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Main results. Of 684 patients evaluated, 79 developed a serious outcome. A clinical prediction rule to predict serious outcomes was created using the following variables: an abnormal electrocardiogram (ECG), a complaint of shortness of breath, hematocrit < 30%, systolic blood pressure < 90 mm Hg, and a history of congestive heart failure. The rule was 96% sensitive (95% confidence interval [CI], 92%–100%) and 62% specific (95% CI, 58%–66%) in predicting a serious outcome. If used as admission criteria, the rule could have reduced the number of admissions by 10%.

Conclusion. The San Francisco Syncope Rule can help predict serious outcomes and, if validated, would be an important tool for making disposition decisions in ED patients with syncope or near syncope.

Commentary

When evaluating patients with syncope or presyncope, the challenge is to determine whether the syncope is caused by a benign physiologic derangement or life-threatening condition. A cause is never identified in 38% to 47% of outpatients, and although malignant causes are uncommon, a missed diagnosis can be devastating [1]. ED patients with syncope have a higher prevalence of arrhythmias, myocardial infarctions, and strokes, and it becomes even more critical in this population to efficiently identify those at risk for serious outcomes. The usual strategy to risk stratify patients with syncope includes a thorough history, physical examination, and ECG, followed by further specialized testing if necessary. Routine use of electroencephalogram, tilt table testing, and cardiac monitoring has a low diagnostic yield. A clinical prediction rule that identifies historical elements or test findings with the greatest predictive value can help in the development of standardized workups that are efficient and minimize the risk of missing a diagnosis.

The cohort assembled for this study was required to have syncope or near syncope as a chief complaint and had a broad range of accompanying complaints, including shortness of breath and chest pain. By excluding patients with a known precipitating cause (eg, intoxication or definite seizure), the authors narrowed the study population to diagnostic unknowns. Patients were followed for 7 days for "serious outcomes," which was defined broadly to encompass the potential consequences of syncope. Fifty predictors were tested for a relationship with the occurrence of serious outcomes. The finding that abnormal ECGs, dyspnea, history of congestive heart failure, and significant anemia or hypotension were significant predictors of the outcome is consistent with previous work and would make for a quick initial clinical screen for these patients.

The authors acknowledge most of the weaknesses and limitations of their study design. Patients were not followed beyond 7 days, and poor outcomes may have occurred outside this interval. The rule was not 100% sensitive and could not replace clinical judgment. It is unclear whether the rule performs better than standard evaluation by ED physicians. Many of these concerns will need to be addressed in a validation study.

Applications for Clinical Practice

The San Francisco Syncope Rule will likely prove a useful tool to risk stratify patients presenting to the ED with syncope using an ECG, history of congestive heart failure or dyspnea, and the presence of anemia or hypotension.

–Review by Josh F. Peterson, MD, MPH

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How Often Do Elderly Patients Receive Inappropriate Medications?

Goulding MR. Inappropriate medication prescribing for elderly ambulatory care patients. Arch Intern Med 2004;164:305–12.

Study Overview

Objective. To describe trends in inappropriate medication prescribing and predictors of inappropriate prescribing among elderly outpatients.

Design. Cross-sectional cohort study.

Setting and participants. National sample of physician office visits and hospital outpatient department visits for patients aged ≥ 65 years during 1995 to 2000. Medication prescribing was reported by either physicians or trained office personnel at the time of the clinical encounter.

Main outcome measures. The primary outcome was the prescription of a medication deemed inappropriate for elderly patients. These inappropriate medications included 38 drugs or drug groups that generally should be avoided in elderly patients as defined by the Beers expert panel. A second outcome included receipt of an inappropriate drug as defined by the Zahn expert panel, which narrowed the Beers list to 19 drugs or drug groups that should always be avoided or rarely are appropriate. Logistic regression models were used to define patient and physician predictors of inappropriate prescribing.

Main results. The prevalence of inappropriate prescribing by the Beers criteria was 7.8% in 1995 and 2000, with no significant time trend in prescribing detected. Similarly, the rate of inappropriate prescribing by the Zahn criteria was 3.7% in 1995 and 3.8% in 2000 without any appreciable trends. The 5 most common inappropriate drugs included propoxyphene (1.5%), hydroxyzine (1.1%), amitriptyline (0.7%), diazepam (0.7%), and oxybutynin (0.7%). The most common drug classes prescribed inappropriately included pain relievers, antidepressants, antianxiety agents, and sedatives. Significant predictors of inappropriate Beers prescribing after adjusting for patient, physician, and visit characteristics included female sex (odds ratio [OR], 2.10), visits to family or general practitioners (OR, 1.41), and number of prescription drugs (OR, 2.62 for 2 drugs [up to OR 6.64 for 6 drugs]). In comparison with patients aged 65 to 69 years, patients over age 80 years were less likely to receive inappropriate medications (OR, 0.64). Similar predictors were observed for inappropriate Zahn prescribing with the exception of no significant finding for family or general practitioners.

Conclusion. Elderly patients receive inappropriate medication prescriptions at substantial rates, particularly for pain relievers, antidepressants, antianxiety agents, and sedatives. Female patients and those receiving multiple medications appear to be at particularly high risk.

Commentary

The proliferation of successful pharmacologic therapies for a variety of medical conditions has improved care for many patients, but it also has created the potential for misuse. Inappropriate prescribing is a concern as adverse drug events have been well described in the outpatient setting for both the general and elderly population [1,2].

Goulding has expanded our knowledge by documenting the rates of inappropriate prescribing on a national level, as well as by targeting high-risk drug classes. In addition, this investigation highlights the fact that despite calls by the Institute of Medicine and others to develop systems to make health care more safe, there has been little change in the rates of inappropriate medication prescribing over recent years.

This investigation is limited by a lack of detailed clinical information such as drug dosages, previous tolerance of prescribed medications, and the occurrence of adverse events resulting from medication usage. However, the use of the Zahn expert panel criteria is helpful in highlighting the persistent use of medications that are very unlikely to be appropriate. Focusing on such high-risk prescribing patterns allows the development of specific systems to improve the quality of prescribing patterns. One potential solution that takes advantage of such focused information and has been used in other settings is computerized clinical decision support, which can direct appropriate prescribing and ultimately reduce adverse drug events [3].

Applications for Clinical Practice

Inappropriate medication prescribing can be expected to continue as the number of new medications available to clinicians continues to rise. Health care providers should focus on developing systems to improve the safety of prescribing patterns in order to reverse this trend. This study provides insight into medications and patient characteristics associated with inappropriate prescribing on a national level; however, future work also should involve the collection of detailed information that allows for the development of focused patient safety initiatives.

–Review by Thomas D. Sequist, MD

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Adherence to Screening Guidelines for Colorectal Cancer: The Impact of Genetic Testing and Counseling

Hadley DW, Jenkins JF, Dimond E, et al. Colon cancer screening practices after genetic counseling and testing for hereditary nonpolyposis colorectal cancer. J Clin Oncol 2004;22:39–44.

Study Overview

Objective. To assess the impact of genetic counseling and testing (GCT) on the use of endoscopic screening procedures and adherence to recommended screening guidelines in asymptomatic at-risk individuals from families known to carry a hereditary nonpolyposis colorectal cancer (HNPCC) mutation.

Design. Prospective cohort study.

Setting and participants. Adults without a prior history of cancer, at 50% risk of carrying their family's previously identified deleterious HNPCC mutation, and who agreed to undergo GCT and fill out questionnaires at baseline and 6 and 12 months post-GCT were included. Data on colonoscopy and flexible sigmoidoscopy screenings that were collected before GCT and 6 and 12 months post-GCT were analyzed. Identification of family members at 50% risk was initiated through a first-degree relative identified as carrying the HNPCC mutation. Genetic testing was offered after comprehensive education and counseling. Cancer screening recommendations based on published guidelines were provided in both the initial genetic and follow-up counseling sessions. Those recommendations included a colonoscopy every 1 to 3 years for mutation-positive persons and general population screening for mutation-negative persons (ie, flexible sigmoidoscopy every 3 to 5 years after age 50 years). Health-related behaviors were assessed by self-report.

Main outcome measures. Use of endoscopic screening and adherence to recommended guidelines for the relevant mutation status. Mutation status, age, sex, employment, and income were analyzed as predictor variables. Use was a dichotomous variable measuring whether a participant had at least 1 endoscopy in a specified time period. Adherence was also a dichotomous variable measuring whether a participant's behavior was consistent with the actual endoscopic screening recommendation within the 12-month period after GCT. Nonadherent individuals were subclassified as hypovigilant if they did not engage in screening when recommended or hypervigilant if they engaged in screening more frequently than recommended.

Main results. Mutation testing determined that 39 individuals (70%) were truly negative and 17 (30%) were positive for a deleterious HNPCC mutation. Among mutation-negative individuals, use of colonoscopy and flexible sigmoidoscopy decreased significantly between pre- and post-GCT ($P < 0.001$ for both). Among mutation-positive individuals, there was no significant increase ($P = 0.24$) in use. Age also was associated with use of endoscopic screening after GCT ($P = 0.03$). Eleven (20%) of 56 individuals were classified as nonadherent with recommendations in the 12-month period after GCT. Mutation status (odds ratio [OR], 7.5; $P = 0.02$) and employment (OR, 8.6; $P = 0.025$) were associated with nonadherence to screening guidelines. More mutation-negative individuals strictly adhered to guidelines than did mutation-positive individuals (87% versus 65%).

Conclusion. Genetic counseling and testing for HNPCC significantly influences endoscopic screening and adherence to colorectal cancer screening guidelines.

Commentary

HNPCC is the most prevalent form of hereditary colorectal cancer, accounting for an estimated 5% of all cases. An individual with a deleterious HNPCC mutation has at least an 80% lifetime risk of developing colorectal cancer. Studies have demonstrated that routine endoscopic screening in these patients reduces the risk and improves survival [1,2].

Hadley et al conducted a small prospective study evaluating the use of endoscopic screening and guideline adherence in a group of HNPCC at-risk individuals. Risk was based on family history, but individuals were classified as either positive or negative in terms of personally having a HNPCC mutation. The authors found that genetic testing and counseling directly influenced adherence with screening guidelines in at-risk individuals. Specifically, screening adherence decreased once genetic testing confirmed a negative HNPCC status. Conversely, screening increased, albeit not significantly, when testing was positive.

The study population was small, and the mutation-positive and mutation-negative groups were unbalanced in size, age, and economic measures, making direct comparisons between

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subsets potentially flawed. As well, the study's outcomes are based on definitions of adherence derived from published guidelines and may not reflect clinical value for individual patients. Individuals who were regarded as hypervigilant in terms of screening behavior were regarded as nonadherent. This subset likely represents a distinct clinical group from those individuals who infrequently or never get screened, the so-called hypovigilant nonadherent subset.

Notwithstanding the limitations and potential selection bias of this small study, the results are intriguing. Understanding screening behavior will be increasingly important as more genetic tests and screening tools become available. Studying screening guideline adherence may help in redefining guidelines themselves and may improve allocation of health care resources. Ultimately, the important question is whether improved adherence leads to improved long-term outcomes such as survival.

Applications for Clinical Practice

Individuals at risk for HNPCC should receive genetic counseling and be offered testing. HNPCC mutation carriers should undergo regular endoscopic screening according to published guidelines. Resources should be developed to help these patients receive counseling and screening.

–Review by David R. Spigel, MD

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A Useful Diagnostic Strategy for Suspected Pulmonary Embolism

Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-Dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med 2004;116:291–9.

Study Overview

Objective. To evaluate a diagnostic strategy for outpatients presenting to the emergency department (ED) with symptoms suggestive of pulmonary embolism (PE).

Design. Prospective cohort study.

Setting and participants. Patients presenting with unexplained new or worsening dyspnea or chest pain were recruited from EDs at 3 European medical centers. Patients were excluded if they took anticoagulation therapy for reasons other than thromboembolism, could not undergo computed tomography (CT) scanning with intravenous contrast, had a creatinine clearance below 30 mL/min, could not provide consent, were pregnant, could not be followed after discharge, were suspected of having a massive PE with shock, or did not undergo the testing specified by the algorithm.

Intervention. Enrolled patients were managed using a diagnostic algorithm to establish or exclude the diagnosis of PE. Clinical probability of PE was assigned using a published prediction rule [1], which clinicians could override. In the first step of the algorithm, PE was considered excluded without further testing if the plasma D-dimer level (rapid ELISA [enzyme-linked immunosorbent assay], Vidas DD, BioMérieux, Marcy l'Etoile, France) was less than 500 µg/L. When the D-dimer was ≥ 500 µg/L, compression ultrasound of the lower extremities was performed, and patients with deep vein thrombosis were treated for thromboembolism. Remaining patients had helical contrast CT performed. Patients with negative CT scans and low or intermediate clinical probability of PE were diagnosed as not having PE. Patients who had high clinical probability of PE but had negative CT scans at this point underwent pulmonary angiography and were treated if PE was detected.

Main outcome measures. Proportion of patients assigned a diagnosis at the various stages of the algorithm and proportion of patients diagnosed as not having PE who developed clinically evident thromboembolism within 3 months.

Main results. Of 1290 patients screened, 965 were included. The prevalence of PE was similar in patients who were included (23%) and excluded (21%). By sequentially following the algorithm, diagnoses were assigned as follows: 280 (29%) patients had PE excluded after a negative D-dimer

measurement, 92 (9.5%) patients had thromboembolism diagnosed after a positive ultrasound, and 574 (59%) additional patients had diagnoses made after CT scan. 124 (13%) patients had PE detected by CT scan, and 450 (47%) patients had PE excluded by having a low or intermediate clinical suspicion for PE and a negative CT scan. Eight patients with high clinical suspicion and negative CT scans underwent pulmonary angiography, which diagnosed PE in 2 patients. Eleven patients with inconclusive findings on CT underwent subsequent testing (ie, lung scintigraphy or angiography), and 4 were determined to have PE. Among the 685 patients for whom PE was excluded by this algorithm and who did not receive anticoagulation for another reason (eg, atrial fibrillation), 7 had clinically evident venous thromboembolism in the subsequent 3 months (1.0% [95% confidence interval {CI}, 0.5%–2.1%]). All of these patients had a positive D-dimer measurement, negative ultrasound and CT scan, and low or intermediate clinical suspicion for PE (thromboembolism occurred in 1.7% of patients [95% CI, 0.8%–3.5%] in the group with these characteristics).

Conclusion. This noninvasive diagnostic strategy provided a diagnosis for 98% of outpatients with suspected PE with a low short-term rate of clinically evident thromboembolism.

Commentary

PE has always presented a formidable diagnostic challenge. Many diagnostic strategies have been investigated [2]. Normal results on pulmonary angiography or lung scintigraphy can effectively rule out PE, but angiography is invasive, and scintigraphy frequently fails to establish a firm diagnosis. CT scanning has emerged as a useful modality in the diagnosis of PE, but it is expensive and there is a small risk involved in the administration of intravenous contrast. A variety of D-dimer tests have been examined as a means of excluding thromboembolism, but most data regarding these tests pertain to individuals with low clinical suspicion of PE [2].

This study by Perrier et al is important for several reasons. It demonstrates that in a large group of patients, the D-dimer ELISA assay that was used did an excellent job of excluding PE in all clinical risk groups and eliminated the need for additional testing in 29% of patients. The authors also showed that by using ultrasound as the next step, 39% of the total population could be given a diagnosis without requiring CT. When clinical risk assessment (which included room air arterial blood gas determination) and CT were combined with these methods, almost all patients received a diagnosis. The study was done at several centers using a variety of CT techniques, thereby adding to the generalizability of these findings.

Clinicians who wish to apply this algorithm should keep several important facts in mind. First, a highly sensitive D-dimer ELISA test was used. Other D-dimer assays may not be as reliable at excluding PE. Second, all patients with negative CT scans already had normal lower extremity ultrasound findings. The use of CT alone to exclude PE in patients with a low to moderate clinical suspicion of PE and positive D-dimer tests may not be as reliable. Last, patients in this study with a low to moderate clinical suspicion for PE, a positive D-dimer, and negative ultrasound and CT tests had a short-term thromboembolism risk of 1.7% (95% CI, 0.8%–3.5%). Future advances in CT technique may further improve PE diagnosis, but at present, a small number of patients with this combination of test results still may have undiagnosed PE.

Applications for Clinical Practice

For patients presenting to the ED with symptoms suggestive of PE, a diagnostic algorithm that uses clinical risk assessment and D-dimer ELISA followed by lower extremity ultrasound and CT scanning when necessary can provide an accurate diagnosis for almost all patients and avoid the need for CT scanning in 39% of patients.

–Review by Stephen D. Persell, MD, MPH

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