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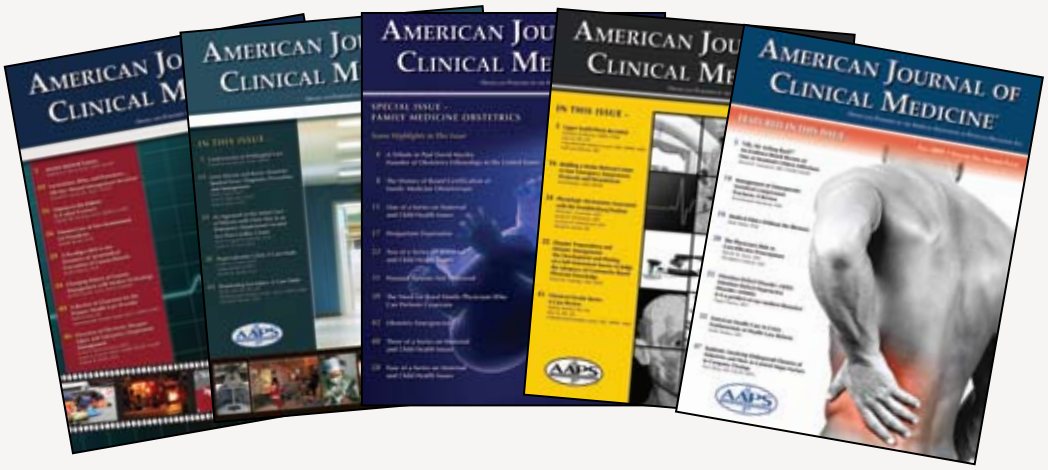

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ISSUE	DEADLINE
Summer 2010	**May 3, 2010**
Fall 2010	**August 3, 2010**
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2010 UPDATE: In 2009, the staff successfully published four editions, and the application for acceptance into PubMed is underway. In keeping with our mission statement, we are proposing to focus on clinical issues of interest to physicians clinically involved with patients in the office and hospital. Competency issues have been critical to our colleagues in the AAPS, and there is a special interest in core competency skills for those physicians who must manage common emergencies and hospital patients.

The Society for Hospital Medicine has specified core competencies in the interpretation of chest radiographs and electrocardiograms. This has been further validated in the bible of primary care procedures (Pfenninger and Fowler 3rd edition 2010). In 2009, the American Board of Family Medicine Obstetrics certified its first physicians. As part of their core curriculum, obstetrical emergencies and the use of ultrasound, as specified in the Advanced Life Support in Obstetrics (ALSO) manual, became core.

The *American Journal of Clinical Medicine* (*AJCM*) is beginning a regular series of clinically-focused cases using radiographic, ultrasound, and ECG images as a means of simulating clinical cases commonly used for competency assessment. These cases do not represent material taken from board examinations, which are confidential. But, in the editor's thirty-five years of experience, they have a probability of occurring on a regular basis for almost all of the specialties within AAPS.

As always, we welcome your comments and opinions.

Wm. MacMillan Rodney, M.D., FAAFP, FACEP
Editor-in-Chief

Back and Neck Pain in Gynecologists

Daniel M. Avery, Jr., MD
Daniel M. Avery, III, BS
Marion D. Reed, MD
Jason M. Parton, MA, MS
E. Eugene Marsh, MD

Abstract

Objective: To determine if back and/or neck pain is common in gynecologists.

Study Design: A 19-question survey was sent to 332 gynecologists listed with the state OB/GYN society. One hundred fifty-nine surveys were returned (47.9%). Descriptive statistical analyses were performed on this sample of 159 gynecologists to study the characteristics of those who experience back and/or neck pain.

Results: Ninety-two of the 159 (57.8%) gynecologists reported back and/or neck pain. The percentages were similar for men (57.3%) and women (61.8%). Physicians experiencing fatigue were more likely to suffer from back and/or neck pain than those who did not. Pain increases with years in practice.

Conclusion: This is a small study, but it suggests that back and/or neck pain is common in gynecologists. Robotic procedures could be the ergonomic answer to the occupational hazards of back and/or neck pain in gynecologists, but this will require more study.

Introduction

Back and neck pain are common complaints among gynecologists. The occupational diseases usually described in the literature for gynecologists are psychological stress, hoarseness, needle sticks, thermal burns through gloves, and face shield contamination.[1-10] Back and neck pain can be due to awkward vaginal surgery, long oncology procedures, long laparoscopy procedures, abdominal and pelvic examinations. Surgery can also be fatiguing work, especially with the increased number of laparoscopic procedures, which require more rigid body postures.[11,12] The actual physical effect of the operation on the surgeon is an important complication of laparoscopic procedures today.[13] Gynecologists have very awkward procedures due to prolonged standing during procedures and unnatural positions.[14] While musculoskeletal complaints have been documented among other specialties, very little has been written in the literature about occupational disease in gynecologists,[14] in particular, with respect to neck and back pain. This paper describes the prevalence of back and neck pain in gynecologists.

The most common musculoskeletal complaints in gynecologists and surgeons are fatigue and back and neck pain. While papers can be found addressing these problems in many disciplines, only eleven papers were found discussing occupational disease in gynecologists and only four of these described back and neck pain.[1,3,5-9,14,15,16] A single paper from the United Kingdom in 2001 describing back pain in gynecologists reported that back pain in this specialty had never previously been reported.[14] The prevalence of back pain in gynecologists in this study was 72%.[14] Fifty-three percent of physicians attributed the pain to the practice of OB/GYN.[3] With nearly three-quarters of the study group having back pain and over half attributing it to the physical practice of OB/GYN, the conclusion of back pain in gynecologists resulting in significant morbidity seems appropriate.[14] The purpose of this study was to study the prevalence of back and neck pain in gynecologists.

Materials and Methods

This study was approved by the Institutional Review Board of the University of Alabama in Tuscaloosa. A nineteen-question survey that could be completed in approximately five minutes

Figure 1: Back and Neck Pain in Gynecologists Survey

General Questions:

1. ___Male ___Female

2. In what age range do you belong?

__30-35 __35-40 __40-45 __45-50

__50-55 __55-60 __60-65 __>65

3. How many years have you been in practice?

__0-5 __5-10 __10-15 __15-20 __20-25 __>25

4. Do you perform?

___Open Procedures ___Laparoscopic Procedures

___Both

5. Please mark all that apply to you:

___ Back pain ___ Neck Pain ___ Shoulder Pain

(If you did not check any conditions above, please skip to question 10.)

6. Check all that apply to you

___ Previous traumatic injury to that part of the body

___ Medical condition that predisposes you to pain in this part(s) of the body

___ Outside hobby that puts you at risk for excess use or strain on this part(s) of the body

7. Of the above, how often does the pain occur?

___ 0-2 times/month ___ 0-2 times/week

___ 2-4 times/week ___daily

8. Has the pain caused you to seek medical attention?

___ Yes ___ No (skip to question 10)

9. Have you used or had any of the following for treatment?

___ NSAIDs ___ Prescribed medication

___ Physical therapy ___ Surgical procedure

Surgical Practice and History Questions:

10. If you perform both open and laparoscopic procedures, what is the approximate percentage of open to laparoscopic?

___100% open ___75% open ___50% Lap

___75% Lap ___100% Lap

11. Do you ever experience fatigue during procedures?

___Yes ___No (skip to question 14)

12. How often?

___only on long days ___1-2/week

___most days in surgery

13. Check all that you think apply to this fatigue:

___Long surgery times

___Open procedures

___Laparoscopic procedures

___Decreased sleep

___Stress from work

___Stress from outside work

___Outside hobbies

14. Check all that you have incorporated into the majority of your laparoscopic procedures:

___ Adjustable monitors

___ Table height adjustment

___ Stools to sit while operating

___ Moments to stretch in long procedures

15. When being trained as a medical student or resident, were you taught to keep proper posture during surgical procedures?

___Yes ___No

16. Do you consider your posture while operating?

___Yes ___No

17. Do you use or have you considered using robotic surgery?

___Yes ___No

18. If you currently perform robotic surgery, check all benefits that you feel apply:

___ Increased quality of surgery

___ Decreased recovery time

___ Increased range of surgical candidacy (i.e., can perform on morbidly obese patients)

___ More comfortable as the surgeon

___ Increased surgeries from referrals

19. If considered, for what reason?

___ To stay on leading edge of technology

___ To be well balanced in all gynecological procedures

___ To increase comfort during a long procedure

___ Necessity due to injury

___ Necessity due to age

Table 1: Sample Characteristics

		N (%)
Experience back and/or neck pain		
	Yes	**93 (58.5%)**
	No	**66 (41.5%)**
Gender		
	Male	**124 (78.0%)**
	Female	**34 (21.4%)**
Age Group		
	30-35	**3 (1.9%)**
	36-40	**18 (11.3%)**
	41-45	**17 (10.7%)**
	46-50	**30 (18.9%)**
	51-55	**34 (21.4%)**
	56-60	**28 (17.6%)**
	61-65	**23 (14.5%)**
	>65	**6 (3.8%)**
Number of years in practice		
	0-5	**4 (2.5%)**
	6-10	**21 (13.2%)**
	11-15	**23 (14.5%)**
	16-20	**25 (15.7%)**
	21-25	**38 (23.9%)**
	>25	**47 (29.6%)**

was designed to establish the prevalence of back and neck pain in gynecologists. An attempt was made to prepare a questionnaire that could be completed in a reasonable amount of time about a topic that was of interest to gynecologists and short enough to enhance maximal participation. The survey was mailed to all 332 obstetrician/gynecologists listed with the state OB/GYN association. Second letters and surveys were sent to gynecologists that did not respond after the first mailing. A total of 159 completed surveys were returned (47.9%). The survey is found in Figure 1. The survey was not validated, but there were a number of positive responses by the respondents after completion of the survey by written and oral comments. The high percentage of responses after two mailings (47.9%) may also suggest interest by respondents.

Demographic and general questions were asked relating to age, sex, years in practice, and whether open, laparoscopic, or both types of procedures were performed. Questions were then asked about back, neck, and shoulder pain, contributing factors for that pain, how often pain occurred, and details about treatment for pain. The next group of questions inquired about the mix of open and laparoscopic procedures, fatigue, and precipitating factors for fatigue. Questions were then asked about changes in laparoscopic procedures that may reduce pain and fatigue and whether they received training in proper posture while operating during medical education. The final group of questions inquired about robotic surgery and possible reasons for consideration.

Results

Ninety-two of the 159 gynecologists (57.8%) reported back and/or neck pain. The percentages were similar for men (57.3%) and women (61.8%). Mature physicians and those with fatigue were more likely to suffer from pain. Descriptive statistical analyses were performed on the sample of 159 gynecologists to study the characteristics of surgeons who experience back and/or neck pain (Tables 1 and 2). A chi-square test of independence was performed on eight of the survey questions to examine the relation between sample characteristics and whether or not the physician experiences back and/or neck pain. The three-category variable related to pain was stratified into a dichotomy of only whether the surgeon experienced back and/or neck pain. The results from the chi-square tests of independence resulted in only one significantly different association, that being the relation between physicians experiencing fatigue and experiencing back and/or neck pain ($\chi^2 = 8.989$, $p < .05$). Physicians experiencing fatigue were more likely to suffer from back and/or neck pain than those who did not experience fatigue. None of the other categories, when compared to whether or not the physician experiences back and/or neck pain, resulted in a statistically significant difference ($\alpha = .05$). However, the cross tabulations show trends emerging for the categories of age group, number of years in practice, and if the surgeon was trained to keep proper posture.

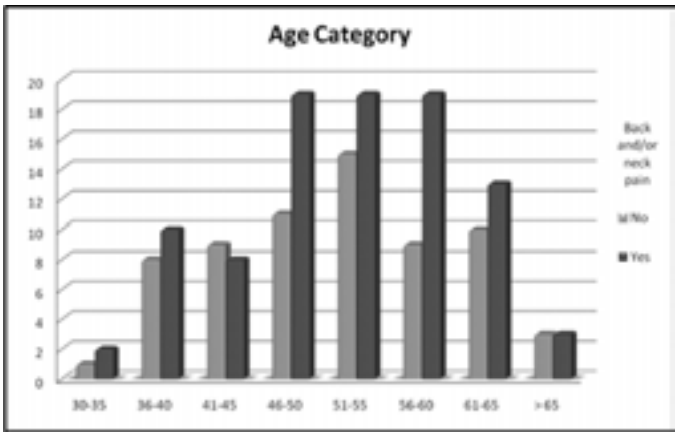
The age group category displayed a substantial spike of experiencing back and/or neck pain for those physicians in one of the age categories, 45-65 years. An explanation for this may be that physicians in younger and older age categories are either too young to experience back and/or neck pain or have utilized techniques to prevent this condition. The category of number of years the physician has been in practice is another variable where a trend seems to emerge. Starting with the 10-15 years category, the proportion of physicians experiencing back and/or neck pain increases until the 20-25 years category. Then the spike reappears at > 25 years in practice. As one would expect, because of the correlation between age category and number of years in practice, this proportional increase is consistent with the descriptive of the age category cross tabulation. The last trend to emerge is the category of whether or not the physician was trained to keep proper posture. Here, the cross tabulation shows physicians who did not have training on correct posture have a higher percent of back and/or neck pain.

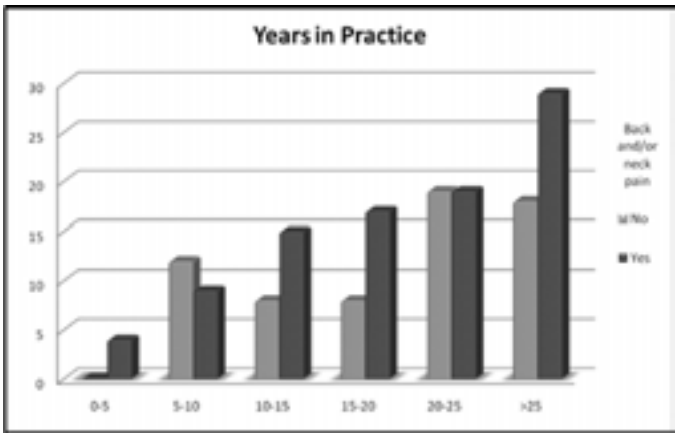
The analysis does show trends emerging from the descriptive cross tabulation but only one statistically significant relationship between the categories of experiencing back and/or neck pain and experiencing fatigue. However, these results do make an argument for a future study with an increased sample size to increase the amount of statistical power. This study sample was

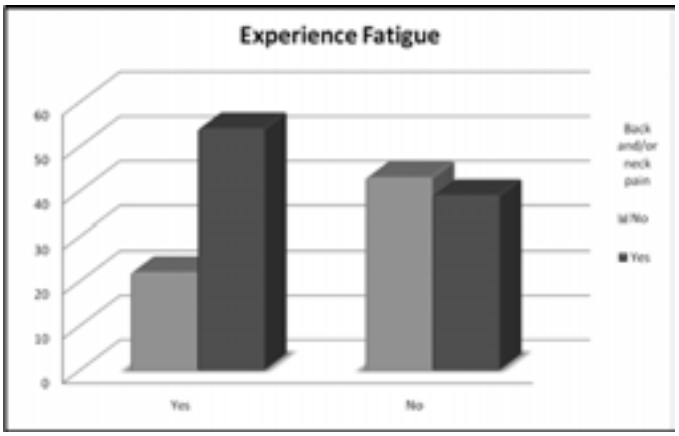
Table 2: Back and/or neck pain *sample characteristics

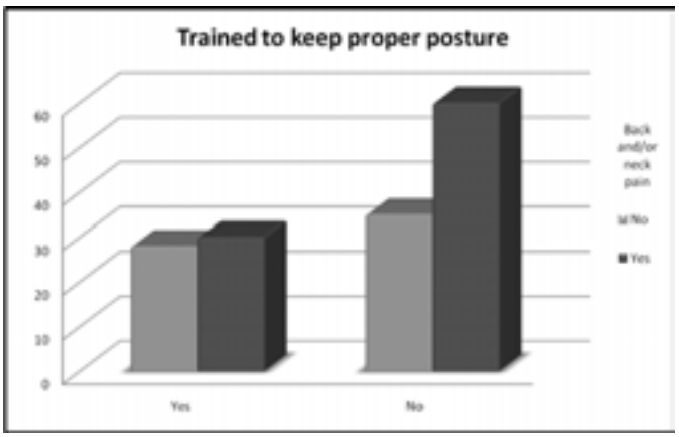
		EXPERIENCE BACK AND/OR NECK PAIN N (%)
Gender		
	Male	71 (57.3%)
	Female	21 (61.8%)
Age group		
	30-35	2 (66.7%)
	36-40	10 (55.6%)
	41-45	8 (47.1%)
	46-50	19 (63.3%)
	51-55	19 (55.9%)
	56-60	19 (67.9%)
	61-65	13 (56.5%)
	>65	3 (50.0%)
Number of years in practice		
	0-5	4 (100.0%)
	6-10	9 (42.9%)
	11-15	15 (65.2%)
	16-20	17 (68.0%)
	21-25	19 (50.0%)
	>25	29 (61.7%)
Procedures performed		
	Open procedures only	3 (50.0%)
	Laparoscopic procedures only	0 (0.0%)
	Both open and laparoscopic	90 (58.8%)
Experience fatigue		
	Yes	54 (71.1%)*
	No	39 (47.6%)
Trained to keep proper posture		
	Yes	30 (51.7%)
	No	60 (63.2%)
Consider posture while operating		
	Yes	64 (59.8%)
	No	26 (57.8%)
Considered using robotic surgery		
	Yes	47 (60.3%)
	No	44 (57.9%)

(* = χ^2 (1, N = 159) = 8.989, p < .05.)









159 yielding a power estimate of 50.3% for the chi-square test of independence.

Comments

Common complaints among gynecologists and surgeons are back and neck pain.[17] While back and neck pain probably increases with age, surgeons and gynecologists who perform laparoscopic procedures have a significant amount of back and neck pain.[11,12,13,14,18] Back and neck pain are a result of static flexion of the neck, awkward positioning to view or manipulate anatomy, or holding retractors for a long procedure. Prolonged positions in lengthy surgical procedures, such as radical oncology procedures, contribute to musculoskeletal stress and back pain.[14] Surgeons often develop intractable neck and back pain, stiffness, painful sensations, and numbness as a result of the procedures they perform, due to the lack of ergonomically favorable conditions.[13] The physical change of the body and suggestion of having increased fatigue in a laparoscopic procedure seems counter-intuitive at first glance. The head and neck positions are usually straight as compared to bent with open procedures, but it is this restricted posture that induces fatigue by requiring fixed head placement. The restricted posture, decreased head mobility, and less weight shifting is also compounded by poor posture, which can cause static muscle loading and fatigue.[12]

Laparoscopic and endoscopic procedures are the surgeries of the future.[20] Almost any traditional operation can be performed endoscopically.[20] Laparoscopic procedures are undoubtedly easier for the patient. Patients have no large incisions, less recovery, shorter hospital stays, and less treatment costs.[20,21] For the patient, laparoscopic surgery involves a "shorter stay, quicker recovery and less analgesic use."[22] However, "one of the most significant complications of laparoscopic surgery is the physical effect on the surgeon himself."[13] Occupational risks and ergonomic challenges are inherent to laparoscopic techniques and instrumentation.[11] Compared to an open procedure, the laparoscopic surgeon assumes a more rigid posture, decreased mobility of the head and neck, and less weight shifting.[11] The more restricted posture readily induces fatigue by limiting the body's natural changes allowable in open procedures.[11] Kant et al. reported that surgeons exhibit frequent static body postures that were harmful and contributed to fatigue.[12]

New procedures place new demands on surgeons. With the increasing evidence of surgeons' fatigue in this new ergonomic environment, changes will need to be made or occupational disease among surgeons will likely increase. But these procedures are evidenced to be more taxing on the surgeon due to tedious instrument techniques and the ergonomic problems mentioned previously. The long instruments manipulated by the surgeon, two-dimensional work space, and limited space are additional factors noted by other authors, which should also be considered in need for recommendations.[18]

One might assume that poor posture suggested to cause fatigue would be related to the outcome. Although the static muscle loading of poor posture causes fatigue as well as impaired psychomotor task performance,[12] one study concluded that poor postural instability does not correlate with poor performance or outcome.[18] The lack of correlation is most likely due to compensatory movements of the surgeon, despite their ergonomic favorability status. The setup for laparoscopic surgery is not typically ergonomic in many fields. Static positioning of the surgeon and stationary monitors set the surgeon up for physical and mental stress leading to neck, shoulder, and even wrist pain.[19]

Robotic procedures could be the ergonomic answer to the occupational hazards of traditional laparoscopy. The robot employs robotic arms with modified laparoscopic instruments to take the full blunt of rigid, static positioning required to use them.[23] The surgeon operates while sitting at a console apart from the operative field in the same suite, which is undoubtedly a more relaxed, ergonomically favorable position. The da Vinci Robotic System® claims more freedom of movement, greater dexterity, and better visualization of the operative field.[23] Reduced discomfort and fatigue, elimination of awkward and static positioning of the surgeon, and comfortable seating make a robotic procedure ergonomically favorable for the surgeon.[24] The role of robotic surgery has exciting potential, which will hopefully be defined in the near future with more research.

One study suggests a treatment approach which includes spatial orientation and hand-eye coordination improvement by sequential phases during residency training.[13] Another more basic recommendation is the development of appropriate posture during laparoscopic procedures, which would theoretically minimize many of the proposed causes of back and neck pain.[13] Other recommendations include self-controlled motorized tables for height adjustment, an endoscopic stool with wheels, and limitation of the number of procedures.[25] But anything that can minimize strain and pain within the realm of the operating room should be considered.[26] Good posture protects the spine.[27] From discussions with colleagues and residents, it seems that more emphasis is being made to students in surgery about proper posture and techniques to reduce discomforts of surgery. Perhaps then bad habits will not be handed down that could develop into some of the detrimental outcomes of surgical specialties, particularly gynecology. The first warning sign of a possible problem is low back pain or strain that does not respond to non-steroidal anti-inflammatory drugs.[27] Rohrich has published a list of recommendations to reduce back and neck pain in surgery:[27]

- Sit when you can in the operating room.
- When sitting, have both feet on the floor.
- Bend the knees when standing for a long period of time and shift weight every 5-10 minutes.
- Operate at the proper table height.
- Keep your head in the middle of your shoulders.
- Take time to stretch the cervical spine and lower back muscles.
- Do extension and flexion exercises for the lower back.[27]

It is important for laparoscopic surgeons who perform long procedures to maintain proper postural stability[18] and to utilize mobile monitors to improve stress on positioning.[19]

Any type of surgery can be physically demanding. Prolonged procedures lead to fatigue and can cause neck and back pain. While laparoscopic and endoscopic surgery touts shorter hospital stays, less cost, and quicker recovery, the effects to the surgeon can be detrimental. Gynecologists negotiate awkward abdominal and vaginal examinations, episiotomy repairs, long radical and laparoscopic procedures that lend to occupational disease. Recommendations are discussed above. Robotic surgery may be part of the answer to the physiologic challenges of laparoscopy, but more research will be needed.

Daniel M. Avery, MD, is Associate Professor and Chair of Obstetrics/Gynecology at the University of Alabama School of Medicine in Tuscaloosa, AL.

Daniel M. Avery, III, BS, is a Senior Medical Student at the University of Alabama School of Medicine, Birmingham. He has a special interest in musculoskeletal disorders and orthopedic oncology.

Marion D. Reed, MD, is Assistant Professor, Chief of Gynecology and GYN Urology, Department of Obstetrics and Gynecology, College of Community Health Services, University of Alabama School of Medicine, Tuscaloosa.

Jason M. Parton, MA, MS, is Epidemiologist and Project Director, Rural Health Institute for Research and Translational Science, College of Community Health Sciences, University of Alabama School of Medicine, Tuscaloosa.

E. Eugene Marsh, MD, is Professor and Dean, Department of Internal Medicine & Division of Neurology, College of Community Health Sciences, University of Alabama School of Medicine, Tuscaloosa.

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Evaluation of Syncope in the Emergency Department

David M. Lemonick, MD, FAAEP, FACEP

Introduction

Syncope is a symptom complex composed of a transient loss of consciousness associated with an inability to maintain postural tone, secondary to a brief decrease in cerebral blood flow that spontaneously and completely resolves and that requires no resuscitation.[1] Accounting for 3% of emergency department (ED) visits and 1% to 6% of all hospital admissions,[2] syncope presents a challenge to emergency practitioners: to differentiate those patients safe for discharge from those who require emergent evaluation and in-hospital management for potentially life-threatening etiologies. The precise cause of syncope can be identified during the initial evaluation in only 20% to 50% of patients.[3] Of note, it is estimated that up to 80% of the causes of syncope that *are* identified during a hospital admission are determined in the emergency department.[4]

While most potential causes of syncope are benign and self-limited, some etiologies are associated with significant morbidity and mortality. Approximately 4% of patients discharged from the ED with syncope return within 72 hours and are admitted or die.[5]

Cardiac arrhythmias and sudden death are the chief short-term complications to be avoided in syncope. In one population-based study, patients with cardiac causes of syncope had double the mortality rate of patients without syncope. The average cost of care per hospital admission for syncope is approximately $5,000, and more than $2 billion a year is spent in the United States on such hospitalizations.[6] The emphasis in the evaluation of the patient who presents to the ED with syncope is on risk stratification and on doing so in an expeditious, cost-effective manner, and in a medico-legally defensible manner. This article will attempt to simplify the clinical approach to the patient with syncope based upon the current literature.

Differential Diagnosis

The differential diagnosis of syncope is extensive (Table 1). In addition, other syncope-like conditions, such as seizure, stroke, and head injury, should be considered during the initial evaluation of a patient with transient loss of consciousness. Seizures may be difficult to distinguish from syncope. Seizure is suggested by: a history of seizure disorder, an abrupt onset associated with head injury, tongue biting (particularly involving the lateral aspect of the tongue), the presence of a tonic phase preceding the onset of clonic activity, unusual posturing or head deviation, loss of bladder or bowel control, age less than 45 years, medication noncompliance, a preceding aura, and prolonged confusion and disorientation after the event.[7]

In contrast to seizure, syncope is often preceded by sweating or nausea and by sitting or standing and has rapid return of orientation upon awakening. Syncope more often occurs in patients older than 45 years, and it is associated with a history of congestive heart failure (CHF) and coronary artery disease (CAD).

Life-threatening causes of syncope include cardiovascular causes, hemorrhage, and subarachnoid hemorrhage (SAH). A "rule of 15s" for syncope reminds us that approximately 15% of the following life-threatening conditions present with syncope: SAH, acute coronary syndrome (ACS), aortic dissection, leaking aortic aneurysm (AAA), and ruptured ectopic pregnancy.[4]

Many of the missed diagnoses of these five conditions that resulted in medico-legal action involved presentations that included syncope. The physician evaluating a patient with brief loss of consciousness should be vigilant for the possibility of carbon monoxide toxicity, SAH, carotid dissection, vertebrobasilar transient ischemic attack, leaking abdominal aortic aneurysm, gastrointestinal hemorrhage, and ruptured ectopic pregnancy.

Table 1: Differential Diagnosis of Syncope

NEURALLY-MEDIATED (REFLEX)
Carotid sinus hypersensitivity • Head turning • Circumferential neck compression (neck tie) • Shaving
Glossopharyngeal neuralgia
Idiopathic postural hypotension
Peripheral neuropathy • Alcoholic • Amyloid deposition • Diabetes • Malnutrition
Situational • Cough • Swallow, defecation • Micturition • Post-exercise • Post-prandial • Others (e.g., brass instrument-playing, weightlifting)
Vasovagal (common faint)
MEDICATION-RELATED
Vasoactive medications • Alpha and beta blockers • Calcium channel blockers • Nitrates • Antihypertensive medications • Diuretics • Erectile dysfunction medications
Medications affecting conduction • Antiarrhythmics • Calcium channel blockers • Beta blockers • Digoxin
Medications affecting the QT interval • Antiarrhythmics • Antiemetics • Antipsychotics/depressants

CARDIOGENIC
Cardiac arrhythmia • Amiodarone toxicity • Atrial fibrillation with Wolff-Parkinson-White syndrome • Atrial flutter • Atrial surgery • AV block • AV canal defects • AV conduction system disease • Sinus node dysfunction • Supraventricular tachycardia • Ventricular tachycardia • Pacemaker or automated internal cardiac defibrillator dysfunction • Brugada syndrome • Catecholaminergic tachycardia • Long QT syndrome
Structural cardiac obstructive lesions • Acute coronary syndrome • Aortic valve stenosis • Atrial myxomas • Hypertrophic cardiomyopathy ■ Cardiac tamponade ■ Aortic dissection
Significant hemorrhage • Trauma with significant blood loss • Gastrointestinal bleeding • Tissue rupture ■ Aortic aneurysm ■ Spleen ■ Ovarian cyst ■ Ectopic pregnancy ■ Retroperitoneal hemorrhage
Pulmonary embolism • Saddle embolus resulting in outflow tract obstruction or severe hypoxia
Subarachnoid hemorrhage
Cerebrovascular • Vascular steal syndromes
Orthostatic hypotension • Drug side effects • Dysautonomias ■ Multiple system atrophy ■ Parkinson's disease ■ Postural orthostatic tachycardia syndrome ■ Pure autonomic failure • Shy-Drager syndrome • Volume loss • Autonomic dysfunction • Deconditioning, prolonged bed rest

Cardiovascular causes are the most common life-threatening conditions associated with syncope, and these can be divided into arryhthmogenic, structural, and ischemic.[8] Syncope from a sudden disruption in cardiac output is the most deadly form of syncope. Arrhythmogenic causes of syncope can include ventricular tachycardia, long QT syndrome, Brugada syndrome, bradycardia (e.g., Mobitz type II or 3rd degree heart block), and significant sinus pauses (i.e., >3 seconds). Lyme disease is a cause of conduction defects that cause bradydysrrhythmia and that present as syncope. Ischemia includes acute myocardial infarction and coronary syndromes. Among structural abnormalities are: valvular heart disease, such as aortic or mitral stenosis, cardiomyopathy (e.g., ischemic, dilated, hypertrophic), aortic dissection, atrial myxoma, and cardiac tamponade.

Non-life-threatening causes of syncope include neurocardiogenic syncope, carotid sinus hypersensitivity, orthostatic syncope, and medication-related syncope. Neurocardiogenic syncope, also known as neurally-mediated, vasovagal, and vasodepressor syncope, is a reflex-mediated bradycardia and hypotension that leads to a brief decrease in cerebral perfusion. Such episodes usually last less than 30 seconds and may be accompanied by tonic-clonic movements, known as brainstem release phenomena, or mycoclonus. In contrast to seizures, sphincter control is maintained in vasodepressor syncope. Neurocardiogenic causes of syncope include micturition and defecation, cough, swallowing, glossopharyngeal nerve, pain, heat, breath-holding, and situ-

ational. These events are due either to increased vagal tone or to inappropriately decreased sympathetic tone.

Medication effects are contributory in 5% to 15% of events, and many common medications can contribute to syncope. These include: alpha and beta blockers, antiarrhythmics, antihypertensive medications, antiemetics, antipsychotics, antidepressants, calcium channel blockers, digoxin, diuretics, erectile dysfunction medications, nitrates, medications affecting conduction and those prolonging the QT interval (Table 2).[9]

QT prolongation is also associated with hypokalemia, hypomagnesemia, hypocalcemia, elevated intracranial pressure, ACS, hypothermia, and hereditary causes. Alcohol is another substance that frequently contributes to syncope. It will be noted that many patients with syncope are taking several classes of these medications at the same time.

Carotid sinus hypersensitivity is typically seen in men older than 40 years and leads to syncope associated with head turning, neck compression, and shaving.

Orthostasis may be responsible for up to one-quarter of the episodes seen in the ED, and it is due to circulating blood volume loss, autonomic dysfunction, deconditioning, and prolonged bed rest. Peripheral autonomic neural dysfunction is seen in elderly patients and in patients with Parkinson's disease, diabetes, multiple sclerosis, and spinal cord injury. The Shy-Drager syndrome is a rare disorder causing recurrent syncope secondary to damage in the autonomic nervous system.

History

Historical features to be elicited in patients with syncope are age, associated symptoms and triggers, position at the time of syncope, onset and duration, exertion as a precursor, presence of seizure activity, medications, prior episodes, family history, and associated injury. Patients and their families will often use vernacular to describe syncope, such as "passed out, "fell out," or "blacked out."

It has been observed that the risk of adverse outcomes after syncope is directly correlated with age.[10] Although risk-stratification schema have used various specific age cut-offs to define a high risk group, age is optimally interpreted within the context of other independent risk factors, such as structural heart disease, in order to define risk. Up to 20% of syncope in older adults is related to cardiac arrhythmia.

Associated symptoms at the time of syncope should direct further investigations. Chest pain suggests ACS or PE, while headache or specific weakness implies a neurological cause of syncope. Acute shortness of breath or leg pain would prompt an evaluation for PE. Headache might suggest SAH or carbon monoxide exposure, while menstrual irregularity or vaginal bleeding might lead to a workup for ectopic pregnancy. Flank or abdominal pain with syncope suggests leaking AAA.

A history of a strong emotional or situational trigger suggests neurocardiogenic causes. Physical or emotional distress, cough,

Table 2: Partial List of Drugs that Prolong the QT syndrome

Generic Name	Brand Name	Class/Clinical Use
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm
Arsenic trioxide	Trisenox®	Anti-cancer / leukemia
Astemizole	Hismanal®	Antihistamine / allergic rhinitis
Bepridil	Vascor®	Anti-anginal / heart pain
Chloroquine	Aralen®	Anti-malarial / malaria infection
Chlorpromazine	Thorazine®	Anti-psychotic/ anti-emetic / schizophrenia/ nausea
Cisapride	Propulsid®	GI stimulant / heartburn
Clarithromycin	Biaxin®	Antibiotic / bacterial infection
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm
Domperidone	Motilium®	Anti-nausea / nausea
Droperidol	Inapsine®	Sedative; anti-nausea / anesthesia adjunct, nausea
Erythromycin	Erythrocin®	Antibiotic; GI stimulant / bacterial infection; increase GI motility
Erythromycin	E.E.S.®	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Halofantrine	Halfan®	Anti-malarial / malaria infection
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia
Pimozide	Orap®	Anti-psychotic / Tourette's tics
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia

Source: www.QTdrugs.org

micturition, defecation, shaving, or standing for a prolonged period at the time increases the likelihood of a benign cause of syncope. A prodrome, consisting of nausea and vomiting, warmth, diaphoresis, and pallor, often precedes neurocardiogenic syncope.

In adolescents a history should be sought for eating disorders, diuretic or laxative abuse, and inhalant abuse. In older patients, a history of Parkinson's disease, multiple sclerosis, and other degenerative conditions should be elicited.

Patient position at the time of syncope is important. Syncope while supine suggests an arrhythmia, while syncope after prolonged standing may reflect a neurocardiogenic cause. Orthostatic syncope follows standing up from a supine or sitting position and is often of benign etiology. A sudden and unexpected onset of syncope without prodromal symptoms implies a more serious cause, such as arrhythmia, while a gradual onset preceded by prodromal symptoms is usually associated with more benign etiologies. The duration of syncope is usually brief, often lasting less than a minute or two. When a syncope-like event persists for more than a few minutes, other conditions, such as seizure, should be considered. It has been estimated that 5% to 15% of patients thought to have syncope have a seizure disorder.[7] Exertional syncope raises concerns about dysrrhythmias and structural heart disease, including outflow obstruction and cardiomyopathy.

A complete list of the patient's medications, especially newly prescribed ones, should be obtained. Particularly important are nitrates, calcium channel and beta blockers, antidysrhythmics, and medications known to prolong the QT interval (Table 2). A family history of sudden death, especially in relatives younger than 45 to 50 years, suggests cardiac syncope, such as the Brugada syndrome. This is a syndrome of sudden death associated with one of several ECG patterns characterized by incomplete right bundle branch block and ST elevations in the anterior precordial leads.

Syncope in patients with a history of congestive heart failure (CHF) has been shown to carry a poor prognosis, even when the event itself was from a benign cause, such as neurally-mediated syncope.[11]

Physical Examination

Physical examination should begin with a complete set of vital signs, although these may have normalized by the time of evaluation. Hypoxemia suggests possible CHF or PE. Pulse deficits and discrepancies of pulses and blood pressures between extremities suggest aortic dissection or subclavian steal syndrome.

Orthostatic blood pressure measurement consists of pulse and blood pressure after five minutes in a supine position, followed by repeat measurements after standing for three to five minutes. A positive result for orthostatic hypotension is defined as a drop in systolic blood pressure of 20 mmHg, a pulse increase of 20 beats per minute or more, or recurrent syncope. This test is neither sensitive nor specific, but a drop in blood pressure below 90 mmHg associated with symptoms can be diagnostic.

Skin and eye examination might show pallor suggestive of anemia and blood loss. The EP should consider potential sources of hemorrhage, including ruptured AAA, ruptured ectopic pregnancy, ruptured ovarian cyst, and ruptured spleen. Intraoral examination will detect evidence of tongue biting to suggest seizure activity. It may also reveal evidence of dehydration. The neurologic examination in syncope is, by definition, normal. Any residual deficit after a syncope-like event should suggest an acute stroke or structural lesion or a profound toxic or metabolic insult. The lung examination should seek evidence of CHF or focal pulmonary signs suggesting PE. Cardiac examination focuses on gallop rhythms, dysrrhythmias, and murmurs. The neck examination identifies transmitted cardiac murmurs and carotid stenoses as well as thyroid enlargement. The detection of a grade III/IV mid-systolic murmur radiating to the neck and loss of S2 splitting is suggestive of critical aortic stenosis. A murmur that gains intensity with Valsalva maneuvers and abolishes with squatting suggests hypertrophic cardiomyopathy. An extra heart sound, either an S3 or S4, may be identified in CHF.

Abdominal examination may reveal a pulsatile mass in ruptured abdominal aortic aneurysm. A rectal examination can identify gross or occult fecal blood.

A thorough head-to-toe examination is essential to detect trauma resulting from a fall. Particular emphasis is placed on the examination of the scalp for lacerations or hematomas, on the face for fractures, on the neck for evidence of trauma, and on the extremities for fractures or dislocations.

Laboratory Examination

The electrocardiogram (ECG) is recommended in the evaluation of most cases of syncope.[12] The American College of Emergency Physicians clinical policy on syncope strongly recommends that an ECG be obtained in the initial evaluation of patients with syncope (Figure 1). It is rapid and inexpensive, and it may identify the etiology of syncope in up to 7% of cases. The ECG may reveal evidence of cardiac ischemia or arrhythmia as the cause of syncope. Myocardial infarction (MI) occurs in up to 3% of syncope patients, and a normal ECG has a negative predictive value for MI as the cause for the syncope of greater than 99%.[8]

ECG evidence of right heart strain may be suggestive of PE. Patients with an ECG that shows sinus rhythm with no new abnormal morphologic changes compared to prior ECGs have been found to be at low risk of adverse events during short-term follow up.[13] In contrast, the presence of an abnormal ECG (defined as any abnormality of rhythm or conduction, ventricular hypertrophy, or evidence of previous myocardial infarction but excluding nonspecific ST-segment and T-wave changes) has been found to be a predictor for arrhythmia or death within one

Figure 1: ACEPs Clinical Policy on Syncope

A. Critical Questions:

1. What history and physical examination data help to risk-stratify patients with syncope?

Level A recommendations:
- Use history or physical examination findings consistent with heart failure to help identify patients at higher risk of an adverse outcome.

Level B recommendations:
- Consider older age, structural heart disease, or a history of coronary artery disease as risk factor for adverse outcome.
- Consider younger patients with syncope that is nonexertional, without history or signs of cardiovascular disease, a family history of sudden death, and without co-morbidities to be at low risk of adverse events.

2. What diagnostic testing data help to risk-stratify patients with syncope?

Level A recommendations:
- Obtain a standard 12-lead ECG in patients with syncope.

Level B recommendations:
- None specified.

Level C recommendations:
- Laboratory testing and advanced investigative testing, such as echocardiography or cranial CT scanning, need not be routinely performed unless guided by specific findings in the history or physical examination.

3. Who should be admitted after an episode of syncope of unclear cause?

Level A recommendations
- None specified.

Level B recommendations
- Admit patients with syncope and evidence of heart failure or structural heart disease.
- Admit patients with syncope and other factors that lead to stratification as high risk for adverse outcome.

Level C recommendations
- None specified.

B. Factors that lead to stratification as high-risk for adverse outcome:

- Older age and associated co-morbidities*
- Abnormal ECG†
- Hct <30 (if obtained)
- History or presence of heart failure, coronary artery disease, or structural heart disease

*Different studies use different ages as threshold for decision making. Age is likely a continuous variable that reflects the cardiovascular health of the individual rather than an arbitrary value.

†ECG abnormalities, including acute ischemia, dysrhythmias, or significant conduction abnormalities.

From: Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department with Syncope. *Annals of Emergency Medicine.* 2007;49(4):431-7.

From: American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Syncope. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with syncope. *Ann Emerg Med.* 2007;49:431-444.

For a complete discussion of the evidence for these recommendations and for definitions of terms, see the full clinical policy, available online at: http://www.acep.org/practres.aspx?id=30060/.

year after the syncopal episode. The one-year mortality of patients with cardiac syncope approaches 30%, and in those with CHF mortality is even higher.[14]

Significant ECG findings include: evidence of ACS, severe bradycardia, prolonged intervals (QRS, QTc), ventricular hypertrophy, and preexcitation and other abnormal conduction (e.g., Wolf-Parkinson-White and Brugada syndrome). Wolf-Parkinson-White syndrome is associated with short P-R interval, a delta wave, and wide QRS complexes on ECG. Patients with a QT interval greater than 500 mseconds may have up to a 50% lifetime risk of sudden death. Congenital long QT syndrome may be identified by the presence of notched, broad-based or peaked T waves and UT waves. Brugada syndrome is an autosomal dominant condition affecting the sodium channel and predisposing the patient to lethal ventricular dysrrhythmias. This syndrome carries a 10% mortality rate per year in symptomatic patients. The ECG in Brugada syndrome shows a complete or incomplete right bundle branch block pattern and ST segment elevations in leads V_1 and V_2. Brugada syndrome usually presents in patients 30 to 40 years old, and it may be responsible for up to 5% of cardiac arrests treated in the emergency department.[15,16] (It should be noted that the elevated prevalence of Brugada syndrome is particularly evident in emergency departments that serve a population with a high number of Southeast Asians.)

Hypertrophic cardiomyopathy is associated with high voltage and deep, narrow Q waves in the lateral leads (I, L, V_5, V_6). Low voltage suggests pericardial effusion and abnormal conduction syndromes.

Patients suspected of having abnormal cardiac rhythms should be placed on a cardiac monitor. Monitoring may detect significant bradycardia (heart rate <30 beats/minute), sinus pauses (particularly those >2 seconds), atrial tachycardias, Mobitz II block, complete heart block, ventricular tachycardia, and frequent or multifocal premature ventricular contractions (PVCs).[17]

Routine laboratory screening in patients with syncope seldom aids in their evaluation and management, is not cost-effective, and is not supported by clinical evidence.[18, 19]

Hypoglycemia should be suspected in all patients with an altered mental status, and a pregnancy test is advised in all women of childbearing age who have syncope. Critically ill patients, those on diuretic medications, and those suspected of volume loss may benefit from measurement of serum electrolytes. Electrolyte studies are indicated in patients with poor oral intake, excessive vomiting or diarrhea, muscle weakness, alcoholism, altered mental status, or recent electrolyte abnormalities. A hematocrit less than 30 increases the risk of adverse short-term events in patients with syncope, and complete blood count should be considered in the patient with syncope who demonstrates hypotension, tachycardia, pallor, or rectal examination positive for evidence of bleeding.[13]

Carboxyhemoglobin levels may be useful in patients who are involved in house fires or if direct combustion is used for in-

door heating. An electroencephalogram may be useful in ruling out epilepsy.

Head computed tomography (CT) and magnetic resonance imaging (MRI) are generally of low yield and are over-utilized in the evaluation of syncope patients. There is no current evidence that a patient with syncope benefits from routine neuroimaging.[20] Given that loss of consciousness requires simultaneous dysfunction of both cerebral hemispheres or of the reticular activating system, it is evident that patients who spontaneously and completely recover without treatment are unlikely to have structural brain abnormalities that would be seen on neuroimaging. Patients without history or examination features that suggest neurologic disease need no further neurological studies. In contrast, patients with a history or physical examination suspicious for new onset seizure, transient ischemic attack, and stroke need further evaluation.

Echocardiography may detect the presence of cardiac valvular anomalies, wall motion abnormalities, elevated pulmonary pressure or right ventricular strain (as is sometimes seen in PE), and pericardial effusions. Echo has been shown to be most useful in patients with a history of cardiac disease or abnormal electrocardiogram findings and when aortic stenosis is suspected clinically. The current literature does not support the routine use of echocardiography as a screening test in patients with an otherwise negative screening evaluation.[21]

In suspected PE, helical CT scan may be indicated. It is noteworthy that patients with PE who present with neurocardiogenic syncope are not at increased risk when compared with other PE patients without syncope.[22]

Head CT and lumbar puncture are indicated in syncope associated with a significant headache suggesting possible SAH. Head CT with angiography or MRI and neurologic consultation should be considered in suspected transient ischemic attack or stroke.

Risk Stratification

Several recent studies have attempted to stratify syncope patients with regard to risk for life-threatening events within 30 days. The Boston syncope rule utilized eight categories of signs and symptoms that placed patients at higher risk for adverse outcomes or death at 30 days (Figure 2). These were: 1) signs and symptoms of ACS; 2) signs of conduction disease; 3) worrisome cardiac history; 4) valvular heart disease by history or physical examination; 5) family history of sudden death; 6) persistent abnormal vital signs in the ED; 7) volume depletion, such as persistent dehydration, gastrointestinal bleeding, or hematocrit < 30; and 8) primary central nervous system (CNS) event.[23]

The authors found that use of this instrument to screen syncope patients yielded a sensitivity of 97%, specificity of 62%, with a negative predictive value of 99%. In their population, admitting only those patients identified by the decision rule would have led to a 48% reduction in hospital admissions. Quinn et al. published the San Francisco Syncope Rule as a means of predicting patients with serious outcomes at one week. Their data suggested that age >75 years, an abnormal ECG, hematocrit < 30, a complaint of shortness of breath, and a history of CHF were all significant risk factors. The San Francisco Syncope Rule had a sensitivity of 96% and specificity of 62%.[13]

Other features that place syncope patients at risk for adverse outcomes include: persistently low blood pressure (systolic <90 mmHg), shortness of breath (either with the event or during evaluation), hematocrit <30 (if obtained), older age, associated co-morbidities, and a family history of sudden cardiac death.

Figure 2: The Boston Syncope Rule

These criteria can be categorized as follows:

1) Signs and symptoms of an acute coronary syndrome (ACS)

2) Signs of conduction disease

3) Worrisome cardiac history

4) Valvular heart disease by history or physical examination

5) Family history of sudden death

6) Persistent abnormal vital signs in the ED

7) Volume depletion such as persistent dehydration, gastrointestinal bleeding, or hematocrit < 30

8) Primary CNS (central nervous system) event

Predicts significant risk factors for poor outcome at 30 days.

From: *J Emerg Med.* 2007;October;33(3):233–239. Predicting Adverse Outcomes in Syncope. Shamai A. Grossman, MD, MS, Christopher Fischer, MD, Lewis A. Lipsitz, MD, Lawrence Mottley, MD, Kenneth Sands, MD, Scott Thompson, BA, Peter Zimetbaum, MD, and Nathan I. Shapiro, MD, MPH.

Figure 3: The San Francisco Syncope Rule

"CHESS" mnemonic

C: history of Congestive heart failure

H: Hematocrit <30%

E: abnormal ECG

S: a patient complaint of Shortness of breath, and

S: a triage Systolic blood pressure <90 mm Hg)

FROM: Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. James V Quinn, Ian G Stiell, Daniel A McDermott, Karen L Sellers, Michael A Kohn, George A Wells. *Annals of Emergency Medicine.* February 2004 (Vol. 43, Issue 2, Pages 224-232). San Francisco Syncope Rule as a means of predicting patients with serious outcomes at one week. Their data suggest that age >75 years, an abnormal ECG, hematocrit < 30, a complaint of shortness of breath, and a history of CHF are all significant risk factors for poor outcome at one week.

Figure 5: The EGSYS Score

- Palpitations preceding syncope - 4 points
- Heart disease and/or abnormal electrocardiogram (sinus bradycardia, second or third degree atrioventricular block, bundle branch block, acute or old myocardial infarction, supraventricular or ventricular tachycardia, left or right ventricular hypertrophy, ventricular preexcitation, long QT, Brugada pattern) - 3 points
- Syncope during effort - 3 points
- Syncope while supine - 2 points
- Precipitating or predisposing factors (warm, crowded place, prolonged orthostasis, pain, emotion, fear) - minus 1 point
- A prodrome of nausea or vomiting - minus 1 point

A score of ≥3 had 92% sensitivity and 69% specificity for cardiac syncope in the validation cohort. During follow-up at a mean of 20 months, patients with a score ≥3 had higher mortality than patients with score <3 in both the derivation (17 versus 3%) and validation cohorts (21 versus 2%).

Source: Del Rosso A, Ungar A, Maggi R, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to general hospital: the EGSYS score. *Heart.* 2008;Jun 2 [Epub ahead of print].

One theme that emerges from a number of recent studies is that patients with an abnormal ECG on presentation or a history of heart disease, particularly structural heart disease (e.g., CHF), are at greater risk for adverse outcomes.

The Evaluation of Guidelines in Syncope Study (EGSYS) is a risk assessment tool that has been prospectively validated (Figure 5).[24] This score consists of the six (out of 52) items found to be most predictive of a cardiac cause of syncope: palpitations preceding syncope (4 points), history of heart disease or abnormal electrocardiogram in the ED (3 points), syncope during effort (3 points) or while supine (2 points), precipitating or predisposing factors (–1 point), and nausea or vomiting (–1 point). A score of ≥3 had 92 % sensitivity and 69 % specificity for cardiac syncope in the validation study. At a mean follow-up of 20 months, patients with a score ≥3 had higher mortality than patients with a score <3 in both the derivation and validation studies.

One study that assessed syncope decision-making by emergency physicians demonstrated excellent patient risk stratification but that disposition decisions often were not consistent with anticipated risk. These physicians chose to admit nearly 30% of patients whom they felt had a less than 2% chance of a serious adverse outcome.[25]

An analysis of the American College of Emergency Physicians (ACEP) clinical policy on syncope found that, by applying their recommendations, all patients with cardiac causes of syncope were identified and that the admission rate could safely have been reduced from 57.5% to 28.5%. These facts must lead to a reassessment of the role of the emergency physician in evaluation and disposition of the patient presenting with syncope.[12]

Management

An algorithmic approach to the syncope patient was suggested by McDermott and Quinn (Figure 4).[1] The first step in this approach to the patient with apparent syncope is to determine whether syncope has actually occurred. Some syncope-like conditions to be considered include seizure, stroke, and head injury. Each of these conditions, though not syncope by definition, requires prompt stabilization, evaluation, and treatment.

The next step is to attempt to determine the cause of the syncope. As outlined above, there are historical, physical examination, and ECG features that suggest specific etiologies of syncope. If the specific cause of the syncope is a serious one (e.g., cardiovascular syncope, ACS, structural cardiac abnormalities, significant hemorrhage, PE, SAH), then admission and specific treatment is required. If a non-serious condition is identified (e.g., neurocardiogenic syncope, orthostatic hypotension, medication-related syncope), then outpatient management is usually appropriate.

If the history, physical examination, and ECG do not suggest a specific etiology of syncope, then the patient is categorized as either high risk or low risk for factors that predict adverse outcome. These high-risk features are: an abnormal ECG (e.g., ACS, dysrhythmias, or significant conduction abnormalities), history of cardiac disease, especially presence of CHF, persistently low blood pressure (systolic <90 mmHg), shortness of breath with the event or during evaluation, hematocrit <30 (if obtained), older age, associated co-morbidities, and a family history of sudden cardiac death. Patients with high-risk features should be admitted and evaluated with continuous cardiac monitoring and other tests as indicated. In the absence of high-risk features, asymptomatic patients with unexplained syncope may be discharged safely with outpatient follow up.

Continuous outpatient ambulatory monitoring (i.e., Holter monitoring) is of limited value in patients with rare episodes of syncope and long intervals between episodes.[26] Implantable cardiac monitors may be considered in these patients. These devices are placed subcutaneously in the pectoral region under local anesthesia. The monitors function as permanent loop recorders, recording rhythm abnormalities automatically or when activated by the patient. These monitors have reportedly led to a diagnosis in up to 90% of patients. Insertable loop recorders are used, especially for the detection of intermittent arrhythmias.[27] Further, one prospective study found that 64% of patients provided with loop recorders experienced an arrhythmia at the time of syncope.[27]

Summary

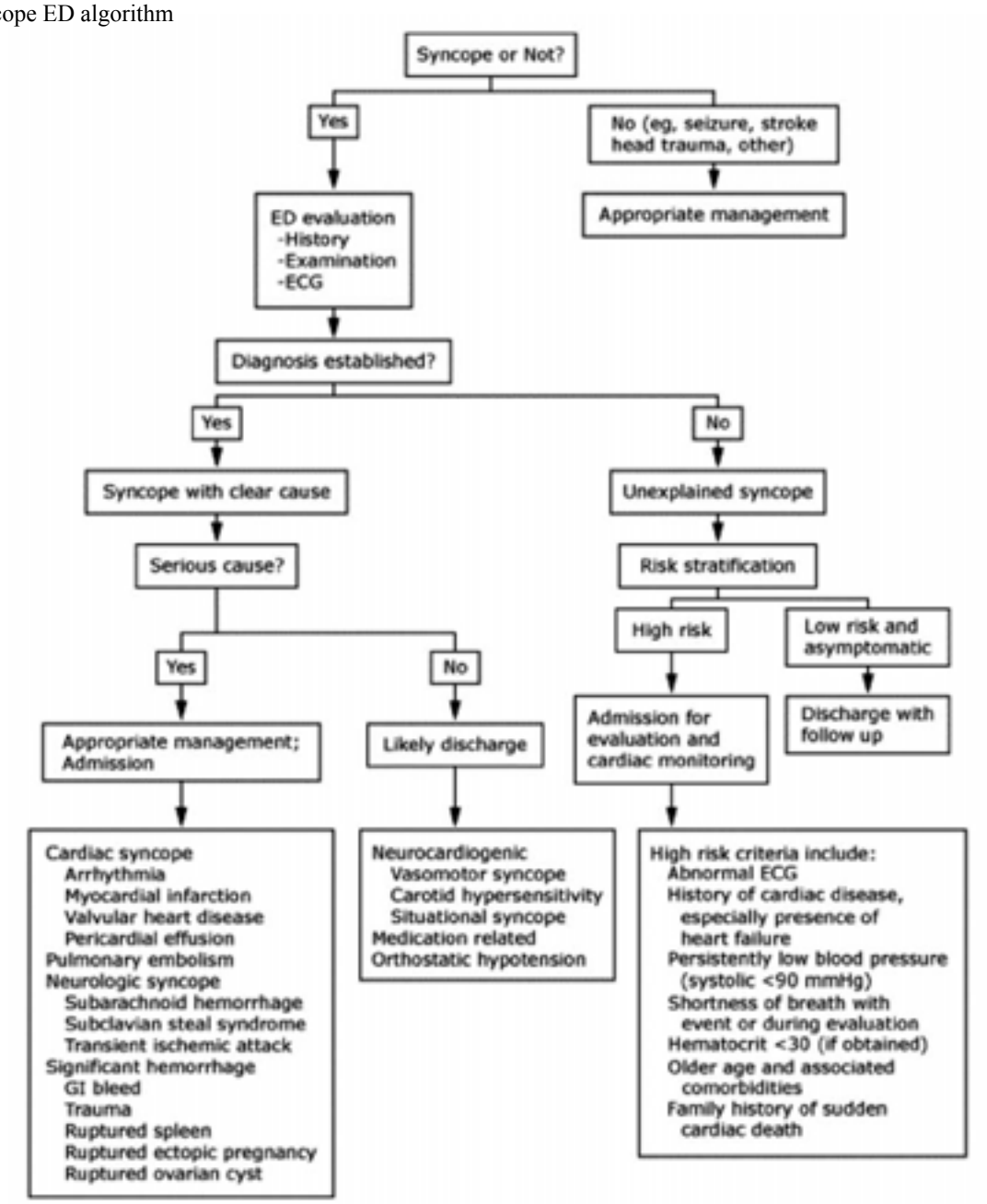
Syncope accounts for 3% of ED visits and 1% to 6% of all hospital admissions. It is estimated that more than $5,000 is spent per inpatient stay for syncope, and that $2 billion a year is spent

in the United States on hospitalization of patients with syncope.[12] In evaluating these patients, the emergency physicians must decide whether a life-threatening condition is present, and he or she must stabilize the patient and provide appropriate disposition. The EP must next identify those who would benefit from specific treatment or intervention and which of the patients who remain without a diagnosis will require further evaluation. The determination of the appropriate setting for this evaluation (inpatient vs. outpatient) becomes central to the decision-making process. Life threats include cardiac syncope, blood loss, PE, and SAH. Other conditions that resemble syncope, such as seizure, stroke, and head injury, must also be considered and stabilized. Further, less dangerous causes of syncope should be identified, if possible, including neurocardiogenic, carotid sinus sensitivity, orthostasis, and medication-induced syncope.

High-risk historical and physical examination features should be elicited, and an ECG should be interpreted to differentiate those patients who are safe for discharge from those who require emergent evaluation of potentially life-threatening etiologies and in-hospital management.

Identification of the cause of syncope is possible in fewer than half of the patients during their initial evaluation. It is possible, however, to use an organized and evidence-based approach to the syncope patient that provides appropriate evaluation and stabilization and safe and cost-effective disposition for these patients.

Figure 4: Syncope ED algorithm



From: McDermott D, Quinn J. Approach to the adult patient with syncope in the emergency department. Version 16.3: October 2008. Available at: http://www.uptodate.com/online/about/contact_us.html. Accessed February 12, 2009.

Originally residency-trained in general and cardiothoracic surgery, Dr. Lemonick has practiced emergency medicine for more than 20 years. He is an attending emergency physician at Armstrong County Memorial Hospital, near Pittsburgh. Dr. Lemonick's previous contributions to AJCM have dealt with biological, chemical, and radiological war casualties, back pain, wound care, peer review, and prehospital care.

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Core Competencies – Chest X-ray

Food Handler with Cough

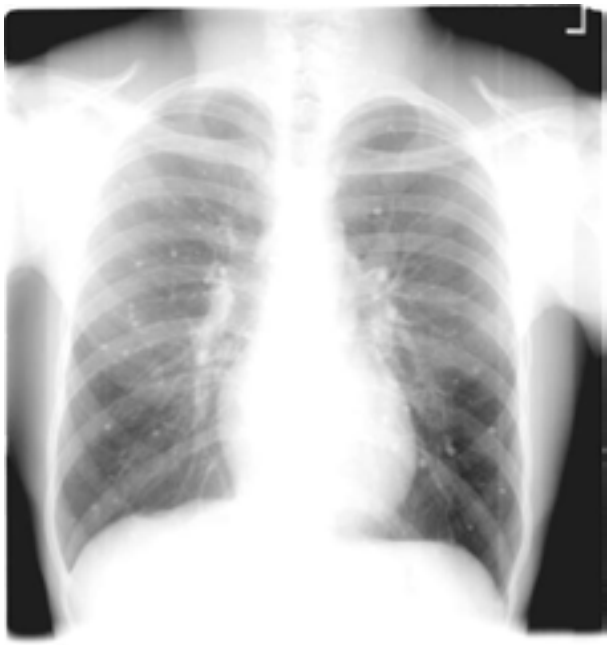
Manoj Mazumder, MD

A 21-year-old African-American food handler from Memphis, who works in a nursing home facility, has experienced increasingly severe nausea and vomiting over the past six days. During the last day he has complained of chest pain, slight nonproductive cough, and a fever. He denies a previous history of allergy, surgery, or hospitalization. He smoked for two years but quit several years ago. He denies TB exposure, hemoptysis, headache, night sweats, and weight loss. He denies cave exploration and exotic pets.

His vital signs are unremarkable: blood pressure 105/73, pulse 64 beats per minute, oral temperature 99.0º Fahrenheit, respiratory rate 16 per minute and unlabored.

His physical examination is unremarkable. The lungs are clear to auscultation and percussion. Pulse oximeter documents SaO_2 of 99%. The peak flow is 450 L/minute. An electrocardiogram is normal, and the hemogram is normal with a white blood cell count of 4.0 $x10^9$/L, and the hemoglobin is 15.1 gms/dl.

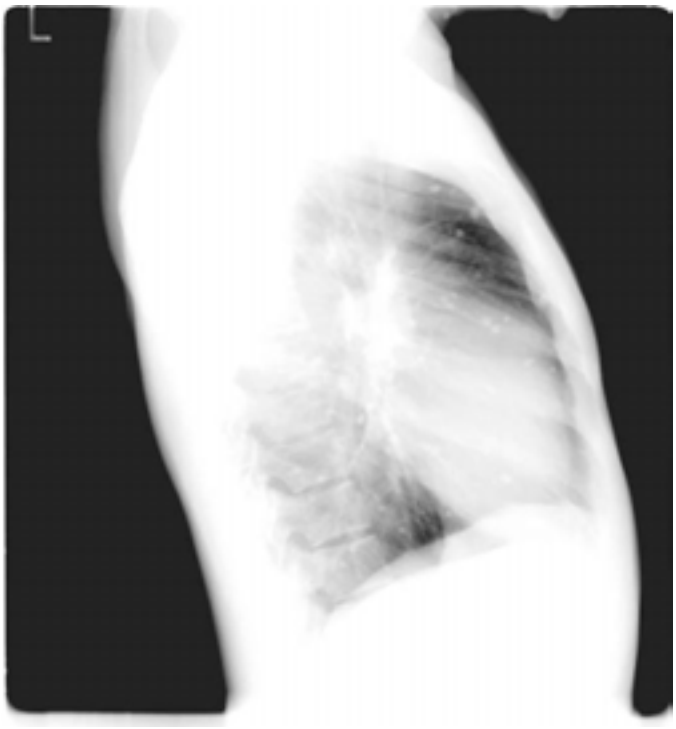
The following chest radiogram is obtained, and clinical questions follow. First, there is a postero-anterior view and then a lateral image.



1. The best interpretation of this image is:
    a. Acute pneumonia
    b. Secondary tuberculosis
    c. Primary tuberculosis
    d. Diffuse bilateral abnormalities of unknown etiology

2. The best management plan would include:
    a. Hospitalization
    b. Immediate referral to the public health department
    c. A PPD skin test with reading in 48-72 hours
    d. Bronchoscopy following AIDs precautions

The patient returns from the hospital where his HIV and bronchoscopy examinations were "normal." A PPD was placed, and two days later the induration was noted to be 9 mm. A lateral image from the first day is reviewed.



3. The lateral image is most consistent with:
   a. Acute pneumonia
   b. Secondary tuberculosis
   c. Primary tuberculosis
   d. Diffuse bilateral abnormalities of unknown etiology

4. This radiograph, present illness, and physical examination are most consistent with:
   a. Blastomycosis
   b. Tuberculosis
   c. Histoplasmosis
   d. Pneumocystis Carinii

5. Management of this case should include:
   a. Immediate termination as a food handler
   b. Quarantine with public health department
   c. Course of medication as outpatient
   d. Routine care with observation for changes

Discussion

In the radiograph both lung fields have multiple scattered small nodules. These were uniformly small, less than 2 mm each. Although there are several differential diagnoses for this pattern, this most likely represents a fungal infection known as histoplasmosis. Tuberculosis and HIV should be excluded, and they were. Inpatient workup was not necessary.

Histoplasmosis is a disease caused by the fungus *Histoplasma capsulatum. H. capsulatum* grows in soil and material contaminated with bat or bird droppings, including poultry. Spores become airborne when contaminated soil is disturbed. Breathing the spores causes infection. The disease is not transmitted from an infected person to someone else.[1] *Histoplasma capsulatum* may infect anyone. Positive histoplasmin skin tests occur in as many as 80% of the people living in areas where *H. capsulatum* is common, such as the midwestern United States, in the Ohio and Mississippi valleys. Among the endemic mycoses it is the most common cause for hospitalization.[2] Its symptoms vary greatly, but the disease primarily affects the lungs. Most individuals with histoplasmosis are asymptomatic.

Since person-to-person transmission of histoplasma is not known, the patient can continue working as a food handler. Transmission by organ transplantation has been reported, however.[3,4]

Distinct patterns may be seen on a chest x-ray. Histoplasmomas are healed pulmonary lesions that appear as residual nodules on chest radiography. These are seen here, but his disease has not reactivated. This military pattern of histoplasmosis is frequently accompanied by calcified hilar adenopathy, but that is not seen here. Chronic histoplasmosis can resemble tuberculosis and can worsen over months or years.

Those who develop clinical manifestations are usually immunocompromised or are exposed to a high quantity of inoculum. Infants, young children, and older persons, in particular those with chronic lung disease, are at increased risk for severe disease. The acute respiratory disease is characterized by respiratory symptoms, a general ill feeling, fever, chest pains, and a dry or nonproductive cough. The disseminated form is fatal unless treated.

Treatment for Pulmonary Histoplasmosis

Clinical practice guidelines for the management of patients with histoplasmosis were updated in 2007 by the Infectious Disease Society of America.[5]

The therapeutic approach to pulmonary Histoplasmosis varies according to the specific disease process, namely:

1. Acute pulmonary Histoplasmosis
2. Chronic pulmonary Histoplasmosis
3. Mediastinal granulomas
4. Fibrosing mediastinitis
5. Broncholithiasis
6. Pulmonary nodules

This patient has asymptomatic pulmonary nodules. Sites of healed *Histoplasma capsulatum* lung infection can evolve into pulmonary nodules that can persist long term.[5,6] They are typically asymptomatic and are identified incidentally on chest x rays or CT imaging. In the setting of isolated nodules, there is no evidence that antifungal therapy is beneficial.[5,7] Antifungal medications are used to treat severe cases of acute histoplasmosis and all cases of chronic and disseminated disease. Mild

disease usually resolves without treatment. Past infection results in partial protection against ill effects if reinfected.[5] *Histoplasma* species may remain latent in healed granulomas and recur due to subsequent cell-mediated immunity impairment.

Diagnosis

Culture of *Histoplasma capsulatum* from bone marrow, blood, sputum, and tissue specimens is the definitive method of diagnosis. Demonstration of the typical intracellular yeast forms by microscopic examination strongly supports the diagnosis of histoplasmosis when clinical, epidemiologic, and other laboratory studies are compatible.

An antigen detection test used on urine and serum is a rapid, commercially available diagnostic test. Antigen detection is most sensitive for severe, acute pulmonary infections and for progressive disseminated infections. It often is transiently positive early in the course of acute, self-limited pulmonary infections. A negative test does not exclude infection.

In this case, these healed pulmonary nodules will require no further investigations. Further, nothing will be gained from antigen tests or skin tests at this time. Surveillance at six to twelve months and as new symptoms arise seems reasonable.

Manoj Mazumder, Department of Family Medicine, University of Arkansas Medical Sciences, Little Rock.

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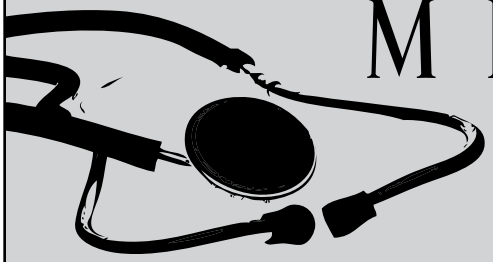
Answers 1-a; 2-c; 3-d; 4-c; 5-d



MEDICAL ETHICS
WITHOUT THE RHETORIC

Mark Pastin, Ph.D.

Mark Pastin, PhD, is president and CEO of the Council of Ethical Organizations, Alexandria, VA. The Council, a non-profit, non-partisan organization, is dedicated to promoting ethical and legal conduct in business, government, and the professions.

Cases presented here involve real physicians and patients. Unlike the cases in medical ethics textbooks, these cases seldom involve cloning, bizarre treatments, or stem cell research. We emphasize cases common to the practice of medicine.

Most cases are circumstantially unique and require the viewpoints of the practitioners and patients involved. For this reason, I solicit your input on the cases discussed here at ***councile@aol.com.*** *Reader perspectives along with my own viewpoint are published in the issue following each case presentation. We are also interested in cases that readers submit. The following case is particularly relevant in these days when healthcare reform – and who is going to pay for it - is on everyone's mind.*

CASE FIVE
LIFE AFTER LIFE?

A woman who was considered perfectly healthy at the time she became pregnant is found to have terminal cancer early in her pregnancy. While there is little chance of the cancer being transferred to the fetus, there is also little chance of the mother surviving long enough for a viable delivery. The women and her husband request that her body functions be maintained, even after she is legally dead, until the baby can be safely delivered. Her physician advises that this is a reasonable although not certainly successful course of action. The issue? According to the hospital where she is receiving treatment, the cost of maintaining her bodily functions would exceed $500,000. Needless to say, a dead patient has no health insurance, and the couple does not have the money. What should be done by the various parties to this case?

This is an actual case. Of course, there are any number of complicating circumstances and additional details; but please address the case on the basis of the information provided. There will be an analysis of this case and a new case in the next issue.

Your input is requested. Email your responses to: councile@aol.com.

CASE FOUR ANALYSIS

Our response to last issue's case is based on comments offered by readers.

In the case presented in the last issue, an ER physician is confronted with a seriously injured minor whose parents advise that their religion prohibits transfusions. The ER physician does not believe that the life of the minor can be saved without prompt attention, which may include a transfusion. Some readers suggested going to court to seek permission to treat the minor in a medically appropriate manner. But the case rules out this otherwise reasonable option due to the limited time available to treat the minor. Several readers pointed out that, although the patient is a minor, the physician's primary obligation is still to the patient. And that obligation includes doing the best you can to save the patient's life.

Ethical, Legal, and Professional Challenges Posed by "Controlled Medication Seekers" to Healthcare Providers - Part 1

Ken Solis, MD, MA

Abstract

Abuse and diversion of controlled prescription medications is a large and growing problem in the U.S. In fact, individuals abusing controlled medications outnumber the abusers of cocaine, heroin, hallucinogens, and inhalants combined. The first of this two-part paper focuses on the pragmatic, ethical, and legal issues that challenge physicians and other providers who must care for someone suspected or confirmed to be using deception to obtain controlled medications for resale, personal recreational use, or other reasons not sanctioned by the medical profession. The second part will focus on a general approach that attempts to minimize potential harms while still addressing legitimate medical needs of these challenging patients. It is hoped that this paper will be a catalyst for deeper and wider discussions and research on this difficult healthcare-related issue.

Introduction

The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations-JCAHO) and other medical authorities have strongly encouraged healthcare providers to more aggressively treat pain after a wave of research indicated that many patients were not having their pain adequately managed.[1,2,3,4] Alas, the sword of aggressive pain control might be double edged. Although correlation does not mean causation, providers have simultaneously also witnessed an increase in the percentage of individuals feigning or exaggerating medical conditions to obtain controlled prescription medications, especially narcotics, for ulterior purposes. For example, according to a 2005 report by the National Center on Addiction and Substance Abuse at Columbia University:[5]

There has been a 94% increase in people abusing prescription drugs between 1992 and 2003 (from 7.8 million to 15.1 million).

In the same time period, there has been a self-reported 140.5% increase in abuse of prescription opioids, a 44.5% increase in abuse of central nervous system prescription depressants, and a 41.5% increase in abuse of prescription central nervous system stimulants.

In 2003, approximately 6% of the U.S. population admitted to abusing controlled prescription drugs, 23% more than the combined number abusing cocaine, hallucinogens, inhalants, and heroin.

Teens have had an especially rapid rise in controlled prescription drug abuse, increasing 542% from 1992 to 2002; and 2.3 million teens (9.3%) admitted to abusing them in 2003.

Statistics available up to 2007 indicate that the trend of increasing abuse of controlled prescription medications has not abated, at least in those aged 18-25.[6] Importantly, the harms from controlled prescription medication abuse are also substantial because of their potential to cause physical or psychological dependency,

Table 1: Characterizing genuine patients versus different types of malingering.

	Has a medical condition?	Truthful?	Legal Behavior?
PATIENT TYPE			
Genuine	yes	yes	yes
Malingerers			
Feigns/exaggerates a condition to obtain medication due to drug dependency.	yes	no	no
Feigns/exaggerates a condition to obtain medication for monetary profit or for its euphoric effects.	no	no	no
Feigns/exaggerates a condition to obtain monetary compensation.	no	no	no
Feigns/exaggerates a condition to avoid a work day.	no	no	yes

add burdens to an already stressed healthcare system, and, especially, because it is estimated that they contribute to nearly 30% of all reported deaths and injuries from drug abuse.[7]

Defining the Problem

"Drug seeking (behavior)" and "drug seeker" are phrases commonly found in the medical literature and in common medical parlance, and multiple definitions of "drug seeking" exist in the literature[8] and medical dictionaries.[9,10] Although some definitions list various behaviors commonly associated with drug seeking, at least one only focuses on a single illicit intent for the sought drug – selling it for profit.[11] However, for the purposes of this paper, "drug seeking" will include both the *general* behavior as well as the intent that is compelling the behavior. Additionally, this paper proposes to use the more precise phrases "controlled medication seeking" and "controlled medication seeker" to avoid including those who might seek an illicit drug, such as heroin, on the street, or even the parent who seeks a non-controlled drug like amoxicillin for their child's viral respiratory infection. This paper defines "controlled medication seeking" as: intentionally feigning or exaggerating a medical condition, or otherwise using deception (e.g., prescription tampering) to obtain a controlled medication (medications that are classified as being schedule II-V of the U.S. "Controlled Substances Act") from the healthcare system for purposes not sanctioned by the medical profession and provider.

What Type(s) of Patients *are* Controlled Medication Seekers?

According to the U.S. Centers for Medicare & Medicaid Services (CMS), a "patient" is an individual who is receiving needed professional services that are directed by a licensed practitioner of the healing arts toward maintenance, improvement or protection of health or lessening of illness, disability or pain.[12] An individual who intends to procure controlled medications from a provider solely for its recreational effects (e.g., euphoria) or for monetary profit, fails to qualify as a genuine patient. Seekers who have an underlying physical dependency to the controlled medication or also have an underlying condition such as chronic pain are genuine patients by CMS's definition – even if their behavior obscures a valid underlying medical condition(s).

Controlled medication seekers can also be categorized as a subset of a "malingerer": those who intentionally produce false or grossly exaggerated physical or psychological symptoms, motivated by external incentives such as avoiding work or military duty; obtaining drugs for financial compensation; or evading criminal prosecution.[13] While all forms of malingering are unethical at face value, some forms are not illegal, e.g., pretending to have back pain to avoid a day at work. Other forms of malingering such as faking a back injury to obtain an insurance claim and drug seeking are illegal, fraudulent acts.

Hence, drug seekers and malingerers are not a homogeneous class of patients, which further complicates their characterization. Table 1 parses how genuine patients and several subsets of malingerers can be categorized in regards to having a genuine medical condition, their truthfulness, and the legality of their behavior. Whether patients who are definitively involved in illegal activity should be reported to law enforcement authorities will be explored in the second part of this article.

Roles and Responsibilities of Patients

Physicians and other healthcare providers have substantial "power" over their patients due to their mastery of special knowledge and skill sets, the healthcare setting which is intimidating or at least often confusing to patients, and the patients' vulnerability when they are ill or injured, to name a few reasons. Therefore, tradition and a great deal of literature rightfully propounds upon the fiduciary duties that providers have to their patients. Perhaps less well known, or at least less publicized, is the caveat that patients also have duties to providers as well. One of the most important duties that a patient has to

providers is to be honest or "candid in discussing their medical problems," as proposed since at least the 1700s by Doctor Benjamin Rush.[14] This assertion is echoed in contemporary times as well by the American Medical Association's Code of Medical Ethics. Section 10.02 of the Code lists eleven patient responsibilities, the first two of which require the patient to be truthful and to give a complete medical history, and the last one that admonishes the patient from initiating or participating in fraudulent health care.[15]

According to the definition given above, controlled medication seekers use deception to obtain a particular medication from providers for ulterior purposes. Of course, besides the immediate breach in ethical decorum and responsibility, lack of patient honesty leads to pragmatic medical problems as well. For instance, even a careful exam and extensive tests cannot definitively refute a patient's complaint of a severe headache – we must ultimately rely on their report of experiencing pain. Even though evaluations exist to help discern some genuine conditions from feigned conditions (e.g., a physical therapy evaluation of low back pain), in many settings such as the emergency department or a busy private practice, a provider might not have the time or the resources to quickly and confidently disprove a patient's claim that they have the alleged condition. In other words, seekers take advantage of the indeterminacy and uncertainty inherent to the practice of healthcare.

Second, the exchange of adequate and honest information between the patient and provider is required for the development of mutual trust necessary for a well functioning patient-provider relationship. If the provider suspects or discovers a ruse, mutual trust is compromised and the seeker risks assuming the role of the "Boy Who Cried Wolf" with the same potential, eventual outcome. Third, the provider is also well aware of the parable's outcome and now must not only wrestle with the uncertainty inherent to medical practice but also the added uncertainty imposed by the unreliable individual: "Is my patient with a history of controlled medication seeking telling the truth *this* time?!" Pursuing the spiraling descent of mistrust even further, sometimes seekers, who know that they are considered to be dishonest by their provider, local emergency department, etc., might decide to delay or forego genuinely needed medical treatment due to fear of disbelief or disdain from the provider. In the final analysis, if an individual is known to use deception to obtain controlled medications for ulterior purposes, the mutual trust critical for developing a well-functioning patient-provider relationship and to practice safe, effective medicine has been seriously undermined.

Importantly from the provider's perspective, seekers also violate the interpersonal rule to not "use" another individual for their own hidden agenda. Controlled medication seekers understand and take advantage of providers' professed duty to help others.[16] Because emergency departments are subject to the federal Emergency Medical Treatment and Active Labor Act (EMTALA), emergency providers also have a *legal* duty to provide at least "stabilizing" care for the complaints with which seekers typically present.[17] Hence, to the healthcare provider's chagrin, seekers try to take advantage of our ethical and legal duty to provide relief from suffering and medical "stabilization."

How Controlled Medication Seekers Compromise Medical Ethical Principles and Duties

Beauchamp and Childress's book, *Principles of Biomedical Ethics,* provides one of the most commonly cited frameworks for contemporary medical ethical discourse.[18] According to their work, determining the ethically correct course of action to make within the healthcare context typically requires that four "mid-level" principles be considered and weighed: autonomy, beneficence, non-maleficence, and justice. Controlled medication seekers can pose significant challenges to the provider's deliberation of all these principles.

Autonomy

Autonomy, or the right of a competent person to make one's choices without coercion, is necessary for the realization of one of the fundamental propositions of a liberal society: no one substantive perspective should be given a "privileged" position,[19] i.e., no person, including a healthcare provider, has the unabridged power to decide what is the "good" for another person. Thus, contemporarily, autonomy has ascended over the older healthcare norm of the physician almost solely determining the best interests of a patient (a.k.a. physician paternalism). Nevertheless, a patient's autonomy is not absolute and can still be overruled by concerns a provider might have that a requested treatment is ineffective, can cause harm to the patient or others, or is contrary to existing laws. Controlled medications have the potential to cause harm to their users via physiological and psychological dependency, compromised cognitive or judgmental abilities, and other serious side effects including death. Controlled medications also have the potential to directly or indirectly impel users to harm others via crime, child neglect, motor vehicle accidents, work absenteeism, and other negative behaviors. Therefore, the state has reduced an individual's autonomy to obtain and use controlled medications via laws that limit how they can be accessed and punish those who irresponsibly prescribe them, obtain them by illegal means, resell them for profit, and so on.

In the state of Wisconsin, the law applicable to controlled medication seeking behavior is quite explicit. According to the Wisconsin Uniform Controlled Substances Act (961.43c): "It is unlawful for any person: To acquire or obtain possession of a controlled substance by misrepresentation, fraud, forgery, deception, or subterfuge." Also, physicians can have their license revoked or be charged criminally for improperly prescribing controlled prescription drugs per the U.S. Controlled Substances Act.[20] However, such indictments rarely occur against physicians (fewer than 1 in 10,000) and only for egregious controlled medication prescribing practices - not for being duped by drug seekers.[21] Additionally, at least one physician was found liable for refilling a narcotic prescription – despite the patient having

a "pain contract" that prohibited it – and the patient subsequently overdosed.[22] In the end analysis, there are legal in addition to ethical reasons to override the autonomy of an individual who uses deception to try to obtain controlled medications.

Beneficence and Non-maleficence

The intent to maximize benefits (beneficence) for and minimize harms (non-maleficence) against patients is perhaps *the* core ethical principle and professed duty of healthcare providers. The seeker most immediately corrupts beneficence by duping the provider into trying to alleviate a condition that does not exist or at least is exaggerated. If a provider suspects controlled medication seeking behavior, the provider will typically be in a quandary to try to steer between the potential harms caused by giving a controlled medication for inappropriate reasons versus the harms of not addressing what might be a genuine condition with the best available agent. If the provider confirms that seeking behavior exists, then he may understandably be reluctant to prescribe the controlled medication to help that patient in the future, even when the problem is genuine – unless perhaps there is objective evidence that the condition does indeed exist (e.g., a bone fracture confirmed by radiography).

The potential to cause harm exists even independent from the side effects of the controlled prescription medication. Many feigned complaints prompt the provider to recommend or institute other medical treatments, diagnostics, or referrals, nearly all of which have some risks – at the very least, financial. Furthermore, because the provider is working with misinformation provided by the drug seeker, he will not be able to accurately weigh the benefits versus the risk of harm for various diagnostic and treatment modalities that need to consider.

Justice

The theories of justice in medical ethics typically refer to the ideals of ensuring equitable distribution of resources (distributive justice) and the avoidance of discrimination.[23] Controlled medication seekers compromise distributive justice by impelling the misdirection of limited material, financial, temporal, and personnel resources away from those with legitimate needs. For example, a drug seeker complaining loudly and disrupting the emergency department because of feigned back pain might receive care before those with genuine, serious medical conditions.

Also, controlled medication seekers cause the misdirection of limited health care financial resources. For example, it would not make financial sense for a seeker without insurance to pay for an emergency department visit, even if they intend to sell the medication because the medical care bills are typically much more expensive than the drug's street value. To illustrate, the street value of hydrocodone is approximately $4-6 per pill and oxycodone is $4-8 per pill.[24] A patient with a headache or back pain will usually incur a "level 2 to 3" charge which is typically more than $500 in a Wisconsin emergency department for both facility and professional fees. If the physician prescribes the typical 10-30 tablets of oxycodone, the subsequent street value would be $40-240 – a loss of $260 or more. If the patient *does* have insurance, the misuse of medical care still causes distributive injustice by contributing to the potential raising of premiums for everyone in the insurance pool.

Conclusion

The growing number of individuals that use deception to try to obtain controlled prescription medications causes numerous pragmatic, ethical, and legal dilemmas to healthcare providers – and potential dangers to the individuals themselves, since the misuse of controlled medications are fraught with many dangers. This paper's review of the major challenges and dilemmas posed by controlled medication seekers undoubtedly will not relieve the angst and frustration experienced by providers that face the difficulties of managing these patients. However, it is hoped that their articulation will at least help us to understand the many sources of that angst and frustration. The next part of this paper will examine the more pragmatic aspects of this difficult healthcare issue and review some of indications that the patient before you might be inappropriately seeking a controlled medication. The second part will also suggest a general approach to managing patients suspected of controlled medication seeking behavior that strives to minimize potential harms while also minimizing the risk of not treating legitimate medical needs.

Ken Solis, MD, MA, BCEM certified, also holds a Master's degree in bioethics and is currently completing a residency in internal medicine in Milwaukee.

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Clinical Trials Fuel the Promise of Plant-Derived Vaccines

Kathleen Hefferon, PhD

Abstract

Heat-stable plant-made (edible) vaccines are inexpensive to produce, can be administered orally, and could be utilized to enhance vaccine coverage in children, particularly in developing countries. Plant-made vaccines can deliver undegraded antigens to the enteric mucosal immune system. A number of clinical trials have produced encouraging results. This review summarizes plant-derived vaccines, the mucosal immune response, and the evidence regarding their use and efficacy.

Introduction

Infection from vaccinable pathogens is a leading cause of mortality in underdeveloped countries. In 1992, an assembly of philanthropic groups, in conjunction with the World Health Organization, established the Children's Vaccine Initiative to develop novel oral vaccines and to improve global accessibility.[1,2] Ideal vaccines would be cheap, safe, portable, and durable. Of note, transgenic plants offer a novel delivery system for vaccine proteins.[3,4] Plants are capable of producing recombinant antigens that retain the same structural integrity and activity as their mammalian-derived counterparts. These transgenic plants safely and effectively deliver non-replicative subunit vaccines through the consumption of edible plants.[5]

The first genetically modified crops were disease-resistant soybean and corn and appeared on the US market in 1996. Since then, transgenic plants have been commercialized in many other countries. Transgenic plants, which exhibit increased pest- and disease-resistance, prevent substantial global production losses. Transgenic plants may become a cost-effective and safe system for large-scale production of proteins for industrial, pharmaceutical, veterinary, and agricultural uses.

The induction of an immune response usually precedes control of mucosally acquired infections. Specifically, the nature of the antigen, the route of administration, and the delivery system utilized determine the systemic and secretory immune responses. Traditional parenteral vaccines, for example, primarily induce IgM and IgG responses, whereas mucosal vaccinations induce both IgG and secretory IgA responses.

Infantile diarrhea and other enteral pathologies are leading causes of morbidity and mortality in developing countries. Heat-stable plant-made vaccines that are administered orally, therefore, have the potential to enhance vaccine coverage in children and infants, particularly in resource-poor regions. Plant-based vaccines delivered orally are well suited for combating gastrointestinal diseases, and this has been the focus of a number of Phase 1 clinical trials.

Plant-derived vaccines deliver protein immunogens to the gut – an active part of the immune system. A significant hurdle impacting protein delivery to the intestinal immune system stems from the fact that many antigens are rapidly degraded within the harsh environment of the digestive tract. Plant-made vaccines offer an advantage as plant cells provide protection and prevent degradation of the antigen as it passes through the gut. Another problem is that many antigens do not become recognized by the gut as foreign and, therefore, do not serve adequately as immunogens. One way to overcome this problem is to use adjuvants, which largely affect the immunogenic context in which an antigen is encountered.

Plants Can Express Vaccine Epitopes and Proteins

Plant transformation, meaning the stable integration of the gene of interest into a plant genome, was originally conducted using

a modified strain of *Agrobacterium tumefaciens,* the bacterial strain responsible for crown-gall disease. Stable plant transformation has several disadvantages, such as long production times and contamination via the escape of transgenes into the environment.[7] These concerns have prompted the development of alternative methods of protein expression, such as the use of plant cell culture bioreactors rather than plants grown in outdoor fields.

Another option is the utilization of plant virus expression systems, which produce large quantities in short intervals. Two types of expression systems based on plant viruses have been developed for the production of immunogenic peptides and proteins in plants: epitope presentation systems (short antigenic peptides fused to the coat protein [CP] that are displayed on the surface of assembled viral particles) and polypeptide expression systems (these systems express the whole unfused recombinant protein that accumulates within the plant). However, insert size limitations and host range restrictions preclude the widespread use of such virus expression vectors for every plant species.[6-8] The choice of expression of the vaccine protein, therefore, becomes a matter of choosing the optimal plant species, whether it be whole plant or cell culture and whether stable transformation or transient expression best fits the nature of the therapeutic protein under investigation and its proposed applications.

There are significant differences between plant-derived and traditional vaccines. Although plants present a promising system for the production of human therapeutic proteins, the majority are glycoproteins. These proteins may have modification pathways that produce a mammalian immune response; humanized plants expressing glycoproteins, which are correctly sialylated and O-glycosylated, may facilitate the production of plant-derived proteins in medicine.[9]

Plant-Derived Vaccines and the Mucosal Immune System

The mucosa of the digestive, respiratory, and urogenital tracts are the sites for most infections. The epithelial interface is protected by innate and adaptive immune pathways which can recognize and eradicate pathogens. This mucosal epithelium overlies organized lymphoid follicles and consists of mucin-producing glandular cells, lymphocytes, plasma cells, dendritic cells, macrophages, cytokines, and chemokines. Antigen uptake, processing, and presentation for induction of mucosal responses take place within this tissue.[11,12]

In the intestine, gut-associated lymphoid tissue (GALT) represents approximately 70% of the body's entire immune system. Peyer's Patches, which form large clusters of lymphoid follicles and are distributed along the length of the small intestine, are involved in the immune surveillance of the intestinal lumen. Peyer's Patches contain various, highly specialized cells known as M (minifold) cells, which deliver antigen from the lumen to antigen-presenting cells, followed by the activation of T cells, B cells, and dendritic cells, which are involved in initiating the primary immune response.[13,14,15]

In the respiratory tract, antigen is taken up into alveolar spaces by antigen-presenting cells, most likely via lymphatosis, to regional lymph nodes, the site of the primary immune response. Antigen-specific B cells are produced and return to the lung, where they differentiate into either antibody-secreting plasma cells or memory cells. The cells migrate via the lymphatic system to regional lymph nodes, where the primary immune response occurs.[16]

Strong mucosal immune responses take place upon introduction of an antigen directly into the respiratory tract. Antibody responses in the respiratory tract can occur either quickly through activation of resident memory B cells, if there has been prior exposure to the pathogen, or, if the host is naive to the pathogen, more slowly through the induction of both systemic and local mucosal immunity. Both IgG and IgA assist in the clearance of invading pathogens with the site of exposure determining the nature of the antibody that is produced. In the case of respiratory pathogens, systemic vaccination, which stimulates systemic IgG and elicits a modest mucosal IgA response, is less effective than mucosal vaccination, which stimulates rapid local and systemic IgA and IgG responses.[16,17]

IgA, the major antibody isotype in mucosal secretions, performs several functions in mucosal immunity. For example, sIgA antibodies can block the entry of antigens into the epithelium. IgA antibodies present in the *lamina propria* adhere to and excrete antigen into the lumen, IgA antibodies transported through the epithelium can neutralize virus production and proinflammatory antigens as well as trigger the release of inflammatory mediators.

Phase 1 – Clinical Trials and Plant-Derived Vaccines

In 1990, *Streptococcus mutans* surface protein A was expressed in transgenic tobacco and given to mice. This transgenic plant material successfully induces an antibody response through a demonstration that serum from immunized mice could react with intact *S. mutans*.[18] Plants were then developed which expressed *E. coli* enterotoxin B subunit (LT-B) and which exhibited successful induction of both mucosal and sera antibody responses.[19,20] Multiple animal and human antigenicity and challenge trials have proven the efficacy of such plant-made vaccines (Table 1).

Plant-Made Vaccines to Treat Diarrheal Diseases

Enterotoxigenic *E. coli* (ETEC) and Norwalk Virus or Norovirus (NV) are devastating diarrheal diseases prevalent in Third World countries with *E. coli*, causing three million infant deaths a year. Administering plant vaccine to nursing or gravid women

Table 1: Examples of Mucosal Immune Response Generated to Plant-Derived Vaccines

DISEASE	PLANT USED	ANTISERA RAISED AGAINST	REFERENCE
Enterotoxigenic E. coli			
ETEC	potato, maize	LT-B	19, 20, 22
Norwalk Virus	potato, maize	NV	21
Hepatitis B Virus	potato	HBsAg	23
Rabies Virus	spinach	Spike antigen	31
Human Papillomavirus	potato, tobacco	L1 capsid protein	25, 26, 27
Anthrax	tobacco	Protective antigen (PA)	28, 29
SARS	tomato, tobacco	S protein	30
Measles Virus	lettuce	MV-H protein	32, 33
Swine transmissible gastroenteritis virus	maize	Spike protein	46
Staphylococcus aureus	cowpea	D2 peptide of fibronectin-binding protein (FnBP)	47
E. coli 0157:H7	tobacco	Intimin protein	48
Strain K88 of enterotoxigenic E. coli	tobacco	FaeG of K88 fimbrial antigen	49
Japanese Cedar pollen allergens	rice	Cry jI, Cry jII	42
Foot and Mouth Disease Virus	alfalfa	VP1	50
Respiratory Syncytial Virus	tomato	F protein	51
Sunflower seed albumin	narrow leaf lupin	SSA	44
Norwalk Virus	tobacco, potato	VLP	21
Influenza Virus	tobacco	B5	34
Plague	tomato	F1-V fusion protein	52
Canine Parvovirus	tobacco, chloroplast	2L2I peptide	53
Tuberculosis	arabidopsis	ESAT-6 antigen	54
Rotavirus	alfalfa	VP6	55

may protect the child through maternal antibodies transferred transplacentally or through breast milk. Norwalk Virus, on the other hand, is composed of a single capsid protein that can self-assemble into virus-like particles (VLPs), which act further to stimulate the immune response.

The first clinical trial to examine whether similar immune responses could be generated in humans using these two antigens involved the feeding of transgenic potato or corn expressing either LT-B or NV to adult volunteers.[20,22] Fourteen healthy adults ingested either 50 or 100 g of raw transgenic potato expressing the vaccine protein or nontransformed potato used as a control; these were randomized in a double-blind fashion. Second or third doses were administered on days seven and twenty-one. Antibody-secreting cells were detected seven days after ingestion of transgenic potato expressing LT-B. Volunteers who ingested potato or corn-based LT-B vaccines developed high increases in LT-B-specific IgG; many of these developed four-fold rises in IgA anti-LT. LT neutralization assays were also performed using Y-1 adrenal cells. Out of eleven volunteers, eight developed neutralization titres which were greater than one. For individuals who ingested two or three doses of transgenic potatoes expressing the NV CP as antigen, 95% developed significant rises in IgA titre. Based on these preliminary studies, both humoral and systemic immune responses can appear to be successfully induced through antigen delivered in consumed plant material.

Hepatitis B Virus (HBV)

Hepatitis B, which causes chronic liver disease, affects over 300 million people worldwide. Hepatitis B Virus surface antigen (HBsAg), the principal antigen used for vaccine production, is a potential transgenic plant product. Like NV capsid protein, HBsAg has been demonstrated to form intact immunogenic virus-like particles. The efficacy of HBsAg produced in transgenic plants and delivered orally has been compared with the oral delivery of the yeast-derived rHBsAg, which is currently being used as an injectable vaccine in mice.[23] Peeled potato tubers were fed to mice at a dose of 42 µg HBsAg per feeding once a week for three weeks. A week after the first two doses were administered, anti-HBsAg antibodies were observed in mice fed transgenic tubers but not in mice fed yeast-derived HBsAg. Antibody levels peaked four weeks after the third dose and returned to baseline levels eleven weeks later. Control mice fed nontransgenic potato did not exhibit an elevated anti-HBsAg antibody response.[23] The strong primary response exhibited by mice fed HBsAg derived from plants may result from the protective encapsulation of the antigen within the potato cell. Digestion of plant tissue within the gut would increase the like-

liness of antigen release near the Peyer's patches and result in a more robust immune response. That intact VLPs comprised of HBsAg were visualized in these potatoes suggests a more immunogenic presentation than the yeast-derived vaccine. Mice primed initially with potato-derived HbsAg, then boosted parenterally with yeast-derived rHBsAg, were also examined in a separate study to determine whether memory B cells had also been established. These mice exhibited a strong secondary response lasting for over five months.

More recently, a double-blind and placebo-controlled Phase 1 human clinical trial was performed using plant-derived HBV vaccine.[24] Transgenic potato tubers that had not been cooked and which expressed approximately 8.5 µg/g HBsAg were fed to previously vaccinated individual volunteers. More than half of those volunteers who ingested one hundred grams of the transgenic potato tubers in the form of three doses exhibited a substantial increase in anti-HBsAg serum titres. No volunteer who ate the nontransformed potatoes provided as controls displayed an increase in antibody titre (Thanavala *et al.* 2005). Results of this study and similar studies conducted by other groups highlight the potential of plant-derived vaccines for those countries which have limited access to therapeutic proteins and modern medical infrastructure.

Human Papillomavirus (HPV)

A major cause of cervical cancer in women, particularly in developing countries, is human papillomavirus. Current vaccines are too expensive and are difficult to distribute widely in these countries. A number of immunization studies involving a plant-derived vaccine against human papillomavirus have been performed using a mouse model. Initial studies by Biemelt et al. (2003) demonstrated that either plant- or insect-derived VLPs, consisting of the L1 capsid protein of HPV, were both immunogenic to an equal degree.[25] Half of mice fed transgenic potatoes expressing HPV VLPs developed L1-specific antibodies. A few years later, Warzecha et al. introduced a plant-optimized version of the L1 capsid protein of HPV into tobacco potato plants, which accumulated higher levels of VLPs.[26] Mice who consumed potato tubers expressing this altered version of L1 elicited a significant enhanced serum antibody response.

The potential of producing a plant-made vaccine against a papillomavirus using a plant virus-based expression vector system has also been investigated. In this instance, the L1 capsid protein of control rabbit papillomavirus (CRPV), often used as a model system for papillomavirus-host interaction studies, was incorporated into a tobacco mosaic virus (TMV)-based vector. Extracts from plants infected with TMV-L1 were shown to protect rabbits from infectious virus upon inoculation.[27]

Anthrax

Anthrax is an acute and fatal disease acquired by inhalation or ingestion of spores and caused by *Bacillus anthracis*, a gram-positive spore-forming bacteria. As a result, anthrax has been classified as a category A biological warfare agent. Protective Antigen (PA), one of the proteins expressed by *B. anthracis*, is named for its ability to elicit a protective immune response. Transgenic tobacco chloroplasts have been shown to accumulate PA to levels as great as 14.2% of total soluble protein.[28] An in vitro macrophage lysis assay demonstrated that PA derived from chloroplasts was fully functional at levels comparable to *B. anthracis*-derived PA used as a positive control. Neutralization of PA was successfully accomplished with sera taken from mice 15 days after the third immunization with extracts of tobacco chloroplast expressing PA. Survival of immunized mice challenged with a lethal dose of anthrax LT (lethal toxin) further demonstrated the immunoprotective properties of chloroplast-derived PA.[29]

SARS

Due to recent outbreaks, there has been an increased incentive for an effective vaccine against the coronavirus which causes SARS (severe acute respiratory syndrome). Pogrebnyak et al. (2005) expressed the N-terminal fragment of the coronavirus spike protein (S1) at high levels in both tomato and tobacco plants.[30] Tomato fruit was lyophilized and fed to mice who exhibited increased IgA titres toward S1 in their feces. When mice were immunized parenterally and later boosted with S1 protein expressed in tobacco roots, IgG titres corresponding to S1 were detected in their sera. More significantly, high IgG1 immune responses and significant IgG2a and IgG2b responses were observed, suggesting that these animals elicited a Th2-type response, as opposed to the Th1-type response found for mice.

Rabies Virus

Rabies causes approximately 55,000 deaths a year in Southeast Asia and Africa but does not receive significant financial attention because it is not a major killer in the industrialized world. The vaccine currently available is too expensive for developing countries. A recombinant plant virus expression vector has been engineered to express the rabies virus spike antigen.[31] Mice fed spinach leaves infected with the recombinant virus particles were able to display an immune response. Further studies indicated that mice, which were immunized orally with this engineered virus and then infected with an attenuated strain of rabies virus, were able to recover rapidly.

Measles Virus

Measles is contracted through the respiratory tract and is highly contagious. The case-fatality rate of measles can be several hundred times greater in the Third World than in developing nations. Over 30 million cases of measles were reported in 2004. Eradication of the virus has been confounded by its highly contagious nature, combined with the difficulty of maintaining and administering the vaccine in countries in which there is a scarcity of refrigeration, medical infrastructure, and syringes required for subcutaneous administration.

Preliminary studies have illustrated that a DNA measles vaccine, when used in conjunction with a plant-derived antigen booster, can evoke a substantial immune response. High-titre MV-neutralizing antibodies were shown to be generated in mice when a plant-derived MV-H protein vaccine was combined with a MV-H DNA vaccine in a prime-boost vaccination strategy.[32] Almost all mice administered first with an intramuscular dose of MV-H and later with orally administered plant-derived MV-H exhibited an IgG response. The results of this study suggest that this heterologous prime-boost approach will be successful for other plant-derived vaccines as well.

In a later study, the MV-H protein was expressed in lettuce and proven to be immunogenic in mice following intraperitoneal injection without an adjuvant or intranasal inoculation with adjuvant.[33] Mice primed with MV-H DNA and boosted with an oral formulation of freeze-dried lettuce expressing MV-H in the presence of an adjuvant elicited the greatest response. Furthermore, the nature of the immune response depended upon the manner in which the MV-H antigen is presented to the immune system. For example, both soluble as well as secreted forms of MV-H were demonstrated to induce a Th2 type response, whereas membrane-bound MV-H protein elicited a Th1 response.

Influenza Virus

Influenza virus is responsible for 300,000-500,000 deaths and three to five million hospitalizations annually. Every flu season, new epidemic strains of influenza A arise due to point mutations within the surface glycoproteins hemmaglutinin (HA) and neuraminidase (NA). These changes enable any new emerging virus strains to evade the host's immune system. Currently, vaccines against influenza virus are produced in chicken eggs, an expensive process with a long production time.

More recently, tobacco plants, which express the full-length HA from the Awyoming/03/03 strain of influenza virus, were developed.[34] This plant-derived HA has been demonstrated to be antigenic both by ELISA and by single radial immunodiffusion assay (SRID). Moreover, plant-derived HA was found to be immunogenic in mice. A high serum IgG titre was observed following the first antigen boost and was enhanced following the second boost to levels comparable to the commercially available egg-produced, formalin-inactivated virus. IgG subtypes were analyzed, with IgG1, IgG2a and IgG2b antibody responses identified, suggesting that both Th1 and Th2 responses were stimulated using the plant-derived vaccine. Additionally, an ELISPOT analysis of spleen cells was used to show that the increase in production of both gamma-IFN and IL-5 in response to challenge resembled that of the commercially purchased inactivated virus. Plant-derived influenza vaccine also induced significant serum hemagglutinin inhibition (HI) and virus neutralizing (VN) antibody titres. The serum HI and VN titres found in mice immunized with plant-derived HA correlated well with levels observed in serum from mice immunized with the commercial virus. The high quality of immune response determined from these experiments demonstrates well the potential for developing an effective influenza vaccine using a plant-based approach.

Monoclonal Antibodies Generated in Plants

Plants have also been engineered to produce a variety of functional Mab. The development of Guy's 13 secretory IgA plantibody technology commenced with the work of Ma et al. (2005) and involved the sexual crossing of four transgenic plants, each expressing both heavy and light immunoglobulin domains, the J chain, and the secretory component.[36] Plants, which could express and correctly assemble all four proteins simultaneously, were screened. Preliminary clinical trials indicated that plant-derived IgA prevented oral colonization by *S. mutans* via passive immunization of the mucosal surfaces by topical application. Since this first study, many Mabs have been produced in plants. A well-studied plant-derived Mab is the anti-rabies human monoclonal antibody, which was developed in tobacco and has been demonstrated to exhibit an anti-rabies virus neutralizing activity and affinity comparable to mammalian-derived counterpart HRIG.[37]

Plant-Made Vaccines, Allergies, and Oral Tolerance

Most substances in the gut are not immunogenic due to the cellular environment at the site of antigen presentation. This lack of response prevents the onset of unnecessary and damaging inflammatory responses to benign substances, which may lead to conditions such as inflammatory bowel syndrome and food allergies.[38,39,40] Oral tolerance, the phenomenon of feeding with a specific protein resulting in the abolishment of subsequent responses to systemic challenge with the same protein, is a reflection of how antigen is processed and presented to T lymphocytes which reside in the mucosa.[41] To examine the ability of plant-derived antigens to induce oral tolerance, Takagi et al. (2005) developed transgenic rice plants expressing mouse T cell epitope peptides specific for pollen allergens of *Cryptomoeria japonica* (Japanese Cedar).[42] The T cell epitope peptides corresponding to Cry jI and Cry jII pollen antigens were expressed together with soybean storage protein glycinin AlaB1b as part of a fusion protein. Mice which were fed transgenic rice were later challenged by feeding with total protein extracts of pollen as the allergen. Oral consumption of transgenic rice to mice prior to systemic challenge resulted in allergen-induced oral tolerance, accompanied by a dramatic inhibition of sneezing. Although the systemic unresponsiveness corresponded with a reduction of pollen allergen-specific Th2-mediated IgE responses and histamine release, the CD4+ T cell proliferative response remained unaffected.[43]

The plant-derived vaccine strategy for oral tolerance has also been demonstrated to successfully suppress asthma-based allergies. Allergic asthma, a chronic airway inflammatory disorder,

is often associated with the presence of activated CD4(+) Th2-type lymphocytes, eosinophiles, and mast cells. Sunflower Seed Albumin (SSA), a common allergen, has been expressed in transgenic narrow leaf lupin (*Lupinus angustifolius L.*).[44] Oral consumption of plants expressing SSA prevented a delayed-type hypersensitivity response. Experimental asthmatic symptoms, such as mucus hypersecretion, eosinophilic inflammation, and enhanced bronchial reactivity, were significantly reduced, while the production of CD4(+) T cell-derived IFN-gamma and IL-10 was increased.[44] These data demonstrate that plant-based vaccines may have potential applications in the protection against allergic diseases, such as asthma.

Real-Time Plant-Derived Pharmaceuticals

As mentioned earlier, one original driving force for generating plant-derived vaccines has been to develop new vaccines and therapeutic agents which target the most devastating infectious diseases found in developing countries. Diarrhea, the major cause of global mortality, and other diseases, which prevail in developing countries, are not being prioritized by the private sector, as there is little hope of return on investment. However, the fact remains that 20% of the world's infants have no access to vaccines, and two million deaths take place each year due to preventable infectious diseases. Plant-derived vaccines would also be useful against those diseases which are rare and whose cures are not well financed, such as dengue fever, hookworm, and rabies. Inexpensive and easy-to-administer, plant-derived vaccines could provide relief to the usual constraints involved in vaccine delivery.

Vaccines have been produced in both food crops and in plant species not routinely eaten, in the greenhouse, open field, and through cell suspension culture. Field-grown plants may fall prey to variations in soil and weather, which can negatively impact the good manufacturing practice conditions required for production of pharmaceuticals in general. Cell suspension culture, on the other hand, can be grown in a precisely controlled environment or even grown continuously, resulting in less expensive downstream processing. While purification of vaccine proteins from plants entails some cost, recent advances in this direction have demonstrated that plant-derived protein purification is less costly and requires fewer steps than mammalian and bacterial protein purification. Indeed, some forms of plant-derived therapeutic proteins, such as topically applied monoclonal antibodies, need only be partially purified, and, as a result, would be even less costly and labor-intensive. Approval for release of the first plant-derived pharmaceutical, a veterinary vaccine for Newcastle Disease in poultry, which was generated from plant cell culture, sets the stage for a new range of proteins produced in plants for use in medicine.

Concluding Remarks

When first cited in the literature, plant-derived vaccines were introduced as "edible vaccine." True to form, the first clinical trial performed within the US required volunteers to consume 100-150 g of raw transgenic potato (Richter et al. 2000). Since this initial trial, researchers have speculated that plant-made pharmaceuticals could be produced in the field and consumed as a routine/local food source. In the world's developing countries, vaccines could potentially be derived from fresh produce or even from an individual's own garden. The advantages to the use of food crops for vaccine production frequently led to public misperceptions as to how these materials would be delivered in a practical sense. Eventually, to control the level of exposure of the antigen or vaccine protein, the production of plant-made vaccines and therapeutic proteins further evolved to meet the standard requirements for the productivity of pharmaceuticals in general by avoidance of the issues of dose variability and assurance of high quality of the product. Edible vaccines are, therefore, more commonly referred to at present as plant-made pharmaceuticals (PMPs), where a plant product is derived from batch-processed plant tissues or a similar processing method, which can then be prescribed by a health-care worker. In the end, the vaccine is more likely to be administered in the form of a capsule, paste, or juice, or even perhaps as a suspension for oral delivery, rather than as a whole tomato or banana.[45]

The results of the pre-clinical and clinical trials of plant-derived vaccines and therapeutic proteins described in this review hallmark the potential of plants to become oral delivery vehicles for vaccines. Those who ingest plant tissue containing vaccine antigen exhibit a greater immune response and recover more rapidly from disease than those who ingest control plants in human volunteer or animal model studies. The provocation of mucosal immunity against a given antigen can be achieved by other means besides oral ingestion. For example, intranasal immunization of vaccine proteins can improve local mucosal immunity and enable large populations to be immunized at less cost. Plant-derived vaccines continue to provide promise and hope for more immunogenic, more effective, and less expensive vaccination strategies against both respiratory as well as intestinal mucosal pathogens of the Third World.

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Kathleen L. Hefferon, Ph.D., Cornell Research Foundation, Cornell University, Ithaca, NY, completed her Ph.D. in Molecular Virology from the Faculty of Medicine, University of Toronto. She is a science writer for the Center for Hepatitis C Research at Rockefeller University.

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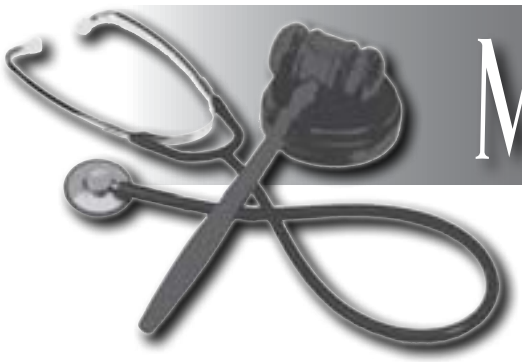

MEDICAL-LEGAL

What Happens When A Physician Is Suspected of Abusing Drugs or Alcohol?

Daniel M. Avery, MD
Kathy T. Avery, RN, BA, MT (AMT)

Abstract

Physicians suspected of abusing drugs or alcohol are reported by a multiplicity of mechanisms. The vast majority of complaints today are sent to the state impaired-physician program. Physicians suspected of abusing drugs or alcohol are usually sent for a residential evaluation and assessment by a team of professionals trained in addiction. Most physicians today are treated at state medical society and licensure commission approved residential treatment facilities. There is life and the practice of medicine after successful treatment, depending on a compliance contract with the state, a treatment plan, and urine drug screens. Most hospitals today are recovery-minded. Relapse of physicians after quality treatment is rare, but, when it occurs usually results in death or prison.

Introduction

Physicians suspected of abusing drugs or alcohol are reported via several mechanisms. A patient, who suspects a physician, may register a complaint with a hospital administrator. Many hospitals have physician wellness or physician impairment committees that will then investigate the complaint. Often, a group of colleagues intervene with a physician about whom they are concerned. A concerned physician, nurse, or pharmacist may express concern about a specific physician. Suspected medical students are usually dealt with by the medical student affairs office. Residents and fellows in training usually become involved with the program director. On rare occasion, a patient or concerned party may register a complaint with the licensure board or state medical society. Self-reports to state medical societies and physician health programs are few and far between. The physician in trouble is usually the last to know. The thought of his/her calling the state impaired-physician program and expressing concern over himself/herself is usually unheard of. Table 1 lists the possible ways a physician is reported.

Table 1: How are physicians reported?

- **Report to hospital administrator**
- **Intervention by colleagues**
- **Complaint to licensure board**
- **Complaint to state medical society**
- **Self-report to psychiatrist for other reasons**
- **Attempt at "private treatment"**
- **Report by suspicious pharmacist**
- **Report by nurse**
- **Report by fellowship or residency director**
- **Report by medical school student affairs office**
- **Referral from the legal system**
- **Self-reporting by the physician himself/herself is very rare**

Report to Impaired Physician Programs

No matter what the point of entry of the concern, ultimately the complaint makes it to the state impaired-physician program, usually an agency of the state medical society. Physicians never self-report, because addiction alters their thinking process; they are the last to know that they are in trouble. In Alabama the appropriate agency is the Alabama Physician's Health Program or "APHP" headed by Dr. Greg Skipper. The program was founded by the late Dr. Gerald Summer as the Physicians Recovery Network or "PRN." Alabama has a very progressive program aimed at rehabilitation, a far cry from the original punitive approach. Records are protected by the Code of Alabama and not discoverable by subpoena. The Program is run by a number of appointed physicians from around the state. Local monitors are usually psychiatrists or addictionologists, who regularly meet with impaired physicians and assist Dr. Skipper with interventions.

The APHP compliance is protective of a physician's medical license, unless that physician does not comply, and then his license is in jeopardy. Failure to comply with recommendations in Alabama, like most states, results in licensure revocation.

Evaluation of Suspected Addiction

The vast majority of complaints about physician addiction are directed to the APHP. All reports are anonymous. Dr. Skipper then investigates the complaint and interviews the physician in question. An evaluation by an addictionologist is almost always recommended. A health professional evaluation and assessment consists of a one-to-four day residential assessment by a team of professionals, including addictionologist, psychiatrist, psychologist, social worker, neurologist, and counselor. A comprehensive history and physical is performed along with urine and blood screens and hair samples for toxicology. The physician-patient is observed in a situation where there is no access to drugs or alcohol. After the assessment is completed, a recommendation is rendered to the state impaired-physician program, consisting of any medical diagnoses, psychiatric diagnoses, and opinion about whether the physician is abusing or addicted to drugs or alcohol, and, if so, a recommended course of treatment. A physician may be abusing drugs or alcohol but not yet addicted. A physician may be neither and simply doing things that are "stupid," such as going to the hospital with alcohol on his breath. If a diagnosis is not clear, a period of monitoring may be recommended.

Diagnoses of Addiction, Abuse, or Neither

For those physicians who are diagnosed with alcohol or drug addiction, almost all states and licensure boards demand residential treatment at an approved treatment facility. In Alabama, diagnosed physicians meet with Dr. Skipper, and they usually decide on a treatment facility. The physician is usually given a choice of several possibilities. Compliance with the APHP protects a physician's license. However, non-compliance means revocation of license, which is not a good choice. Basically, the licensure commission holds a physician's license over his head to get treatment, which in the long run is a good thing.

Residential Treatment

Once a treatment facility is selected, the physician requests a leave of absence from his hospital administrator, training program, if he is a fellow or resident, or medical school, if he is a student. Practicing physicians make arrangements to be away from their practice for a period of time, ranging from thirteen weeks to one year. As stated above, there is no current effect on license with compliance.

Physicians are usually given a choice of several approved treatment programs. Not all states have approved treatment programs. Talbott-Marsh Recovery Campus in Atlanta was one of the first treatment facilities designed primarily for healthcare providers. It is considered the "gold standard" of care, and physicians from all over the world go there for treatment. No other program boosts the success rate of Talbott-Marsh, which is greater than 90%. In some cases, detoxification may need to be performed first, before actual treatment. This may be performed locally or at a treatment center.

The term "residential treatment" means, in essence, that you live there, apart from medicine, family, problems, and stresses of life, and completely relearn how to live. One lives with

Table 2: Residential Treatment

- **Detoxification if needed**
- **Living with recovering physicians**
- **Good nutrition**
- **Sleep**
- **Exercise**
- **Group therapy**
- **Individual therapy**
- **Specific counseling**
- **Marital & couples counseling**
- **Psychological testing**
- **Psychiatric testing**
- **Treatment of psychiatric diagnoses**
- **Alcoholic Anonymous**
- **Narcotics Anonymous**
- **Caduceus**
- **Family Week**
- **Discharge Planning**

three to seven other recovering physicians, varying in length of treatment and recovery. There is a complete restructuring of life with good nutrition, sleep, exercise, group, individual and family therapy, specific counseling, treatment of psychiatric diagnoses, Alcoholic Anonymous, Narcotics Anonymous, Caduceus, and Family Week (Table 2). It can be a wonderful experience, but it is also life-changing.

Life After Treatment

Most physicians complete treatment because the state licensure commission holds their license over their head. Physicians see treatment as a means to a new life and the ability to return to practice. The success rate for quality treatment is greater than 90%. The recidivism rate is low among healthcare professionals. Most physicians do well, regain their practices, their self-esteem, and do well professionally. Most serve as a knowledgeable resource about addictions to their patients and colleagues. Most will end up helping others. Ninety-nine percent of patients are understanding, glad to see their physician returned, and gladly acknowledge their honesty.

The real work begins after treatment. Treatment provides the tools for the job ahead – recovery. All state medical societies and licensure commissions require at least a five-year advocacy contract. In reality, *RECOVERY IS FOREVER!* There is no magic pill that keeps a physician from using drugs and drinking alcohol. As the "Big Book" of Alcoholics Anonymous says, "It is a simple program but not an easy one. Don't drink, don't do drugs, go to meetings, talk to people in recovery, read the "Big Book," avoid old playmates and playgrounds." Life after discharge consists of a number of factors outlined in Table 3. They include integration back into family and work, work restrictions of 60 hours per week, proctoring, mentoring, AA, NA, Caduceus, group therapy, After Care, family therapy, urine drug screening, self-assessment, relapse prevention, and an advocacy contract with state impaired-physician program and state medical society. Also essential is a primary care physician and dentist, who have knowledge of addiction, and treatment center revisits. The physician must also meet with the hospital administrator, physician health committee, and malpractice insurance carrier.

Advocacy Contract with State

Every state in this country requires that a physician completing treatment sign an advocacy contract with the state impaired-physician program and/or state licensure commission. This contract is essential for hospital privileges, malpractice insurance, and most practices. While most states only require a contract for five years, hospitals, health insurance carriers, and malpractice companies require such a contract and advocacy for the duration of a physician's practice life. The contract with the state requires the items listed in Table 3. Thereby, most recovering physicians today participate with the state forever. Most malpractice carriers will allow one treatment for addiction but usually consider that physician high risk with a higher premium rate.

Table 3: Treatment After Discharge

- **Integration back into family**
- **Integration back into work**
- **Work restrictions (60 hours/week)**
- **Proctoring**
- **Mentoring**
- **Alcoholics Anonymous**
- **Narcotics Anonymous**
- **Caduceus**
- **Group therapy**
- **After care**
- **Family therapy**
- **Urine drug screening**
- **Self-assessment**
- **Relapse prevention**
- **Advocacy contract with state**
- **Primary care physician**
- **Primary care dentist**
- **Treatment center revisits**
- **Meeting with hospital administrator**
- **Meeting with the physician health committee**
- **Meeting with the malpractice carrier**

Urine Drug Screening

Urine drug screening is an integral part of state and licensure contracts and recovery. Most drug screens are random. Initially screens are once a week, progressing with time to once a month. After five years, most advocacy contracts go to every quarter. Screens may also be used for bad outcomes and any suspicion of drug or alcohol use. Drug screens are observed and follow the "chain of command." They are reviewed by a certified medical review officer or the state director of the physicians' health program. A positive drug screen must be investigated. Urine drug screens can only be performed at an approved collection site.

"Can I go back to my old practice and hospital?"

After all of the above is done, the question remains whether a physician can go back to his old job and practice at his old hospital. Most of the time, it is possible but not always. It depends heavily on how much damage was done. Usually 99%

of patients are glad to have the physician back, are understanding, and will use the physician as a resource; 1% are not and they will go elsewhere. Most hospitals today are very recovery-minded, provided the physician does what he is supposed to do and is compliant with his contract.

Relapse

Despite quality treatment, approximately 1% of physicians will relapse at some point in time, usually early most of the time. Relapse is often disastrous. Recurrent relapse has very deleterious results on license, privileges, and practice. Untreated, the end result of addiction is long-term impairment, loss of license, loss of income, loss of family, loss of health, loss of everything, and, ultimately, loss of life or life in prison.

Conclusion

Most physicians do well with treatment, return to a normal life, family, and practice, and are compliant with advocacy contracts. Most of their patients are understanding and forgiving and will use them as a valuable resource for themselves.

Daniel M. Avery, MD, is the Associate Professor and Chair of Obstetrics/Gynecology at the University of Alabama School of Medicine in Tuscaloosa, AL.

Kathy T. Avery, RN, BA, MT (AMT), is Clinical Nursing Supervisor for the University of Alabama Student Health Center.

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Tender Abdominal Mass from Colic Artery Pseudoaneurysm in a Patient with Chronic Pancreatitis

Deepak Sharma, MD, FACP

Abstract

This case presents an unusual etiology of a tender abdominal mass in a patient with a history of chronic alcoholic pancreatitis who presented to the emergency department with abdominal pain. The case underscores the importance of maintaining a wide differential diagnosis in recurrent pancreatitis so as to avoid a potentially lethal, if rare, complication. Appropriate imaging and consultation were essential to achieve a satisfactory result.

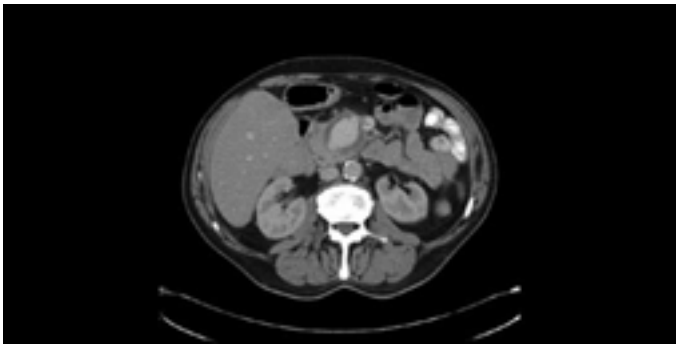
Introduction

Chronic pancreatitis is frequently encountered in the emergency department. The usual presenting complaint is abdominal pain. Often, after multiple trips to the emergency department, evaluation and treatment are primarily focused on symptom control; detailed history and physical examination are usually lacking. Vascular complications of chronic pancreatitis are uncommon and frequently overlooked. The incidence rate of visceral pseudoaneurysms confirmed by angiography is estimated to be about 10%.[1] Pseudoaneurysm is a rare but serious complication of chronic pancreatitis. It is believed to be a result of auto-digestion of the vascular wall by pancreatic enzymes. Mortality rates can reach as high as 40%, depending on the site, characteristic, and therapeutic modality employed.[2] Mortality rates exceed 90% without treatment.[4]

Narrative

A 61-year old man presents to the emergency department with a four-day history of dull upper abdominal discomfort that radiates to the back. The patient has a past medical history including coronary artery disease, chronic back pain, and recurrent pancreatitis. Pancreatitis has been attributed to chronic heavy alcohol ingestion. Patient is a migratory worker and hence has had very poor and inconsistent medical follow-up. His physical examination includes normal vital signs. The abdominal examination revealed a tender, firm abdominal mass in the epigastric area. The mass is not pulsatile, and there is no clinical thrill or bruit. Stools were heme-occult positive. His lab values included WBC 6200 per cubic mm, hgb 10.8 gm/dl. Amylase and lipase were within normal limits. The abdominal mass was further investigated with post-infusion CT scan of the abdomen and pelvis. The scan showed a large, hypervascular lesion within the head of the pancreas that had characteristics suspicious of a pseudoaneurysm without a definite feeding vessel (Figure 1). Subsequently, an abdominal Doppler sonogram was performed, which revealed a pronounced arterial flow within the lesion. The lesion was believed to be a pseudoaneurysm originating from an artery or possibly an arteriovenous fistula. Patient was admitted to the hospital and subsequently underwent a selective angiogram of the celiac trunk and the superior mesenteric artery

Figure 1: Pseudoaneurysm without definitive feeding vessel



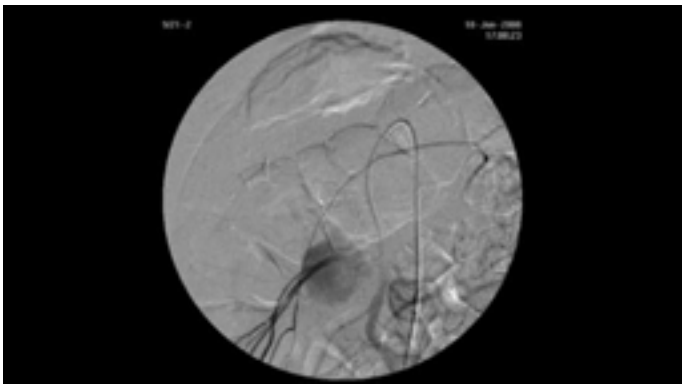
(Figure 2). No feeding pseudoaneurysm was seen in any of the branches of the celiac trunk. The superior mesenteric artery arteriogram revealed a large pseudoaneurysm of the colic branch of the superior mesenteric artery. It appeared to originate with 1 cm of the origin of the right colic artery. The neck of the pseudoaneurysm was ill defined; hence, it could not be engaged for selective embolization. Since the vessel supplied a large portion of the bowel, proximal/distal parent vessel embolization trapping technique ran a significant risk of bowel ischemia and was not performed. An EGD was performed to rule out any mucosal erosion from the pseudoaneurysm. It showed a small duodenal ulcer with no active bleeding. A final diagnosis of pseudoaneurysm of the colic branch of the superior mesenteric artery was thus established. Patient was referred to vascular surgery for further evaluation, as percutaneous embolization of the pseudoaneurysm could not be performed. Unfortunately, patient refused any further treatment and left the hospital against medical advice.

Discussion

Pseudoaneurysm is a rare but serious complication of pancreatitis. The following three mechanisms account for pseudoaneurysms related to pancreatitis: 1) severe inflammation and enzymatic auto-digestion of a pancreatic or peri-pancreatic artery producing arterial disruption; 2) an established pseudocyst eroding into a visceral artery, resulting in conversion of a pseudocyst into a large pseudoaneurysm; 3) a pseudocyst eroding the bowel wall with bleeding from mucosal surface. Splenic artery is the most commonly involved in pancreatic pseudoaneurysm.[3] It may be due to the fact that it runs along the pancreatic bed before reaching the spleen and is most vulnerable to the erosive effects of pancreatitis. It accounts for almost 30-50% and is followed by gastroduodenal artery (10-15%) and the inferior and superior pancreatico-duodenal artery (10%). Other blood vessels mentioned in the literature include superior mesenteric artery, hepatic artery, gastric artery, dorsal pancreatic artery, gastroepiploic artery, middle colic artery, aortic artery, and portal vein.

Incidence of pseudoaneurysm is low in pancreatitis. However, in patients undergoing angiography there has been reported an incidence as high as 10%.[1] Most patients are males with a history of alcoholism (80-90%) with episodic chronic pancreatitis and secondary pseudocyst formation. Highly variable clinical symptoms include the following: 1) anemia of unexplained cause; 2) recurrent or intermittent hematemesis or hematochezia in patients who have pancreatitis, particularly when due to chronic alcohol abuse or trauma; 3) rapid enlargement of a pseudocyst or a pulsatile abdominal mass, especially in the presence of abdominal bruit and hyperamylasemia. Recognition of this rare complication is extremely important. It has a reported mortality of up to 40% with treatment and up to 90% without treatment.[4] The bleeding is usually brisk but varies from short, repeated, and self-limiting episodes to massive hemorrhage requiring emergency laparotomy. The frequency of bleeding from a pseudoaneurysm during an episode of pancreatitis is 5-10%. This rate is higher with pseudoaneurysm

Figure 2: Angiogram of celiac trunk and superior mesenteric artery



associated with a pseudocyst (15-20%). Other infrequent complications include arteriovenous fistula formation and extrahepatic biliary tract obstruction.

Treatment of visceral pseudoaneurysm remains controversial. Various percutaneous[5,6] and open surgical techniques have been described with varying success.

Conclusion

Pseudoaneurysm is a rare vascular complication of pancreatitis. In the literature review in MEDLINE over the past thirty years, I did not find any reported cases of pancreatitis-induced pseudoaneurysm of the right colic artery. Although this condition is rare, there are frequent grave complications; clinicians involved in the care of patients with pancreatitis need to be aware of this complication. This will enable a prompt diagnosis and definitive treatment.

Deepak Sharma, MD, FACP, is Co-Chair, Department of Emergency Medicine at Rapides Regional Medical Center, Alexandria, LA.

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Why Are Very Few Autopsies Performed Today?

Daniel M. Avery, MD

Thirty years ago autopsies were performed regularly in both teaching and private hospitals. In fact, teaching hospitals had to have a certain percentage of deaths certified by autopsy as part of the educational process. Today, autopsies are rare. Most that are performed are for very specific purposes, usually litigation-oriented. Complete autopsies are very unusual today.

Years ago autopsies were requested to find out exactly what was wrong with the patient who had expired. It was a learning experience. If a resident in training had a patient expire, it was part of the educational process to attend the autopsy and learn what had actually happened as part of the learning process about practicing medicine. The resident could see first-hand what he may have missed and did not diagnose. Interesting cases and very educational cases were presented at grand rounds, including a presentation of the clinical course, presumed diagnoses, and autopsy findings. The pathology house staff and attendings presented the findings with the gross organs and microscopic slides on kodachromes.

Interesting cardiac cases were presented at grand rounds with the dissected heart. A neuropathologist often presented interesting brain cases at neurology and neurosurgical grand rounds. Medical students, house staff, fellows, and attendings saw things first-hand.

Today, most autopsy requests are to determine what the physician missed and should have been able to find out. In other words, most hospital autopsies are requested with litigation in mind. Most hospital pathologists have no interest in the legal arena and are never encouraged to pursue what the clinician missed or should have known. Table 1 lists the usual reasons autopsies are requested. The most common reason that requested autopsies are not performed is cost.

Table 1: Reasons Autopsies are Requested

Litigation
Litigation
Litigation
Litigation
Litigation

Many autopsies are limited to specific organs or regions of the body, such as the chest or head. The only areas in which complete autopsies are performed are forensic autopsies at the coroner or medical examiner's office. Soon, autopsies will be a dying art.

Daniel Avery, MD, is Associate Professor, Department of Obstetrics & Gynecology, College of Community Health Services, University of Alabama School of Medicine, Tuscaloosa.

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