Users' Guides to the Medical Literature

XXIV. How to Use an Article on the Clinical Manifestations of Disease

W. Scott Richardson, MD
Mark C. Wilson, MD, MPH
John W. Williams, Jr, MD, MHS
Virginia A. Moyer, MD, MPH
C. David Naylor, MD, DPhil
for the Evidence-Based Medicine Working Group

Clinicians rely on knowledge about the clinical manifestations of disease to make clinical diagnoses. Before using research on the frequency of clinical features found in patients with a disease, clinicians should appraise the evidence for its validity, results, and applicability. For validity, 4 issues are important—how the diagnoses were verified, how the study sample relates to all patients with the disease, how the clinical findings were sought, and how the clinical findings were characterized. Ideally, investigators will verify the presence of disease in study patients using credible criteria that are independent of the clinical manifestations under study. Also, ideally the study patients will represent the full spectrum of the disease, undergo a thorough and consistent search for clinical findings, and these findings will be well characterized in nature and timing.

The main results of these studies are expressed as the number and percentages of patients with each manifestation. Confidence intervals can describe the precision of these frequencies. Most clinical findings occur with only intermediate frequency, and since these frequencies are equivalent to diagnostic sensitivities, this means that the absence of a single finding is rarely powerful enough to exclude the disease. Before acting on the evidence, clinicians should consider whether it applies to their own patients and whether it has been superseded by new developments. Detailed knowledge of the clinical manifestations of disease should increase clinicians' ability to raise diagnostic hypotheses, select differential diagnoses, and verify final diagnoses.

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CLINICAL SCENARIO

You are a general internist working in a teaching hospital paged to the emergency department to evaluate a 58-year-old man with new-onset pain in his chest and back. On the way to the emergency department, you think of myocardial ischemia as your leading hypothesis and you wonder whether aortic dissection should be actively considered in this patient.

In the emergency department, the patient describes to you the sudden onset of severe pain in the center of his chest radiating to his neck and mid back. He has long-standing hypertension, for which he takes a diuretic. You find a normal thoracic wall, clear lungs, equal pulses, a diastolic murmur of aortic regurgitation, and diastolic hypotension with blood pressure of 162/56 mm Hg. The electrocardiogram shows left ventricular hypertrophy but no signs of ischemia or infarction. The first set of cardiac enzyme levels is normal. The portable chest radiograph shows widening of the mediastinum. An arterial blood gas evaluation shows mild respiratory alkalosis and normal oxygenation. By now, your suspicion of acute aortic dissection has grown, so you arrange definitive testing for this diagnosis and consult with the cardiothoracic surgical team, after explaining the situation to the patient and family.

While you wait for the test results, the resident in the emergency department

Author Affiliations: Departments of Ambulatory Care and Research, South Texas Veterans Health Care System and Medicine, University of Texas Health Sciences Center at San Antonio, San Antonio (Drs Richardson and Williams); Department of Medicine, Wake-Forest University School of Medicine, Winston-Salem, NC (Dr Wilson); Departments of Pediatrics and Internal Medicine and the Center for Evidence-Based Medicine and Population Health, the University of Texas Health Sciences Center at Houston (Dr Moyer); and Department of Medicine and Office of the Dean, Faculty of Medicine, University of Toronto, Ontario (Dr Naylor). The original list of members (with affiliations) appears in the first article of the series (*JAMA*. 1993; 270:2093-2095). A list of new members appears in the 10th article of the series (*JAMA*. 1996;275:1435-1439). The following members of the Evidence-Based Working Group contributed to this article: Eric Bass, MD, MPH, Gordon H. Guyatt, MD, MSc, Les Irwig, MBBCh, PhD, and Hui Lee, MD, MSc.
Reprints: Gordon H. Guyatt, MD, MSc, Department of Clinical Epidemiology and Biostatistics, Room 2C12, 1200 Main St W, McMaster University Faculty of Health Sciences, Hamilton, Ontario, Canada L8N 3Z5.
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asks you about this patient and whether aortic dissection really needs to be actively considered. Together, you review the findings found useful in determining whether a patient is having a myocardial infarction[1] and then discuss the clinical findings seen with aortic dissection. The resident asks whether the normal pulses and equal blood pressures in the arms can rule out dissection without further testing. You reply, "I don't know. If we knew the frequencies of the clinical findings in aortic dissection, we could better interpret our examination and select his differential diagnosis. Rather than guess, why don't we look this up while we wait for his test results?"

THE SEARCH

You begin by articulating your knowledge gap as a question: "In patients with confirmed acute aortic dissection, how frequently would a detailed and careful evaluation yield each of several clinical findings, such as pain radiating to the back, pulse asymmetry, diastolic hypotension, or diastolic murmur?" You turn to a networked computer in the emergency department that gives you full access to MEDLINE from the hospital's library, which you search using strategies reviewed elsewhere.[2,3] In the MEDLINE file since 1966, you combine medical subject headings *aneurysm, dissecting* (5027 citations) and *aortic aneurysm, thoracic* (1699 citations) with *aortic dissection* as a text word (2330 citations) to yield a set of 6410 citations. Next, you use the floating subheadings *di* for diagnosis (applied to articles that include clinical findings from patient examination) and *co* for complications (indicates conditions that coexist or follow the specified disease process). Combining these sets yields 86 citations, which drops to 33 when you limit to adult patients and to the English language. Scrolling through these titles, you find a relevant citation by Spittell et al[4] that is linked to the full text online in your library.

UNDERSTANDING CLINICAL MANIFESTATIONS

In busy clinical practice, diagnosis is our daily bread. As we see sick persons, we classify their illnesses as instances or cases of disease,[5-11] to serve them by using the available knowledge about what is wrong, what it may mean, and what might be done to maximize their well-being.[9-11] To categorize illnesses, we use a classification system, or taxonomy of disease, with diseases representing the classes into which illnesses are grouped.[5-7] These taxonomic categories are generally defined by similarities in the illnesses of afflicted persons, including similarities of clinical features, anatomic abnormalities, physiologic derangements, causative microorganisms, or genetic and molecular lesions.

If we are to classify our patients' illnesses into diseases, we need to know the features by which different diseases are recognized and discriminated. In other words, we need to know the clinical manifestations of each disease that we expect to diagnose. We use the terms *clinical findings* and *clinical manifestations* interchangeably to mean findings that the clinician can gather directly from the patient, during the medical interview or the physical examination (we find less useful a rigid distinction between symptoms and signs).[6]

How specifically can we use knowledge of the clinical manifestations of disease for clinical diagnosis? First, when initially evaluating a patient's illness, single findings or clusters of findings can cue us to raise diagnostic hypotheses. In the clinical scenario, the sudden (rather than crescendo) onset of pain and the radiation of the pain to the back triggered the hypothesis of aortic dissection. Thus, when we recognize that a patient's illness includes features seen in a given disease, we "activate" that diagnostic possibility for further inquiry. Without such knowledge, the clinical features will not cue hypotheses, so we may fail to consider the correct diagnosis.

Second, knowing the clinical manifestations of disease can help us when selecting a patient-specific differential diagnosis and when deciding whether to use further testing to actively exclude a disorder. In the clinical scenario, while some of the patient's features (chest pain and risk factors for coronary atherosclerosis) suggest myocardial ischemia, other features (pain onset and radiation) suggest aortic dissection, so you plan to pursue testing for both. Thus, while aortic dissection is less common than myocardial ischemia, it is serious and treatable, so the presence of some of its features in this patient has led you to place dissection on your short list of active alternatives to be excluded.[12] In general, when considering an uncommon disease, experienced clinicians use the presence of 1 or more of its clinical manifestations, combined with knowledge of disease probability, prognosis, and responsiveness to treatment, to help them decide whether to actively consider this condition along with more common diseases. With incomplete or inaccurate knowledge of the clinical manifestations of diseases, we risk selecting flawed differential diagnoses.

Third, after diagnostic testing is completed and interpreted, we can use the clinical manifestations of disease in verifying a patient's final diagnosis.[13] Before concluding that a diagnosis is correct, we (often implicitly) test how well it explains the patient's illness, compared with the alternative possibilities. As shown more explicitly in TABLE 1, verifying a patient's final diagnosis depends heavily on detailed knowledge of the clinical manifestations of disease. While ideally a final diagnosis should explain that all the patient's findings should be coherent with the patient's observed pathophysiologic state, the best fit among the alternatives, the simplest explanation overall, the only possibility not yet disproved, and the 1 hypothesis that best predicts the patient's course, in actual practice, we often accept diagnoses that meet only some of these considerations. If our knowledge of the clinical manifestations of disease is inaccurate, we risk prematurely accepting an incorrect diagnosis or pursuing further testing despite good verification of the correct diagnosis.

What lessons can we learn from the frequencies of clinical manifestations of disease? First, textbook descriptions of disease may emphasize the presence of

classic findings that are hallmarks of the diagnosis. Yet when studied systematically, such manifestations may be uncommon, and if we were to rely on their presence to diagnose the disorder, we would miss many cases. For example, hemoptysis has been described as a hallmark of acute pulmonary embolism, yet when 327 patients with angiographically proven pulmonary emboli were examined, only 30% were found to have hemoptysis.[14] Second, the reverse lesson can be learned, because some manifestations may be more common than usually believed. For instance, the murmur of aortic regurgitation was found in 40 of 124 patients with confirmed aortic dissection, suggesting that clinicians should purposefully seek this finding in suspected cases.[15] Similar to these examples, most findings occur with intermediate frequencies. Since these frequencies are equivalent to diagnostic sensitivities, these intermediate values mean that individually, most findings cannot rule out disease. Since specificities or likelihood ratios cannot be obtained from studies of the clinical manifestations of disease, we are unable to revise our estimates of disease probability using these findings alone. The third lesson represents the exception to this general rule. A few manifestations of disease might be so common that they occur in virtually all diseased patients. As the proportion of diseased patients with a similar finding nears 100%, the absence of this finding becomes powerful for excluding the disease. This is because as the sensitivity goes to 100%, the false-negative rate approaches 0, effectively ruling out the disorder.[16-18]

How does the knowledge about clinical manifestations of diseases fit with other knowledge for use in diagnostic thinking? Expert diagnosticians that we have known or have read about appear to have detailed knowledge of 4 kinds: (1) remembered cases of real patients they have cared for; (2) knowledge of clinical problems, including which diseases cause them and how likely those are; (3) knowledge of the accuracy and precision of test results; and (4) knowledge of the clinical manifestations of diseases.[19,20] They can draw on this extensive knowledge as they proceed through the diagnostic steps of raising diagnostic possibilities, selecting a patient-specific differential diagnosis, choosing and interpreting diagnostic tests, and verifying a patient's final diagnosis. These 4 forms of knowledge complement each other, and no single form can replace the others for their intended uses. Knowledge of the probability of diseases that cause a clinical problem is particularly useful for selecting a patient's differential diagnosis and estimating pretest probability.[12,18] Knowledge of the likelihood ratios of test results is most useful for choosing and interpreting diagnostic tests and estimating posttest probability.[16-18] Knowledge of the clinical manifestations of disease is useful for raising diagnostic possibilities, selecting differential diagnoses, and verifying a patient's final diagnosis. In an archery analogy, if pretest probability is how we aim our arrows and the power of diagnostic tests is the strength of our bow, our disease taxonomy (based on clinical manifestations) contains the targets we shoot toward.

Where can we find knowledge about the frequencies of the clinical manifestations of disease? One source is from clinical experience, either our own or of others.[19-21] Here, we focus on the other major source of this knowledge, the medical literature, eg, the article about aortic dissection retrieved by the search.[4] This Users' Guide will help you understand articles about the clinical manifestations of disease, judge their validity, and decide whether to use them in refining your disease taxonomy for clinical diagnoses (TABLE 2).

Before doing that, it is important to be clear about what these articles cannot do. First, studies of the clinical manifestations of a disorder generally include patients only if they are known to have that specific disorder and exclude patients with other diseases. This means that such studies cannot provide evidence about how well the clinical findings discriminate between diseases, such as through likelihood ratios for these findings.[16-18] Second, since the study sample includes patients with only 1 disorder, studies of the clinical manifestations of disease cannot provide evidence about the probability of different diseases in patients with a given clinical problem.[12] Third, studies of the clinical manifestations of disease generally do not provide informa-

Table 1. Explicit Tests for Verifying a Patient's Diagnosis

Adequacy
• Does this diagnostic hypothesis adequately explain all the patient's clinical findings?
• If not, does it explain the patient's important findings?
Coherence
• Does this diagnostic hypothesis fit the pathophysiologic state observed and/or inferred in this patient?
• Thus, is this hypothesis pathophysiologically coherent?
Primacy
• Does this diagnostic hypothesis provide the best fit to the pattern of the patient's illness?
• Is there no hypothesis that fits the patient's illness better?
Parsimony
• Is this diagnostic hypothesis the simplest explanation of this patient's illness?
• Is there no hypothesis that is simpler?
Robustness
• Is this diagnostic hypothesis robust to attempts to falsify it?
• Has it escaped disproof?
Prediction
• Does this diagnostic hypothesis best predict the subsequent course of the patient's illness?
• Is there no hypothesis that predicts the patient's course better?

Table 2. Users' Guides for Articles on the Clinical Manifestations of Disease

Are the results of the study valid?
Primary guides:
• Was the presence of disease verified using credible criteria that are independent of the clinical manifestations under study?
• Did the patient sample represent the full spectrum of those with this disorder?
Additional guides:
• Were clinical manifestations sought thoroughly, carefully, and consistently?
• Were the clinical manifestations classified by when and how they occurred?
What were the results?
• How frequent were the clinical manifestations of disease?
• How precise were the estimates of frequency?
• When and how did these clinical manifestations occur in the course of disease?
Will these results help me in caring for my patients?
• Are the study patients similar to my own?
• Is it unlikely that the disease manifestations have changed since this evidence was gathered?

tion about how reliably clinicians gather these findings.[22,23]

THE GUIDES

Are the Results Valid?

Was the Presence of Disease Verified Using Credible Criteria That Are Independent of the Clinical Manifestations Under Study? This question addresses 2 closely linked issues. First, how sure are investigators that the study patients really did have this particular disease to explain their illnesses and not other diseases? While clinicians often encounter tentative diagnoses in practice, in a research study such diagnostic uncertainty could introduce bias, because the patient sample might include not only patients with this disease but also other diseases. To minimize this bias, investigators can use a set of explicit diagnostic criteria and include in the study sample only patients who meet these criteria. Ideally, for every disease there would be a set of widely accepted diagnostic criteria, including 1 or more well-established reference standard tests that can be applied reproducibly in a blinded fashion. Reference standards can be anatomic, physiologic, radiographic, or genetic, to name a few. To judge how the presence of disease was verified, look for which standards were used, how they were used, and whether the standards are clinically credible.

Second, are the diagnostic criteria independent of the clinical manifestations under study? When no reference standards exist, investigators' degree of diagnostic certainty is much lower. In these situations, known sometimes as *syndrome diagnosis*,[5] diagnostic criteria still can be made and used. They usually comprise a list of clinical features that must be present for the diagnosis to be made. For instance, the definition of chronic fatigue syndrome uses an explicit set of clinical features as diagnostic criteria.[24] Such explicit criteria often represent an advance over an implicit haphazard approach and for a time may be the best available method for clinical diagnosis.

However, trouble can arise when investigators use clinical manifestations to make the syndrome diagnosis, select the patient sample, and then examine the frequency of these same clinical findings in the study patients. This testing of manifestations that are incorporated into the definition creates circular reasoning that can bias upward the frequencies of these findings in the study sample, known as *incorporation bias*. For example, in a study of manifestations among 36 patients with relapsing polychondritis, the investigators used diagnostic criteria based on several characteristic clinical findings.[25] Although this study may be the best available method for clinical diagnosis, incorporation bias is inevitable and it limits the inferences we can draw about the frequency of manifestations. In judging the independence of verifying criteria, compare the list of these criteria with the list of clinical manifestations studied to examine for overlap.

Spittell et al[4] studied 235 patients whose aortic dissections were confirmed by surgical intervention (n=162), autopsy (n=27), or radiographic studies (n=47). Thus, the diagnoses of study patients appear to have been verified using clinically credible means that are independent of the clinical manifestations.

Did the Patient Sample Represent the Full Spectrum of Those With This Disorder? By selecting a specific disease for research, the investigators determine the population from which the study patients should be selected. Ideally, the study sample mirrors the whole population of those with the disease, so that the frequency of clinical manifestations in the sample approximates that of the population. Such a patient sample is termed *representative*, and the more representative the sample is, the more accurate the resulting frequencies of clinical findings. Conversely, the less representative the study sample, the less confident we can be that the frequencies of clinical manifestations found are accurate.[26]

To judge the representativeness of the study sample, we suggest 3 tactics. First, examine the setting from which study patients come. Patients seen in referral care settings might have higher proportions of unusual findings or illnesses difficult to diagnose, yielding different frequencies of clinical manifestations than patients in community practice.[27] Second, examine the methods the investigators used to identify and include the study patients and exclude others. Were all the important demographic groups (age, sex, race, etc) included? Were any important subgroups excluded that would threaten the validity of the results? Third, examine the description of the study patients' illnesses. Are patients with mild, moderate, and severe symptoms present? If different clinical patterns of disease are known, does the sample include patients with each pattern?

Combining these 3 considerations, you can judge whether the spectrum of included patients is full enough that the study can yield valid results about clinical manifestations of this disease. For instance, in a study of patients with thyrotoxic periodic paralysis, the investigators included in the sample only the 19 patients who were hospitalized during an episode of paralysis, excluding 11 patients who were diagnosed during the study period but who were not admitted.[28] To the extent that hospitalized patients may have worse or different clinical manifestations than those not admitted, such a restriction might introduce bias into the study.

Investigators may deliberately choose the task of describing the manifestations of a disease in a purposefully narrowed target population, whether demographic (eg, a study of the findings of myocardial infarction in the aged[29]), prognostic (eg, a study of the clinical findings in patients with fatal pulmonary embolism[30]), or by site of care (eg, a study of the findings in patients with ruptured abdominal aortic aneurysm who present to internists, not emergency departments[31]). In such situations, you can look to see whether the study sample is representative of the limited target population.

Spittell et al[4] reported a study of patients treated at the Mayo Clinic, which provides both community hospital care

and tertiary referral care. The study sample had patients with aortic dissection that was both acute (<2 weeks) in 158 patients (67%) and chronic (≥2 weeks) in 78 patients (33%). In 60 patients, the initial clinical impression was a diagnosis other than aortic dissection. The sample included patients with sudden death, including 10 out-of-hospital cardiac arrests and 5 in-hospital cardiac arrests. It also included 11 patients without pain but with other symptoms, along with 33 patients without pain or other symptoms who had abnormal chest radiograph findings. Thus, the study patients had a wide array of clinical presentations and may be sufficiently representative of the full spectrum of this disorder.

Were Clinical Manifestations Sought Thoroughly, Carefully, and Consistently? This criterion addresses 3 closely related issues. First, were study patients evaluated thoroughly enough to detect clinical findings if they were present? Within reason, the more comprehensive the workup, the lower the chance of missing findings and drawing invalid conclusions about their frequency. Second, how did the investigators ensure that the information they gathered was correct and free of distortion? Were symptoms inquired about in neutral nonjudgmental ways? Were patients examined by skilled examiners? The more carefully the data were gathered, the more credible the resulting frequencies will be. Third, how consistently was the evaluation carried out? Inconsistent assessments might yield erroneous frequencies of disease manifestations.

You may find it relatively easy to judge the thoroughness, care, and consistency of the search for manifestations when the patients were evaluated prospectively using a standardized diagnostic approach. It becomes harder to judge when patients were studied retrospectively after their investigation was complete or when the evaluation was not standardized. For example, in a retrospective analysis of disease manifestations in 68 patients with lumbar spinal stenosis, the investigators do not describe the search for clinical findings in enough detail for us to judge how well they protected against biased ascertainment.[32] Ordinarily, a prospective study of clinical manifestations of disease will provide more credible results than a retrospective study.

Spittell et al[4] retrospectively reviewed the charts of their patients after the clinical evaluations were completed. The diagnostic workup of these patients is not described explicitly. The tables of results include much detail about the clinical examination, suggesting a careful approach, but uncertainty remains about whether the investigators avoided bias during workup.

Were the Clinical Manifestations Classified by When and How They Occurred? Clinical manifestations of disease can range from the permanent to the fleeting. They can occur early, late, or throughout the course of the disease. The most complete information about the timing of disease manifestations might be obtained if the investigators began collecting data the instant the disease starts in each patient and continued collecting through the end of the illness. Since knowing this "zero time" with certainty is impossible for most diseases, investigators can use the next strongest approach, that of targeting all findings that occur from the onset of patients' first symptoms of this illness episode. Studies that do not start collecting at the beginning of the episode, or that do not report the timing of evaluation relative to symptom onset, may have inadvertently missed findings, and our confidence in their validity decreases. For instance, in a study of the clinical manifestations in 92 patients with fatal pulmonary embolism, investigators recorded findings for just the 24 hours before death, so they may have missed transient but important clues to the diagnosis that occurred before then.[30]

Studies of this type also can describe qualitative findings that are useful in clinical diagnosis, particularly when triggering initial diagnostic hypotheses. For instance, the pain of aortic dissection is often described as a tearing or ripping sensation that is located in the center of the torso and reaches maximal intensity quite quickly.[15] Just as with the temporal aspects, these qualitative descriptions are more credible if they were gathered deliberately and carefully.

Spittell et al[4] describe the clinical manifestations of dissection at presentation for patients with both acute and chronic aortic dissection. They also describe the location of pain in relation to the site of dissection, the various clusters of pain with other findings, along with unusual findings such as hoarseness and dysphagia. Thus, despite the retrospective design, the investigators appear to have classified the temporal and qualitative features accurately enough to provide valid results for patients with acute dissection. We may be less confident in the results for chronic dissection, since early findings might have been missed.

What Were the Results?

How Frequent Were the Clinical Manifestations of Disease? Studies of clinical manifestations of disease often display the main results in a table listing the clinical findings, along with the number and percentages of patients with each of those manifestations. Since patients usually have more than 1 finding, these proportions are not mutually exclusive. Some studies also report the number of patients with any of the findings, either in total or by particular group.

Spittell et al[4] report that 168 patients (74%) initially had acute onset of severe pain, 35 (15%) were asymptomatic but had abnormal chest radiograph findings, and 15 (6.3%) experienced cardiac arrest or sudden death. Of the 235 patients, 217 (92.3%) had a cardiac examination recorded; 22 (11%) had murmurs of aortic regurgitation detected. Pulse deficits were uncommon, occurring in 14 (6%) patients. Thus, the diagnostic sensitivity of pulse deficit is only 6%, so that using pulse deficits to exclude dissection would lead to missing 94% of cases.

How Precise Were These Estimates of Frequency? Even when valid, these measured frequencies of findings are only estimates of the true frequen-

cies. You can examine the precision of these estimates using their confidence intervals (CIs). If the authors do not provide the CIs for you, you can calculate 95% CIs with the following formula:

$$95\%\ \mathrm{CI} = p \pm 1.96 \times \sqrt{(p\,[1-p])/n}$$

Here p is the proportion of patients with the finding of interest, and n is the number of patients in the sample.[33] This formula becomes inaccurate when the number of cases is 5 or fewer, so approximations have been developed for this situation.[34,35]

For instance, consider the clinical finding of pulse deficit, found in 14 of the 217 patients in whom it was sought by Spittell et al.[4] Using the above formula, we would start with $p = 0.06$, $(1 - p) = 0.94$, and $n = 217$; this yields a CI of 0.06 +/- 0.03. Thus, the most likely frequency of pulse deficit is 6%, and it may range between 3% and 9%.

Whether you consider the CIs sufficiently precise depends on how you expect to use the information. For example, for a finding that occurs in 50% of cases, you might examine for it but not plan to use its absence to exclude the diagnosis. If the CI for this estimate ranged from 30% to 70%, it would not change your expected use of the information, so the result may be precise enough. On the other hand, for a finding that occurs in 98% of patients, you might hope to use its absence to help you rule out the diagnosis. If the CI for this estimate ranged from 80% to 100% (half of the prior 40-point range), it could mean that using this finding to exclude the diagnosis might lead you to miss up to 20% of patients. Such a result would be too imprecise to rule out this disorder.

When and How Did These Clinical Manifestations Occur in the Course of Disease? Research on the clinical manifestations of disease can yield additional insights beyond the frequency of findings. Some studies will report on the temporal sequence of symptoms, characterizing symptoms as *presenting*, prompted patients to seek care; *concurring*, did not prompt care but were present initially; or *eventual*, not present initially, but found subsequently. For instance, in 100 patients with pancreatic cancer, investigators described weight loss and abdominal pain as presenting manifestations in 75 and 72 patients, respectively, while jaundice, commonly taught as a key presenting sign, was found in only 24 patients.[36] In addition to chronology, such studies can also describe the location, quality, intensity, aggravating and alleviating factors, situational context, and associated findings for important manifestations.

Spittell et al[4] describe in detail the symptoms at initial assessment, both as individual findings and in clusters (their Tables 3, 6, and 7). The authors also describe the location of pain and its association with the site of dissection (their Tables 4 and 5). The delayed manifestations are not described in much detail.

Will the Results Help Me in Caring My Patients?

Are the Study Patients Similar to My Own? This question is about whether the clinical setting and patient characteristics are similar enough to yours to allow you to extrapolate the results to your practice. The closer the match, the more confident you can be in applying the results. Ask yourself whether the setting or the patients are so different from yours that you cannot use the results.[37] Do your patients come from a geographic, demographic, cultural, or clinical group that you would expect to differ importantly in the ways in which this particular disorder is expressed? For instance, the presenting symptoms of acute myocardial infarction were found to differ with advancing patient age, when studied in 777 elderly hospitalized patients; syncope, stroke, and acute confusion were more common and were sometimes the sole presenting symptom.[29]

Spittell et al[4] studied patients who were seen at the Mayo Clinic with aortic dissection. The referral filters through which patients arrived are not described, although you know that Mayo provides community hospital care for Olmsted County residents along with referred care for others. Of the 235 patients, 158 (67%) were men, like your patient. The study patients ranged in age from 17 to 94 years, with a mean age very close to your patient. The patients are not described with respect to comorbid conditions, socioeconomic status, race, or cultural background. Thus, while some uncertainty remains, these patients are sufficiently similar to the patient in the scenario that the results could be extrapolated.

Is It Unlikely That the Disease Manifestations Have Changed Since This Evidence Was Gathered? As time passes, evidence about the clinical manifestations of disease can become obsolete. New diseases can arise and old diseases can present in new ways. New disease taxonomies can be built, changing the borders between disease states. Such events can so alter the clinical manifestations of disease that previously valid studies may no longer be applicable to current practice. For example, consider how much the arrival of human immunodeficiency virus disease has changed our concept of pneumonia caused by *Pneumocystis carinii*.[38,39]

Similar changes can occur as the result of progress in health science or medical practice. For instance, early descriptions of *Clostridium difficile* infection emphasized severe cases of life-threatening colitis. As diagnostic testing improved and awareness of the infection widened, milder cases were documented and a broader variety of presenting manifestations was recognized.[40] Treatment advances can change the course of disease so that previously common clinical manifestations might become less frequent. Also, new treatments bring the chance of new iatrogenic disease, which may combine with underlying diseases in new ways.

The study by Spittell et al[4] was published in 1993 and reports on patients seen from 1980 to 1990. You know of no new diseases arising since then that would change the clinical features of dissection. Both testing for suspected dissection and treatment for hypertension (major risk factor for dissection)

have changed during this period, but you expect they would not change the presenting clinical features of acute dissection.

RESOLUTION OF THE SCENARIO

Based on the evidence from Spittell et al,[4] you and the resident agree not to use the absence of pulse deficit to rule out aortic dissection. Given the presence of the aortic regurgitation murmur and the diastolic hypotension, along with the patient's known risk and the absence of findings for myocardial infarction, the resident now agrees with your suspicion of dissection. When completed, this patient's aortogram confirms aortic dissection of the ascending aorta and arch, complicated by aortic regurgitation.

We recommend applying these Users' Guides to identify good evidence about the clinical manifestations of disease. As you do so, this detailed knowledge of the clinical findings of disease should increase your ability to raise diagnostic hypotheses, select differential diagnoses, and verify your final diagnoses.

While this article was in press, another study of the clinical manifestations of this disease was published, based on 464 patients with acute aortic dissection collected from 12 international referral centers.[41] Overall, the frequencies of clinical findings were similar; for instance, pulse deficit was found in 15.1% and diastolic murmur in 31.6%.

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REFERENCES

1. Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. Is this patient having a myocardial infarction? *JAMA*. 1998;280:1256-1263.
2. Hunt DL, Jaeschke R, McKibbon KA, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, XXI: using electronic health information resources in evidence-based practice. *JAMA*. 2000;283:1875-1879.
3. McKibbon KA, ed. *PDQ Evidence-Based Principles and Practice*. Hamilton, Ontario: BC Decker; 1999.
4. Spittell PC, Spittell JA, Joyce JW, et al. Clinical features and differential diagnosis of aortic dissection: experience with 236 cases (1980-1990). *Mayo Clin Proc*. 1993;68:642-651.
5. Wulff HR. *Rational Diagnosis and Treatment: An Introduction to Clinical Decision-Making*. 2nd ed. Oxford, England: Blackwell Scientific Publications; 1981.
6. King LS. *Medical Thinking: An Historical Preface*. Princeton, NJ: Princeton University Press; 1982.
7. Murphy EA. *The Logic of Medicine*. 2nd ed. Baltimore, Md: Johns Hopkins University Press; 1997.
8. Flegel KM. The case for "a case of . . . " [editorial]. *CMAJ*. 1997;157:286.
9. Glass RD. *Diagnosis: A Brief Introduction*. New York, NY: Oxford University Press; 1996.
10. Barondess JA, Carpenter CCJ, eds. *Differential Diagnosis*: Philadelphia, Pa: Lea & Febiger; 1994.
11. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. 2nd ed. Boston, Mass: Little Brown & Co; 1991:4-5.
12. Richardson WS, Wilson MC, Guyatt GH, Cook DJ, Nishikawa J, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, XV: how to use an article about disease probability for differential diagnosis. *JAMA*. 1999;281:1214-1219.
13. Kassirer JP, Kopelman RI. *Learning Clinical Reasoning*. Baltimore, Md: Williams & Wilkins; 1991:32-33.
14. Bell WR, Simon TL, DeMets DL. The clinical features of submassive and massive pulmonary emboli. *Am J Med*. 1977;62:355-360.
15. Slater EE, DeSanctis RW. The clinical recognition of dissecting aortic aneurysm. *Am J Med*. 1976;60:625-633.
16. Jaeschke R, Guyatt GH, Sackett DL, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, III: how to use an article about a diagnostic test, A: are the results valid? *JAMA*. 1994;271:389-391.
17. Jaeschke R, Guyatt GH, Sackett DL, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, III: how to use an article about a diagnostic test, B: what are the results and will they help me in patient care? *JAMA*. 1994;271:703-707.
18. Sackett DL, Straus SE, Richardson WS, Rosenberg WMC, Haynes RB, eds. *Evidence-Based Medicine: How To Practice and Teach EBM*. 2nd ed. Edinburgh, Scotland: Churchill Livingstone; 2000.
19. Schmidt HG, Norman GR, Boshuizen HPA. A cognitive perspective on medical expertise: theory and implications. *Acad Med*. 1990;65:611-621.
20. Bordage G. Elaborated knowledge: a key to successful diagnostic thinking. *Acad Med*. 1994;69:883-885.
21. Regehr G, Norman GR. Issues in cognitive psychology: implications for professional education. *Acad Med*. 1996;71:988-1001.
22. Department of Clinical Epidemiology and Biostatistics. Clinical disagreement, I: how often it occurs and why. *CMAJ*. 1980;123:499-504.
23. Department of Clinical Epidemiology and Biostatistics. Clinical disagreement, II: how to avoid it and learn from one's mistakes. *CMAJ*. 1980;123:613-617.
24. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, and the International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med*. 1994;121:953-959.
25. Trentham DE, Le CH. Relapsing polychondritis. *Ann Intern Med*. 1998;129:114-122.
26. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med*. 1978;299:926-930.
27. Fletcher RH, Fletcher SW, Wagner EH. *Clinical Epidemiology: The Essentials*. 3rd ed. Baltimore, Md: Williams & Wilkins; 1996.
28. Manoukian MA, Foote JA, Crapo LM. Clinical and metabolic features of thyrotoxic periodic paralysis in 24 episodes. *Arch Intern Med*. 1999;159:601-606.
29. Bayer AJ, Chadha JS, Farag RR, Pathy MS. Changing presentation of myocardial infarction with increasing age. *J Am Geriatr Soc*. 1986;34:263-266.
30. Morgenthaler TI, Ryu JH. Clinical characteristics of fatal pulmonary embolism in a referral hospital. *Mayo Clin Proc*. 1995;70:417-424.
31. Lederle FA, Parenti CM, Chute EP. Ruptured abdominal aortic aneurysm: the internist as diagnostician. *Am J Med*. 1994;96:163-167.
32. Hall S, Bartleson JD, Onofrio BM, Baker HL, Okazaki H, O'Duffy JD. Lumbar spinal stenosis: clinical features, diagnostic procedures, and results of surgical treatment in 68 patients. *Ann Intern Med*. 1985;103:271-275.
33. Altman DG. Confidence intervals [appendix]. In: Sackett DL, Straus SE, Richardson WS, Rosenberg WMC, Haynes RB, eds. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. Edinburgh, Scotland: Churchill Livingstone; 2000:233-243.
34. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? interpreting zero numerators. *JAMA*. 1983;249:1743-1745.
35. Newman TB. If almost nothing goes wrong, is almost everything all right? interpreting small numerators. *JAMA*. 1995;274:1013.
36. Gudjonsson B, Livistone EM, Spiro HM. Cancer of the pancreas: diagnostic accuracy and survival statistics. *Cancer*. 1978;42:2494-2506.
37. Glasziou P, Guyatt GH, Dans AL, Dans LF, Straus SE, Sackett DL. Applying the results of trials and systematic reviews to individual patients [editorial]. *ACP J Club*. 1998;129:A15-A16.
38. Walzer PD, Perl DP, Krogstad DJ, Rawson PG, Schultz MG. *Pneumocystis carinii* pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med*. 1974;80:83-93.
39. Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with AIDS and patients with other immunodeficiency states. *Ann Intern Med*. 1984;100:663-671.
40. Caputo GM, Weitekamp MR, Bacon AE, Whitener C. *Clostridium difficile* infection: a common clinical problem for the general internist. *J Gen Intern Med*. 1994;9:528-533.
41. Hagan PG, Nienaber CA, Isselbacher EM, et al. The international registry of acute aortic dissection: new insights into an old disease. *JAMA*. 2000;283:897-903.