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Methods Development

Applied forensic epidemiology, part 1: medical negligence

MD Freeman[1]*, PJ Cahn[2], FA Franklin[2]

Abstract

Introduction

The evaluation of the causal relationship between an alleged act of medical negligence and an adverse health outcome is an essential element of a medical malpractice legal action. In such an action, the question of causation is also known as the "but-for" question; *i.e.* but for the negligent act, would the plaintiff still have suffered the adverse outcome at the same point in time? Forensic epidemiology provides a systematic approach to the investigation of causation, with conclusions suitable for presentation in a medicolegal setting. Such an evaluation relies on the following steps: (1) the application of the Hill criteria to first arrive at a conclusion that an investigated negligent action was a plausible cause of an adverse outcome; (2) an assessment of the temporo-spatial relationship between the negligent action and the first indication of the adverse outcome and (3) quantification of the probability of causation via an estimate of the risk of injury associated with negligent action versus the risk of known contemporaneous alternative causes of the adverse outcome. In this first of a three-part series on applied forensic epidemiology, we demonstrate forensic epidemiology methods with a description of the investigation of the probability of causation in three cases of serious neurologic injury following an alleged act of medical negligence.

Conclusion

Causation in cases of alleged medical malpractice is commonly disputed. In cases in which direct specific causation is not a viable alternative (i.e. the diagnosis can have multiple causes), the indirect evaluation of specific causation via the methods described in this article provides a reliable methodologic framework for the quantification of the probability of causation suitable for presentation in a court of law.

* Corresponding author
Email: forensictrauma@gmail.com

[1] Oregon Health & Science University School of Medicine, Departments of Public Health & Preventive Medicine and Psychiatry, Portland, Oregon, USA
[2] Forensic Research & Analysis, Portland, Oregon, USA

Introduction

Causation plays a pivotal role in the evaluation of legal actions involving an allegation of medical negligence. Once it is established that an action (either commission or omission) has occurred and that an adverse health outcome has followed that action, there are two questions that must be answered in order for the claim to advance legally. First, the action (alleged 'hazard') must be plausibly related to the adverse outcome. In legal settings, this relationship is often referred to as general causation[1]. Next, it must be demonstrated, on a more likely than not basis (>50% probability), that in the absence of exposure to the hazard, the outcome would not have occurred in the individual[1,2]. In a tort action for personal injury, this is known as the 'but-for' question; but for the hazard, would the plaintiff still have suffered the adverse outcome at the same point in time? The process of answering this question is referred to as specific or individual causation. With this information, a fact finder can make a further determination of negligence and damages.

The practice of forensic epidemiology (FE), also referred to as legal epidemiology, is generally described as concerning the intersection of epidemiology and law. More specifically, FE provides a systematic approach to the investigation of general and specific causation in civil and criminal matters[3–5]. In a clinical setting, the evaluation of causation is invariably performed by clinicians (e.g. a patient's ischaemic stroke was caused by his uncontrolled high blood pressure), and as such it is rare that a causal determination is ever revisited or challenged. In the legal setting, however, causation is routinely disputed. FE evaluation of specific causation differs from the clinical evaluation of causation in that the former focuses on an analysis of the risk of injury or disease from the investigated hazard versus the competing risk of the injury or disease absent in the exposure to the hazard, whereas the latter focuses more on the differential diagnosis and patient history[6].

In many instances, there is no need for an FE evaluation of causation in a legal setting; e.g. it is unlikely that there will be a dispute over cause of death when the hazard is a gunshot wound to the head. This form of specific causation is *direct*, since there is a high degree of specificity between the diagnosis of the condition and the cause of the condition; i.e. the death was caused by a gunshot wound, and such wounds are only caused by gunshots. Direct specific causation is only practical when the diagnosis and the cause are essentially inseparable.

In circumstances in which medical negligence is alleged as a cause of an adverse outcome, it is rare that there are not at least several alternative explanations for the outcome, including

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that it was a natural consequence of the disease or injury necessitating the medical care in the first place. In such cases, there will be differing opinions on causation, typically provided by clinicians on either side of the legal dispute. The differences of opinion often stem from disputes over the magnitude of the competing causes of the outcome, and described (either quantitatively or qualitatively) in terms of competing risks. This form of specific causation evaluation is *indirect*, in that there is nothing about the diagnosis that is specific to only one possible cause. Risk is a population-based parameter, intended to describe the probability of a particular outcome, and opinions regarding risk are ultimately based on epidemiologic concepts and data. Thus, the purpose of FE in medical negligence actions is to provide an evidence-based foundation for opinions of comparative or relative risk (RR) intended to indirectly address the ultimate question of specific causation.

In the present article, the first of a three-part series on the applications of FE in civil and criminal courts, we describe the methods and data sources used in the investigation of general and specific causation in cases of alleged medical negligence and illustrate the methods with the analyses of three actual cases.

Causation and the law

In the law, a legal element of negligence is whether or not the plaintiff's exposure to the defendant's conduct proximately caused the plaintiff's injuries[7]. Negligence law operationalises the proximate cause element as a showing of harmful conduct that falls within the scope of liability (i.e. risk, used here qualitatively). Whether the harmful conduct is within the scope of risk is gauged by the concept of foreseeability. As the probability of risk increases, the more foreseeable that harm becomes and, in turn, a greater foreseeability enhances the likelihood that the conduct falls within the scope of liability. As a result, whether the defendant's conduct is a proximate cause of harm becomes a function of risk probability. The court must ask what risks the defendant should have anticipated at the time he acted and compare those risks with the injury that actually occurred. The 'risk rule' approach adopted by the law provides an analytical basis for consistent decision-making.

The RR is an epidemiologic metric used to quantify general causation or the association between an exposure and the risk probability of disease or injury (i.e. harm)[8]. Given that proximate cause and general causation are conceptually linked by the probability of risk, then, inherently, epidemiology becomes the most suitable tool to assess proximate cause and, ultimately, inform the legal question of liability. If there is no direct evidence of causation for either an investigated or alternative cause then a general causal inference can inform a specific causation determination[1,9]. Epidemiological evidence of a RR informs specific causation by providing the probability or likelihood that the exposure caused harm in a randomly selected case is at least the proportion described by the attributable fraction (AF) and indicated by effect magnitude of the RR. Together, the RR and AF inform the reader of the minimum number of excess cases among the exposed population that can be attributed to the exposure and not the total or maximum number of cases that can be attributed to the exposure[10].

A study presenting a RR supports a finding of specific causation (i.e. actual cause), particularly when accompanied by case-specific evidence that supports causation and rules out independent alternate causes as more probable. The extent to which a group-based study outcome reflects the increased risk to an individual depends on the individual's similarity to the subjects in the study population, with regard to substantial predictive characteristics. This legally accepted approach to specific causation reflects the counterfactual inquiry process used in FE known as differential aetiology[11]. Unlike the differential diagnosis approach of medical causation, differential aetiology generally does not rely on a single case and frequently offers a more robust examination of causal risk. Although inherently designed to address general causation, the jurisprudential view of epidemiological studies is that they are strong evidence of specific causation[9].

The Hill criteria: indirect estimation of the probability of specific cause

Specific causation is assessed in FE via adaptation of the Hill criteria to the circumstances of an individual case[3,12]. The Hill criteria, named for a 1965 publication by Sir Austin Bradford-Hill, consist of nine criteria or 'viewpoints' by which population-based determinations of causation can be made when there is substantial epidemiologic evidence linking a disease or injury with an exposure[13]. The nine criteria, and how they can apply to a specific causation analysis, are as follows:

1. *Strength of association:* Strength of association is generally considered to be the most important determinant of causation. Most simply stated, a strong association is more likely to indicate a causal relationship than is a weak association. Strength of association is typically quantified by RR (the frequency of the condition among the exposed versus unexposed populations), but can also be measured in general causation by the percentage decrease of an illness or injury in society if the injury cause were to be eliminated.

   In specific causation, the strength of association is evaluated by comparing the risk of injury or disease associated with

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exposure with the hazard to the risk of the same injury or disease occurring at the same point in time as the exposure in the specific individual, but absent the hazard. Strength of association in specific causation is closely associated with the proximity, either temporal or spatial, between the exposure and the outcome. Absent confounding, the closer the exposure is to a plausibly related outcome in time or space, the more likely it is that there is a causal association.

2. *Consistency:* The repetitive observation of a causal relationship in different circumstances strengthens the causal inference. Evidence of consistency can come from multiple studies of varied populations. In specific causation, consistency may also come from evidence gathered in case clusters or outbreaks.
3. *Specificity:* In general causation, this refers to the degree to which an exposure is associated with a particular outcome or population. Specificity of a high degree is a relatively rare attribute, as most exposures can cause various diseases or injuries (e.g. cigarette smoking does not *only* cause lung cancer). The concept of *reverse* specificity, the degree to which an outcome is associated with an exposure, is one that may be important in specific causal evaluations as well. For example, mesothelioma is only associated with asbestos exposure, and therefore evidence of the disease is equal to evidence of the cause[14].
4. *Temporality:* Hill only described sequence with regard to temporality; that the 'horse not come before the cart'. Temporal sequence is the *sine qua non* of specific causation that must be present in order to proceed with further analysis. Two other parameters of temporality are also important to consider in evaluating specific causation:
    a. Temporal plausibility: The outcome may not occur before or after the effect range of the hazard. For example, some foodborne illnesses (i.e. campylobacteriosis) only manifest after a matter of hours or days of incubation, and thus an individual who falls ill within minutes of eating undercooked chicken at a restaurant in which *C. jejuni* is found on the food preparation surfaces was not plausibly made ill by the consumption of the chicken, despite other collateral evidence suggesting causality. Alternatively, the otherwise unexplained death of a patient occurring 3 days after receiving an injection of a short-acting opiate (i.e. hydromorphone) is not plausibly related to the injection.
    b. Temporal latency: For an outcome that occurs within the hazard period (HP), the quantification of the latency between the exposure and the first indication of disease or injury can be important in assessing the causal association. As an example, a death in a hospital patient that occurs within 20 min of an injection of hydromorphone is much more likely to be associated with the injection than one that occurs 3 h later, largely because the cumulative risk of competing causes of the death is directly related to the latency period between the exposure to the hazard and the first sign of the adverse outcome.
5. *Biological gradient:* The outcome increases monotonically with increasing dose of exposure (also known as 'dose–response'). This criterion has most relevance in specific causation assessments of adverse drug reactions and exposure to toxic substances. Multiple exposures to increasing levels of a drug or other harmful substance that result in a corresponding increase in injury response is strong evidence of specific causation in an individual case.
6. *Biological plausibility:* The observed association can be plausibly explained by known scientific principles. Hill put little stock in plausibility, asserting that it was a criterion '*that I am convinced we cannot demand',* as detailed scientific evidence describing an injury or disease mechanism may lag behind observational evidence of a consistently observed causal association[8]. Although Hill only referred to this criterion as plausibility, for the purposes of this discussion, we are referring to it as biological plausibility in order to distinguish this criterion from general plausibility, as discussed later in this article. As a practical matter, biological plausibility is typically easily established for the majority of causal assessments. A common error with plausibility assessments is to transpose low pre-event probability of injury and implausibility of injury[7].

    As an example, laceration of the iliac artery during a total hip replacement procedure is very rare[15]. The rarity of such a complication does not make it *implausible* that the injury would occur in a surgery that requires the use of sharp instruments in the vicinity of the iliac artery. In the context of causation, plausibility and implausibility should not be considered as complements with no middle ground (as is the case with possibility [a probability of >0] and impossibility [probability of 0]). A causal relationship that may not be generally considered biologically plausible (reasonable) is not necessarily considered implausible (unreasonable), as the mechanism by which the relationship exists may simply be unknown at the present time. This is not to say, however, that when implausibility is well established

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that it should or can be ignored. Implausibility is present when a well-established biological principle must be violated in order to proceed with a causal assessment. An example of an implausible relationship would be the new onset of a Parkinson's disease-related tremor within hours of a biopsy performed under local anaesthetic. To attribute the tremor to the biopsy simply because it followed it closely in time, and at the same time ignore the implausibility of the relationship, is to commit the *post hoc ergo propter hoc* fallacy.

7. *Coherence:* A causal conclusion should not fundamentally contradict present substantive knowledge—it should 'make sense' given current knowledge.
8. *Experiment:* In some cases, there may be evidence from randomised experiments on animals or humans. Absence of experimental evidence of an injury or disease mechanism should not be confused with evidence against an investigated causal relationship.
9. *Analogy:* An analogous exposure and outcome may be translatable to the circumstances of a previously unexplored causal investigation.

An additional causal criterion that was not mentioned by Hill but which has been included by subsequent authors as an important feature of specific causation when an exposure is repeated over time is cessation/dechallenge–rechallenge[16–20]. The concept of dechallenge–rechallenge is straightforward: does the adverse effect improve or resolve in a temporally appropriate manner when the exposure is stopped or the degree of exposure is lessened (dechallenge) and does it return in a temporally appropriate manner when the exposure is reinstated or the degree of exposure is increased? The dechallenge–rechallenge criterion is obviously unhelpful for evaluating causal associations for traumatic injury, or single exposures to drugs and other potentially noxious substances (where there will not be a re-exposure), but in the context of medical negligence, it is ideal for evaluating causation between repeated exposures and adverse events.

Steps to the assessment and quantification of the probability of specific causation when medical negligence has been alleged as the cause of an adverse outcome

(1) A generally plausible relationship between the alleged act of negligence and the adverse outcome must be first deemed to be present. This is accomplished in one or both of two ways: (i) the relationship is widely accepted as generally plausible, a fact that is typically established via review of previously published biomedical literature or (ii) via application of the seven Hill criteria that address the question of general causation. In order of decreasing utility and/or availability of evidence, these criteria are as follows: coherence, analogy, consistency, specificity, biologic plausibility, experiment and biologic gradient). General plausibility in the context of a specific causation evaluation refers to what is both *possible* (i.e. not established as impossible) and *reasonable.* It is not the same as Hill's use of *plausibility,* which was more specific to the biologic mechanism by which the hazard acted in order to cause the outcome (and thus is sometimes referred to as *biologic* plausibility). A hypothetical example of a generally plausible relationship that cannot meet Hill's plausibility criterion would be an outbreak of gastroenteritis among independent patrons of a restaurant. Even if the microorganism responsible for the outbreak is not identified (and thus biologic plausibility cannot be examined), the general plausibility question is easily satisfied by other criteria, including coherence, analogy and consistency. There is no set number of criteria that must be met to satisfy a conclusion of general plausibility; this is a judgement to be made by the investigator[1].

(2) The risk of injury associated with the hazard (hazard risk [HR]) is quantified via available epidemiologic data or study. This evidence may come from previously published well-designed epidemiologic study, or it may come from analysis of information from existing data. There are some situations in which there is no need to quantify the risk of injury from a hazard because there is no reasonable dispute that the injury is certain when the hazard is present. An example would be death following the alleged failure to provide treatment for a cardiac arrest. Common sense, as well as cardiac physiology and medical experience, tells us that it is nearly certain (>95% probability) that an untreated cardiac arrest will result in death[21]. The causation question in such a case might relate to the strength of a competing cause of death (e.g. sepsis) for which it is alleged that the injury would have occurred regardless of the exposure to the hazard.

(3) The temporal proximity between the hazard and the outcome is quantified (the HP) via the evidence specific to the case, typically gleaned from a careful review of the medical record, and/or interview of fact witnesses.

(4) The base rate at which the injury or condition would be expected to occur during the HP absent the exposure (the base risk or BR_{HP}) is quantified via epidemiologic data or study. Two assumptions are inherent in assessing the BR; first that the underlying base rate is relatively consistent over time, and second, that the risk posed by the hazard is

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independent of the BR. A basis for estimating BR may come from previously published well-designed epidemiologic study, or it may come from *ad hoc* analysis of information from an existing database. In many cases, the BR will be derived from annual incidence data, and thus, in order to derive an estimate of the daily or even hourly risk (depending on the HP) the annual rate must be relatively stable, or it must be adjusted to reflect the alteration of base rate over time specific to the individual.

(5) The risk of injury associated with the hazard is compared with the risk of injury absent the hazard, resulting in a ratio that describes comparative risk (CR), with an associated 95% confidence interval. CR is similar in concept to a RR or odds ratio and in some cases is identical, but it differs in that it only compares substantive competing risks that are relevant to the individual at the time of the exposure. The equation for CR is

$$\frac{HR}{BR_{HP}} = CR$$

The CR ratio is related to the attributable risk percent, also known as the probability of causation (PC), as follows[22]:

$$\frac{CR-1}{CR} \times 100\% = PC$$

The result of the analysis, either a CR or PC, is compared with a standard of what is 'more likely true than not', and thus a CR of ≥2.0 (95% CI >1.0 lower boundary), or a PC of ≥50%, serves as indirect evidence of specific causation suitable for presentation in a legal setting. A PC of >50% indicates that a randomly selected individual from a population of exposed and injured people would not have the injury if the exposure had not occurred, on a more probable than not basis. The results of the analysis are applicable to a specific plaintiff to the extent that the predictive characteristics of both the hazard and the plaintiff as he would have been pre-exposure, relative to the adverse outcome, are adequately accounted for in the study populations.

The two types of error that can be made with an indirect assessment of specific causation are Type I, in which it is concluded that there is a causal relationship when there is not, and Type II, in which it is concluded that there is not a causal relationship when there is. It is important that a description of the potential for each type of error that is inherent in a causal analysis is presented for the fact finder to help assess the accuracy of the conclusion.

Case presentations

In the following section of this report are three case studies in which we describe serious neurologic injuries following alleged acts of negligence. The cases serve as exemplars to illustrate the previously described method for the indirect evaluation of specific causation in medical negligence legal actions in which the primary dispute was the CR of competing explanations for the adverse outcome, and the general plausibility of the relationship between the alleged hazard and the adverse outcome was previously established. The cases are described in the following fashion: (1) a brief history of the salient and undisputed facts is provided; (2) the alleged negligent act is described; (3) the opposing or defending theory is described; (4) the CR elements are given, including the identification of the alleged hazard and adverse outcome, an assessment of the HP between the alleged hazard and the first manifestation of the adverse outcome and an estimation of both the HR and the BR and (5) the CR is quantified and presented as a PC. See Table 1.

In all of the cases, an *ad hoc* analysis of data abstracted from a US national hospital database was conducted in order to provide an estimate of a HR and/or a BR. The database used for the analyses was the Nationwide Inpatient Sample (NIS) of the Healthcare Utilisation Project of the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services[23]. The NIS is the largest inpatient care database in the United States, containing a stratified sample of approximately 20% of hospitalisations from community hospitals in the country, which amounts to approximately 8 million hospitalisations that are recorded annually. The sampling frame for the NIS is a sample of hospitals that comprises approximately 95% of all hospital discharges in the United States. The data are weighted to provide a national estimate of the annual incidence of diagnoses, treatments, outcomes and other recorded variables for patients admitted to all US community hospitals.

All of the statistical analyses described for the cases were performed using SAS Version 9.2; SAS Institute Inc., Cary, NC.

Case 1

Partial paralysis following alleged failure to treat acute ischaemic stroke with thrombolytic therapy resulting in permanent paralysis

A 46-year-old female, with history of recent transient ischaemic attack, experienced sudden onset of right facial droop and right-sided extremity weakness (hemiparesis). Paramedics arrived 6 min later and found her on the floor and unable to speak (aphasic). She was transported to a primary stroke centre within 1 h of the onset of symptoms, and following computed tomography (CT) scan of the head that was negative for haemorrhage, she was diagnosed with an early ischaemic stroke in progress. The emergency department physician did not order thrombolytic therapy with tissue plasminogen activator (t-PA). A repeat CT scan revealed a new area of acute ischaemia in the distribution of the left middle

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Table 1 Causal elements in the three described case studies

	Case 1	Case 2	Case 3
Investigated hazard	Failure to timely treat an ischaemic stroke with thrombolytic agent	Cervical spine manipulation	Failure to timely diagnose and treat a brainstem herniation after lumbar puncture
Adverse outcome	Hemiparalysis	Vertebral artery dissection and associated stroke	Upper cervical spinal cord infarct
Alternate hazard/ explanation	Injury would have occurred regardless of treatment	Injury was of unknown cause and coincidental to manipulation	Injury is not predictable and occurs regardless of lumbar puncture
Hazard period	1.5 h	2 h	2 h
Hazard risk	Frequency of adverse outcome given no treatment	Frequency of adverse outcome given manipulation	Frequency of adverse outcome given lumbar puncture
Base risk	Frequency of adverse outcome given treatment	Frequency of adverse outcome given no treatment	Frequency of adverse outcome prior to lumbar puncture
Comparative risk	2.13 to 1	163 to 1	10.8 to 1
Probability of causation (%)	53	>99	91

cerebral artery. Eighteen days later, the patient was discharged from the hospital to a rehabilitation unit. At discharge, she remained aphasic and with right hemiparesis.

The plaintiff alleged that the failure to treat the patient with thrombolytic therapy resulted in the observed permanent neurologic sequelae, whereas the defence countered that the patient would have suffered the permanent neurologic injury regardless of the thrombolytic therapy, had it been given. It was agreed by both sides that the t-PA could have been administered within 90 min of the onset of the symptoms, as contraindications to administration had been ruled out by this time.

Plausibility of the putative cause is well established, as treatment with t-PA is generally accepted as improving favourable outcome in ischaemic stroke when administered up to 4.5 h following the onset of symptoms[24–26].

In order to assess the CR of the adverse outcome given treatment versus no treatment, an analysis of data from the Nationwide Inpatient Sample was undertaken. First, relevant ICD-9 diagnostic and therapeutic codes were identified and used to access data from the NIS for women aged 18–50 years with ischaemic stroke discharged living in a 4-year period that culminated with the year of the plaintiff's stroke (2005–2008). Thromboembolic stroke was defined using 434.×1, t-PA administration was identified with 99.10 and the outcomes of interest were paralysis that was categorised as follows:

0: No paralysis

1: Minimal paralysis as defined by 344.3×, 344.4×, 344.5, 438.3×, 438.4×, 438.50, 438.51, 438.52.

2: Moderate paralysis as defined by 344.1, 344.2, 438.2×, 438.53.

3: Severe paralysis as defined by 344.0×, 344.81.

The following parameters for inclusion or adjustment were identified based on the published indications and contraindications for t-PA administration, using the appropriate ICD-9 codes[27]: Age < 17, intracranial haemorrhage, coma, elevated partial thromboplastin time [PTT], anticoagulant use, history of prior stroke, seizure at stroke onset, history of hypertension, abnormal glucose levels, myocardial infarction and pregnancy. Standard logistic regression was used for patient with a 'good' versus 'bad' outcome (paralysis coded 0/1 vs. 2/3) and paralysed versus not, collapsed outcome binary models. The analysis was performed with SAS 9.2 procedure Surveylogistic to account for the complex sampling design of the NIS and adjusted for haemorrhage, coma, PTT status, anticoagulant use, prior stroke, seizure, previous MI, hypertension and abnormal glucose.

The analysis yielded an estimated 85,586 women aged 18–50 years with ischaemic stroke admitted to US hospitals who would have been eligible for treatment with t-PA. Among these women, there were 82,840 with good outcome and 2,745 with a bad outcome and 2,758 who were treated with t-PA. After accounting for all of the contraindications for t-PA administration, the adjusted odds ratio of a good versus bad outcome when t-PA was administered versus when it was not was 2.13 (95% CI 1.09, 4.14).

The OR of 2.13 was accepted as the case-specific CR and converted to a PC of 53%. As a result, it was concluded that the most probable

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cause of the plaintiff's permanent hemiparesis was the failure to administer t-PA.

Case 2
Manipulation of the cervical spine followed by vertebral artery dissection and stroke resulting in permanent paralysis
A 28-year-old previously healthy male presented for a first evaluation to a chiropractor for a recent onset of knee pain. As part of the therapy of the first visit, the patient underwent a manipulation of the cervical spine that included rapid rotation of the head and neck. Approximately 2 h following the manipulation, the patient began to feel that the left side of his body was numb and weak. The next morning his condition had worsened and he was unable to summon assistance. He was transported to an emergency department where he was found to have left hemiparesis, facial paresis and dysarthria. A CT angiogram of the head and neck revealed a dissection of the right vertebral artery, and an MRI of the brain demonstrated an acute infarct of the right basal ganglia. Upon discharge from the hospital, the patient remained partially paralysed. The patient had no known risk factors for stroke or arterial disease.

The plaintiff alleged that the rotational manipulation of the cervical spine was performed prior to an examination that demonstrated that the procedure could be performed safely on the patient (generally accepted best practice), and the ensuing improper manipulation resulted in a dissection of the right vertebral artery, which in turn resulted in the formation of a thrombus that embolised into the vertebrobasilar vasculature and caused the subsequent ischaemic stroke.

The defence countered with the assertion that the stroke was secondary to unknown factors, and the timing of it in relationship to the cervical manipulation was purely coincidental.

The relationship was deemed plausible in as much as explanation that rotation of the neck will produce strain on the vertebral artery (making the injury explanation coherent). Additionally, the injury mechanism is analogous to other forms of low-level neck trauma that have been associated with vertebral artery dissection[28]. Consistency is also present, as the injury has been demonstrated consistently in a variety of populations exposed to the hazard[29,30]. Further, despite some controversy, the relationship is generally accepted in the biomedical literature as being at least plausibly causal[31].

For the CR assessment, the risk of dissection/stroke from a cervical manipulation was estimated from the literature. Such estimates range from as frequent as 1 in 20,000 patients to as little as 1 in 5,846,381 manipulations[32]. The lower risk figure was selected for the analysis to reduce the chance of Type I error.

In order to evaluate the BR of spontaneous stroke during the 2-h HP, NIS data were accessed for men with vertebrobasilar stroke (ICD-9 codes 433.2×) in the 25–29 age group for the same year in which the stroke occurred (2009). These values were compared with the number of men in the United States in the same year in the same age group[33]. The results of this analysis were as follows: in 2009, there were an estimated 42 cases of vertebrobasilar stroke among all men aged 25–29 who were admitted to US hospitals. Of note, there were only six cases that did not result from some external trauma and thus could be considered spontaneous (20 were associated with a traffic crash, 11 due to assault with a firearm and 5 were due to unarmed assault). The same year there were an estimated 9,744,000 men of the same age living the United States. Thus, the annual incidence of all vertebrobasilar stroke was approximately 1 stroke per 216,533 men in the 25–29 age group in the United States in 2009. This figure, based on all strokes regardless of cause, was used for the CR estimate in order to again reduce the chance of Type I error. The annual incidence equates to a BR of approximately 1 in 948 million during the 2-h HP.

The CR resulting from this analysis is thus 1 in 5.8 million/1 in 948 million = 163 to 1 (95% CI 10, 2,613) in favour of the manipulation as the cause of the stroke. This value was converted to a PC of >99%. As a result, it was concluded that the most probable cause of the plaintiff's vertebrobasilar artery dissection and associated stroke was the cervical spine manipulation.

Case 3
Failure to timely diagnose and treat a neurologic complication of meningitis resulting in spinal cord stroke and paralysis
An 18-year-old previously health male college student fell ill with fever, chills, nausea and vomiting and over a 24-h period became incoherent and combative. He was transported to a hospital and after evaluation was diagnosed with a suspected case of meningococcal meningitis. A head CT scan demonstrated oedema in the brain. The following day, a lumbar puncture was performed on the patient in order to confirm the diagnosis, and 2 h later his condition deteriorated dramatically; he was agitated and combative despite sedation. After 6 h, his condition worsened further; his pupils were unequal and he was not responding to painful stimuli. A subsequent CT scan demonstrated increased oedema and herniation of the base of the brain through the foramen magnum (the opening at the base of the skull through which the spinal cord passes). Approximately 12 h after the lumbar puncture, intravenous mannitol therapy was initiated to reduce the intracranial pressure, but with no benefit. The patient was found to be a complete upper cervical quadriplegic secondary

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to an infarct of the high spinal cord, with no sensation or movement from the chin down, and dependent upon mechanical ventilator for respiration.

The plaintiff alleged that the failure to rapidly recognise and reverse the brainstem herniation resulting from the combination of increased intracranial pressure (evidenced by the cerebral oedema in the first CT scan), and the sudden decrease in spinal canal pressure following the lumbar puncture, was the cause of the high spinal cord injury. The defence asserted that brainstem herniation is a relatively common and unpredictable complication of meningitis, and as such an unpredictable and unpreventable complication, unrelated to the lumbar puncture. The defence further asserted that once the brainstem compression had occurred, the adverse outcome was unpreventable.

It is widely recognised in clinical medicine that herniation of the brain stem may occur during or after a lumbar puncture, and most typically in a patient with increased intracranial pressure[34]. Even if it was not well documented, the relationship meets the coherence, consistency, plausibility, analogy and dose–response criteria.

The CR analysis in this case was approached from two different perspectives; the first was from hazard perspective; i.e. if a patient with meningitis suffers from a brainstem herniation following a lumbar puncture how likely is it that the complication was due to the procedure rather than the natural course of the disease? The answer to this first question was found in a previously published study of the CT scans of 445 children with bacterial meningitis admitted to a large paediatric referral centre hospital[35]. The authors documented time from lumbar puncture to herniation in 19 episodes of herniation. Twelve of the 19 herniations occurred in the first 10 h after lumbar puncture, whereas the seven others occurred over six other 10-h periods ($P < 0.001$, two-tailed Fisher's exact test; odds ratio 32.6 (95% confidence interval 8.5 to 117.3). As the authors provided information regarding the frequency of herniation in the 6 h prior to and following the lumbar puncture, a *post hoc* analysis of the data indicated that, among those patients with herniation, the condition was 10.8 times more frequent in the 6 h following puncture (95% CI 1.4, 85.2).

A second approach to the CR question in this case was from the BR perspective; i.e. how likely is it that a patient with a brainstem herniation will suffer from a permanent injury, including an infarct of the spinal cord with associated paralysis, or a neurologic injury of similar severity, assuming prompt clinical recognition of the condition?

An analysis of NIS data for 2000–2010 was undertaken to address this question. First, the relevant ICD-9 diagnostic codes for meningitis (all causes), brain compression and serious adverse events, including stroke, paralysis and coma, were identified, and then the corresponding data were pulled for patients aged 30 and less. The results of the analysis were as follows: there were a total of 684,654 hospitalised patients with a diagnosis of meningitis. Out of this group, there were 2,991 (0.4%) who were diagnosed with brainstem compression/herniation. Among the patients with brainstem compression, there were 345 cases of cerebral stroke (11.5% total), with 168 cases of associated hemiplegia and no cases of spinal cord stroke. Based on this analysis, it was concluded that (1) brainstem compression is a rare complication of meningitis and (2) when brainstem compression/herniation occurs during hospitalisation and the condition is (presumably) diagnosed and treated rapidly, in 88.5% of cases there is no serious adverse outcome.

In order to evaluate the probability that the lumbar puncture was related to the brainstem herniation, the CR of 10.8 was converted to a PC of 91%, indicating that the most likely cause was the lumbar puncture. As a secondary conclusion, the defence theory that the spinal cord infarct was unpreventable given the presence of the brainstem compression was also rejected as unlikely.

Discussion

The three cases described in this article give a varied but limited view of the applicability of the methods described herein as a means of assessing indirect specific causation in medical malpractice actions. In all the three cases, causation was the primary contested issue, and in none of the cases was there a basis for a direct specific causal assessment. The medical experts on either side of the cases either opined regarding which of the possible causes they deemed to be most likely (both plaintiff and defence experts), or they opined that there was no way to know which of the possible causes was the most likely (only defence experts). Although in all the three cases the analysis supported the theory of causation put forth by the plaintiff (that the allegedly negligent conduct was the cause of the adverse outcome), the methods described herein are unrelated to the side (plaintiff or defendant) for which the analysis is performed, and thus the outcome of the analysis is, by design, non-partisan. If the underlying predictive facts of the case are accurately detailed, the confounding factors are identified and accounted for, and the data analysis is adequately matched to the relevant facts of the case, then the results of the indirect assessment of specific causation described herein should be the most accurate quantification of the true causal relationship between the alleged hazard and the adverse outcome available.

In these cases, and in the authors' experience generally, there is a lack of scrutiny regarding how causal assessments are made in medicolegal

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settings. Most often, they are simply given by medical experts as a personally held belief as to what seems most *likely* without any quantification of *how* likely. This approach is often referred to incorrectly as the 'differential diagnosis' approach to causation. The name is incorrect, as the medical expert is not differentiating between possible diagnoses to explain a set of signs and symptoms in a patient; rather, the expert is choosing between possible causes of a diagnosis based on an assessment of which cause presents the highest risk. If this practice sounds like an intuitive or speculative approach to the evaluation of CR described in this article, it is because that is precisely what it is. In all the three case studies presented herein, there were medical experts who opined on CR of cause based on either personal experience or their understanding of previously published epidemiologic study. The courts tend to allow such testimony without question, in part because there are no widely known alternatives, and also because causal determinations are most commonly made by the same clinicians who diagnosed the condition in question. The lack of a systematic approach to causal determinations in medicolegal settings serves as an invitation for speculation, and even abuse, given the financial incentives to medical experts who provide causation testimony in court.

A common theme in all the three cases described here is the fact that the analysis was performed on behalf of the injured party bringing suit, and the result of the analysis favoured the injured party. This should not be taken as a sign of a biased or unfair analysis, but rather representative bias in the selection process by which cases are accepted for analysis. In most instances, the initial impression of a demonstrable causal relationship gleaned from a summary of the case facts is born out by the subsequent analysis. Often, this is because of prior experience with similar fact patterns, or because the competing explanations are obviously quite remote. In cases in which the initial impression is that there is not likely to be a demonstrable causal relationship, there is typically no subsequent analysis. Thus, the cases that undergo a full analysis are also those cases most likely to result in a conclusion that is aligned with the interests of the party requesting the analysis. This is not always the case, however, and in cases with unique causation questions for which no prior analysis has been performed and no literature exists, the results of the analysis may be disappointing to the retaining party.

The concept of CR versus RR is one that is largely unique to a medicolegal application. CR consists of a comparison between two or more plausible causes that are known to be present in a specific case, whereas RR is a comparison between exposure and non-exposure. As a practical matter, common competing causes of injury can be eliminated from an investigation by the medical facts in a case, and it is solely the opposing theories of causation put forth by the plaintiff and defendant that require quantification and comparison. This exigency makes a CR evaluation a more pragmatic, economical and accurate approach to evaluating specific causation in a medicolegal setting than RR, in many circumstances.

It is worth noting that a causation assessment is accomplished via assessment of comparative, rather than absolute risk, and that the two are easily confused in a legal setting. As an example, in the second case study described above in which a manipulation of the cervical spine was closely followed in time by a vertebral artery dissection and stroke, the HR used for the CR assessment was 1 in 5,846,381. Thus, it is reasonable to conclude that if a patient is manipulated, it is very unlikely that he will suffer a stroke (i.e. the probability of stroke given a manipulation is low). This is not the causation question, however. 'What is the risk of a stroke associated with a manipulation?' is a different question than 'the patient had a stroke minutes after having a manipulation; what is the probability the manipulation was the cause of the stroke?' It is only by comparing the risk of the injury associated with the manipulation to the risk of the injury due to all other causes acting on the individual at the same point in time that the meaning of a 1 in 5.8 million risk of injury is given context for a causation assessment.

This is not to say that the indirect method of assessing specific causation described in this article is without potential error or weaknesses. The indirect evaluation of specific causation is Bayesian at its core; based on the modification or conditioning of probabilities with relevant evidence that is specific to the investigated case. Possible causes must be considered or rejected in an unbiased and fair manner. A failure to consider relevant and predictive evidence may result in a fatally flawed and incorrect causation analysis. Conversely, the judgement as to what is relevant and predictive in the analysis of a specific case is by its nature a subjective process, based on the experience and knowledge of the forensic epidemiologist. A basic understanding of the physiologic, therapeutic and pathologic processes at the centre of an alleged act of medical malpractice is crucial prior to embarking on an analysis of a general or specific causation.

Conclusion

Epidemiology is a science that is primarily directed at the investigation of effects in populations given known causes. FE, on the other hand, is focused on the investigation of the most probable cause given known

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effects and exposures in an individual. The principles are generally the same, but the applications are modified in order to meet the needs of a legal setting, which is what is the *most likely* cause.

Causation in cases of alleged medical malpractice is commonly disputed. In cases in which direct specific causation is not a viable alternative (i.e. the diagnosis can have multiple causes), the indirect evaluation of specific causation via the methods described in this article provides a reliable methodologic framework for the quantification of the PC suitable for presentation in a court of law.

Conflict of interests

All three authors provide consultation in medicolegal litigation.

Abbreviations list

AF, attributable fraction; BR, base risk; CR, comparative risk; CT, computed tomography; FE, forensic epidemiology; HP, hazard period; HR, hazard risk; NIS, Nationwide Inpatient Sample; PC, probability of causation; PTT, partial thromboplastin time; RR, relative risk; t-PA, tissue plasminogen activator.

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