effects of acyclovir and prednisone used alone or in combination at the onset of acute zoster on pain and quality of life during the subsequent 6 months.

Population studied Patients referred for the study by community physicians and university clinics included 208 immunocompetent adults over age 49 years with a rash clinically consistent with herpes zoster. Those receiving antiviral drugs within the last 4 weeks, those with rash present for more than 72 hours, and those with cancer, hypertension, osteoporosis, or insulin-dependent diabetes mellitus were excluded. Of the remaining 201 patients, 52% were women, 70% were white, and 22% were over 70 years of age. Their initial pain severity was fairly equally distributed between none or mild, moderate, and severe pain.

Study design and validity The 201 patients were randomly assigned to one of four treatment groups: (1) acyclovir (800 mg 5 times per day) and prednisone (60 mg/day days 1-7, 30 mg/day days 8-14, and 15 mg/day days 15-21); (2) acyclovir and prednisone placebo; (3) prednisone and acyclovir placebo; or (4) two placebos. All research personnel were blinded to the assignments until all data were gathered. Patients were evaluated daily until their skin had completely healed, and then monthly for a total of 6 months. Blood and urine samples were obtained weekly for 4 weeks to assess treatment toxicity. Progression of symptoms was analyzed using the Kaplan-Meier method, and results were presented as risk ratios derived from a Cox regression model. This model analyzed the effects of acyclovir and prednisone independently, and adjusted for significant covariates.

Outcomes measured Outcomes measured included new vesicles, extent of healing, pain severity, ability to sleep without interruption from pain, effect on usual activity, and analgesic requirements recorded at each visit.

Results Fifteen of the 35 reported risk ratios reached statistical significance. Neither acyclovir nor prednisone led to earlier resolution of postherpetic pain. During the first month, acyclovir was associated with earlier crusting and healing of lesions and with an earlier return to usual activities. Patients treated with prednisone were more likely to report cessation of acute pain, discontinuation of analgesics, and a return to uninterrupted sleep and usual activities during the first month only. The number needed to treat (NNT) could not be calculated from the data reported in the article.

The four groups discontinued medication use at similar rates. Adverse events such as gastrointestinal symptoms (most common), edema, increased white blood cell counts, and altered liver function tests were more common among patients receiving acyclovir or prednisone (NNT = 10), but these differences did not reach statistical significance,

Recommendations for clinical practice **Because the authors presented risk ratios exclusively, making calculation of NNTs impossible, this study is of little use to clinicians attempting to weigh the risks and benefits of acyclovir or prednisone for patients with herpes zoster.3 As in other studies, corticosteroids did not prevent postherpetic neuralgia. While two other randomized trials have shown statistically significant improvements in early symptoms in patients treated with corticosteroids,1,2 these changes have been modest and short lived, leading the authors of both studies to recommend against their use. In addition, the current study found no statistically significant effects of acyclovir on postherpetic neuralgia. By contrast, a recent overview4 that pooled data from 313 patients in three studies of oral acyclovir found a decrease in mean pain duration from 85.6 to 49.1 days and an NNT of 12.5 to prevent one case of postherpetic pain persisting for 6 months.**

In summary, physicians should continue to consider the use of acyclovir without corticosteroids for patients with severe pain or involvement of the first trigeminal branch, and for those at high risk of developing postherpetic neuralgia.

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