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An Ethical Hierarchy for Decision Making During Medical Emergencies

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Abstract

Evidence from well designed clinical trials may guide clinicians, reduce regional variation, and lead to improved outcomes. Many physicians choose to ignore evidence-based practice guidelines. Using unproven therapies outside of a randomized trial slows recruitment into clinical trials that could yield information on clinical and economic efficacy. Using acute stroke therapy as an illustration, we present an ethical hierarchy for therapeutic decision making during medical emergencies. First, physicians should offer standard care. If no standard care option exists, the physician should consider enrollment into a randomized clinical trial. If no trial is appropriate, the physician should consider a non-randomized registry, or consensus based guidelines. Finally, only after considering the first three options, the physician should use best judgment based on previous personal experience and any published case series or anecdotes. Given the paucity of quality randomized clinical trial data for most medical decisions, the "best judgment" option will be used most frequently. Nevertheless, such a hierarchy is needed because of the limited time during medical emergencies for consideration of general principles of clinical decision making. There should be general agreement in advance as to the hierarchy to follow in selecting treatment for critically ill patients. Were more clinicians to follow this hierarchy, and choose to participate in clinical trials, the generation of new knowledge would accelerate, yielding rigorous data supporting or refuting the efficacy and safety of new interventions more quickly, thus benefiting far more patients over time.

Introduction

Practice guidelines based on evidence from well designed clinical trials may reduce regional variation and lead to improved outcomes[1]. Government agencies or for-profit companies may deny funding for new or novel care if no supportive evidence is yet available from ongoing clinical trials[2]. Physicians in practice continue to make medical decisions every day, sometimes with but often without the benefit of available evidence from the literature, and frequently without regard for the need to enroll patients in trials that will provide needed evidence. It is not clear what causes physicians to depart from or resist adoption of evidence-based practice guidelines, but the influence of non-medical factors could play a determinative role. In particular, the choice of appropriate care during medical emergencies is difficult, given the short time available to consider options; decision making plans should be in place before the emergency so that decisions are made quickly and without regard to non-medical considerations. Recently, acute therapy choices for many cardiovascular and cerebrovascular disorders may be driven by the availability of high-remuneration

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interventions.[3] Such decision making has led to slow recruitment into clinical trials due to competition for patients by alternative procedures.

The timely completion of randomized clinical trials can yield information on clinical and economic efficacy that guides all practitioners, benefits patients directly, and in many cases saves money for the health care system. Anecdotal cases and personal series are not regarded as definitive evidence for setting practice standards and health care policy[4]. Anecdotal evidence rarely yields the best care for patients, except in the case of truly gifted and experienced clinicians; such gifts do not generalize into widespread practice.

Using acute stroke therapy as an illustration, we present an ethical hierarchy for therapeutic decision making during medical emergencies. We contend that such a hierarchy is critical for three reasons. First, there is limited time during emergencies for debate or discussions among practitioners regarding ethical approaches to decision making. A plan should be debated and discussed prior to the emergent situation so that all practitioners are in agreement or at least in concurrence with the hierarchy. Second, it is important to clearly and quickly communicate the medical team's recommendations to the patient and surrogate decision makers. For this communication to be clear it is paramount to delineate a generally agreed upon hierarchy of therapeutic options so that the patient does not receive conflicting recommendations. Third, patients need to be informed that a clinical trial approved by the local Investigational Review Board may offer potential benefits to both the patient and society.

Case

A 41-year-old male presented with acute onset of mutism and left-sided hemiparesis. He lacked significant past medical or contributory family history, but his occupation, motorcycle mechanic, included significant bending and stretching of the neck. His wife noted symptoms to be maximal at onset and immediately called 911. Physical examination 80 minutes later included normal vital signs, no cardiac murmur; right gaze preference; left-sided homonymous hemianopsia, hemi-anesthesia, hemiplegia, hemi-neglect; and mutism for a total National Institutes of Health Stroke Scale (NIHSS) score of 17. Noncontrast CT images of the brain showed a hyperdense right middle cerebral artery and extensive early ischemic changes. All other laboratory findings were unremarkable and the patient received standard dose intravenous rt-PA 105 minutes after onset. One hour later, however, the patient did not improve and was approached for enrollment into the MR RESCUE protocol (Clinicaltrials.gov identifier NCT00389467). After full discussion of the risks and benefits, the wife consented on behalf of the patient, who then underwent urgent MRI and MRA imaging (Figure 1) that confirmed a significant ischemic lesion in the territory of the right middle cerebral artery distal to a non-visualized internal carotid artery. After randomization, the patient was taken to the neuro-interventional suite where a mechanical embolectomy was performed (Figure 2). The next day the patient showed significant improvement, with a total NIHSS of 7 for persistent left-sided weakness and dysarthria.

In approaching this case, we followed the ethical hierarchy used in our Stroke Center over the past 15 years (Table). In our opinion, patients should first be offered proven therapy based on sound, accepted evidence. If no standard care option applies, the patient should be offered the opportunity to participate in a randomized clinical trial. If no trial is available, or if the patient does not qualify for available trials, the next best option is to offer therapies as part of Phase 4 registries, or for which there exists a Human Device Exemption approval from FDA so that at least data are collected on such cases. Finally, only after exhausting all other options, the physician will use best judgment based on previous personal experience and any published case series or anecdotes. Given the paucity of quality randomized clinical

trial data for most medical decisions, the “best judgment” option will be used most frequently.

1. Standard Care

We contend that patients should generally be offered standard care that is buttressed by evidence and that has been accepted by the medical community, while recognizing that the term “standard of care” has different meanings in different contexts [5]. In legal settings the term “standard of care” would be defined differently from our intended meaning here. Solely for the purpose of this review, we consider therapy proven safe and beneficial in properly designed, randomized, controlled, blinded clinical trials with meaningful endpoints as the “standard” with the greatest likelihood of helping the patient. Critically, the patient should fit the sample chosen for study, that is, the clinician must be aware of the inclusion and exclusion criteria used in the trial. Trial results generalize most appropriately to patients who fit the study criteria most closely[6]. The beneficial effects of the therapy may also accrue to patients who do not fit, but the further away from the ideal study population an individual is, the lower the likelihood the patient will benefit (Figure 3).

Experienced clinicians often contend that intensive knowledge about an individual patient—a detailed history, physical, laboratory evaluation, and differential diagnosis—yields greater benefits to patients than knowledge of randomized clinical trials[7]. In other words, an experienced physician might trust his own instincts and judgment more than impersonal or aggregate data from randomized controlled clinical trials. We certainly agree that medical decision making must begin with detailed knowledge of a patient’s individual condition and that every physician must first attempt to find the very best treatment for the patient, “duty of personal care”[8]. We contend that ethical decision making then includes consideration of applicable evidence-based therapeutic recommendations for standard care. The clinician must judge whether or not the individual patient fits the applicable criteria in the evidence-based guideline. For example, in the case presented, the patient appeared to fit accepted criteria for the use of intravenous rt-PA, so this was given. There is evidence that patients with the hyperdense artery sign have a smaller treatment effect after IV t-PA.[9] While some practitioners routinely take such patients directly to intra-arterial intervention, we believe that the best action for this patient is to follow the ethical hierarchy and first give the accepted evidence based therapy. If a patient differs from the accepted guidelines, for example if he were of extreme age, then the likelihood of favorable response would be lower, though still relatively similar to the ideal study population (Figure 3). If the patient were even further dissimilar to the ideal study population, for example, if his symptoms began more than 6 hours prior to evaluation, then, as borne out by the published literature, his likelihood of favorable response would be significantly lower[10]. In these outlier situations, the standard of care would no longer apply because the patient is too dissimilar to the study population used in the RCT to define the standard of care. If standard of care does not apply, the ethical clinician should move on to the next level in the hierarchy.

As therapies are approved and move from investigational to standard care, the use of post-marketing registries is becoming a more common request by the FDA[11]. Clinicians should be encouraged to collect information on treatments that move into a post-marketing surveillance period in order to confirm safety and perhaps benefit in a broader public sector. One highly unethical use of registries has been criticized: some Phase 4 registries have paid clinicians at a rate well above true costs for using the preferred device or drug. We assert that such registries are not used for research but rather for marketing and are unethical[12]. Payments to physicians for participation in post-approval registries should be commensurate with the effort needed to collect the data, and sufficient to motivate physician participation without creating an inappropriate incentive to prescribe based solely on financial considerations.

Post-approval registries required by the European Medicines Agency (EMEA) after regulatory approval of alteplase for acute stroke in the European Union serve to illustrate the successful use of such registries.[13] As a condition of approval, all practitioners who used the drug were required to submit a small amount of data to a centralized database, the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST). The data included the time of stroke onset, CT scan result, time of thrombolysis, patient gender, pre-stroke modified Rankin score, presence of risk factors (hypertension, diabetes mellitus, smoking, etc), patient's stroke subtype, pretreatment NIHSS scores, and stroke etiology. Outcome measures included 24-hour post-treatment NIHSS, CT results at 24–48 hours, incidence of hemorrhagic complications, mortality, adverse events, and 3-month modified Rankin scores.

The purpose of SITS-MOST was to confirm the efficacy and safety of acute thrombolytic therapy in widespread use, i.e., beyond specialized centers that had participated in the randomized clinical trials. In fact, the use of alteplase for acute stroke proved safer and more effective in SITS-MOST than the active treatment groups of the pivotal randomized controlled clinical trials.[14–15]

2. Randomized Clinical Trials

The value of randomized controlled clinical trials is no longer questioned, but controversy remains about the proper role of trials, the ethical design of trials, and the definition of true "informed" consent[4, 6–7, 16–17]. For common diseases, the only valid approach to testing new therapy is the blinded, randomized, properly controlled and powered trial.

Most available data suggest that patients enrolled in trials may benefit, regardless of the treatment group into which they are randomized [18,19]. If there is improved outcome among control group patients, compared to natural history, this may reflect case ascertainment bias: trials require healthier patients. A case can be made, however, that placebo-treated patients receive greater monitoring and risk factor management leading to improved outcome. While improvements in health care delivery, including improved primary and preventive care, may erase some of this "clinical trial effect," for the moment we can assert that patients in trials receive more, and likely better, care than patients not in trials.

In addition to closer monitoring, clinical trial enrollment is the best option for the patient to receive new therapies. The organizers of clinical trials are required by regulation and ethics to remain aware of secular developments that could benefit enrolled patients, and to provide these benefits via protocol amendment during the course of the trial. In the extreme example, should the clinical trial terminate prematurely for showing benefit, trial participants are generally the first to receive that new treatment. For example, when the North American Symptomatic Carotid Endarterectomy Trial (NASCET) ended prematurely due to an overwhelming benefit in favor of carotid endarterectomy, trial organizers recommended contact and re-evaluation of all patients in the nonsurgical arm for possible surgery.[20]

Apart from direct benefit to the trial participants, the far-reaching value of randomized clinical trials is the expeditious evaluation of new therapies in a rigorous manner. There are numerous examples of therapies that "ought to work" but fail to show benefit in rigorous clinical trials. For example, in vascular neurology the concept of the salvageable penumbra has motivated many to urge early re-canalization based on imaging criteria thought to demonstrate the penumbra (Figure 4).[21] The mismatch between diminished perfusion and diffusion-weighted injury was assumed to represent salvageable brain. Clinical trials were organized to test this hypothesis, and one such trial, Magnetic Resonance and Recanalization of Stroke clots Using Embolectomy (MR-RESCUE), seeks to test directly if mismatch

indeed predicts improved likelihood of response to urgent recanalization. Unfortunately, many practitioners have assumed that the mismatch hypothesis is valid and are using perfusion data to make clinical decisions. Using mismatch or other similarly unvalidated imaging criteria to select cases, these practitioners recommend immediate recanalization using interventional therapies of uncertain benefit. We argue that an ethical hierarchical approach would direct such patients into randomized clinical trials such as MR-RESCUE until the mismatch hypothesis is either confirmed or refuted.

While the visual simplicity of mismatch is very appealing, at least one randomized clinical trial failed to confirm that mismatch validly predicts likelihood of response to a thrombolytic.[22] One possible explanation for this failure is that the visual approach to mismatch identification may be invalid.[21] Further work is needed to refine a truly valid mismatch algorithm before imaging can guide clinical decision making. We would argue that the clinicians who routinely assumed that the mismatch hypothesis was valid and proceeded to intervene with invasive procedures behaved unethically in two ways. First, without regard to the limitations of the image analysis technology, they selected therapy for patients using imaging data that have not been validated for such a purpose. Second, by selecting patients for intervention empirically, clinicians have delayed progress of the randomized controlled clinical trials needed to answer the questions rigorously. The time needed to complete careful, rigorous clinical trials is long in any event; treating patients with unproven therapies and denying them inclusion in a readily available clinical trial further delays the completion of the study that could yield true and valid data regarding the efficacy of the proposed intervention.

Recently, patients' obligation to participate in clinical trials has been justified using a "public good" argument[23]. We would extend the public good argument to include physicians. If local resources prevent trial participation, clinicians should at least consider arranging for referral of appropriate patients to other centers where pertinent trials are underway. Systems that are streamlined to intentionally bypass standard care and randomized clinical trials to move patients straight to empiric management are egregious examples of unethical medical decision making. Offering participation in a randomized clinical trial should be as much a part of routine clinical practice as prescribing approved medications or therapies. New systems designed to allow Emergency Medical Services to proactively transport patients to specialized centers (STEMI centers, trauma centers, stroke centers) will necessarily solve a portion of this problem. Since many patients present by private transportation to sites that do not have clinical trials, however, regulatory agencies should streamline the methods for obtaining consent and transferring patients to sites that do have clinical trials.

The choice to treat a patient with unapproved or untested empiric therapy (no matter how strongly the clinician believes in that therapy) exposes the patient to risks, provides no proven benefit, and eliminates the opportunity to enroll the patient into an available clinical trial. On an individual level, this choice guarantees one patient the consequences—benefit or harm—of that particular choice and deprives that patient of 1) closer monitoring associated with trial participation, 2) access to possible benefits of the modality under study, and 3) more rapid access to future improvements. On a societal level, however, this choice destroys any possibility of moving a therapy from an empiric, untested level to the standard care level, by delaying or blocking the randomized clinical trials needed to establish efficacy and safety rigorously. From the stand point creating a public good, such a choice is unethical[23]

3. Consensus-derived Practice Guidelines and Registries

Specialty medical societies regularly issue statements regarding accepted clinical practices. Depending on the level of underlying evidence, these statements may be labeled advisories,

parameters, or guidelines. Only those statements that are supported by the highest quality data, usually from randomized clinical controlled trials, are labeled guidelines, and the level of evidence is usually characterized by a grading system.[24] Frequently, however, a statement is based on a lesser level of evidence, and in this case the clinician should recognize the difference between a practice advisory or parameter compared to a guideline based on the best possible evidence. We contend that therapeutic recommendations based on published statements of consensus, advice, or practice parameters fall below standard care and randomized clinical trials in the ethical hierarchy (Table) because such recommendations neither are based on rigorous data nor do they generate data via a trial. A large number of therapeutic decisions made by clinicians will fall into this category owing to the absence of published data or ongoing trials. Nevertheless, we believe that clinicians have an ethical duty to attempt, first, to apply published standards of care, then to attempt to find a randomized trial for their patients, before applying published statements of consensus or advice.

In some instances a disease or condition is so rare that designing a clinical trial to determine the effectiveness of the treatment is not feasible. Device manufacturers can apply to the FDA for a humanitarian device exemption (HDE) when the disease affects less than 4,000 individuals in the United States annually. Similar to a clinical trial of an investigational device, facilities must seek IRB approval for humanitarian use devices (HUDs). Once a device is listed as a HUD, the device can be marketed solely for that purpose. In these very limited situations, and in the absence of care standards and germane trials, we agree the use of a HUD should be provided as a treatment option to patients.[25]

4. Empiric therapy or best judgment

The majority of patients will not fit the criteria for any of the first three tiers of the hierarchy. Here the clinician must draw on published anecdotes and case series, personal experience, and judgment[7]. We argue that tailored therapy should fall last in the ethical hierarchy for several reasons. First, not every clinician will have the needed background, experience, judgment or temperament for creating tailored treatments, especially in an emergency situation. For the majority of clinicians, in fact, following the ethical hierarchy we propose could likely yield more appropriate decision making. Second, it is critical to remember that clinical trial results and standard care must be applied ONLY to the extent a patient fits the criteria; the more the patient differs from the criteria, the lower the chance of benefit (Figure 3). The ethical hierarchy contains an implicit assumption that clinicians will NOT apply standard care to inappropriate patients, that is, clinicians should not thoughtlessly follow a “cookbook” approach to decision making. The careful and ethical physician would evaluate each individual patient in a specific context, following the hierarchy with thoughtful rigor, until an appropriate choice can be made for each patient uniquely.

Empiric therapy driven by best judgment often works. Few could argue the need for a randomized controlled trial of antibiotic treatment for bacterial pneumonia. We agree that some interventions are so successful that a randomized controlled trial would be senseless. We do argue, however, that proposed interventions appearing to be obviously successful number far fewer than one would assume reading the anecdotal literature. Further, we agree with those who argue that physicians have primary responsibility to their patient, before considering the needs of society or third parties such as payers or regulators [26]. Empiric or tailored therapy is last in the hierarchy precisely because the first three tiers hold more likelihood of benefit to the individual patient. In addition, adding more patients to clinical trials meets the larger needs of society, but for the reasons outlined above, we contend the first 3 tiers—and clinical trial enrollment specifically—are the most ethical choice for the individual patient.

The value of clear and effective diagnosis is beyond dispute, and is a necessary pre-condition to entering the ethical hierarchy for decision making. We respectfully differ from those who would argue that a proper diagnosis is sufficient to allow the skilled clinician to create a tailored therapy. Not only does the individual benefit when clinicians follow an ethical hierarchy for choosing therapy, but society as a whole benefits from the data collected by randomized clinical trials and registries. Were more clinicians to follow this hierarchy, and to participate in clinical trials, the generation of new knowledge would accelerate, yielding rigorous data supporting or refuting the efficacy and safety of new interventions more quickly, thus benefiting far more patients over time.

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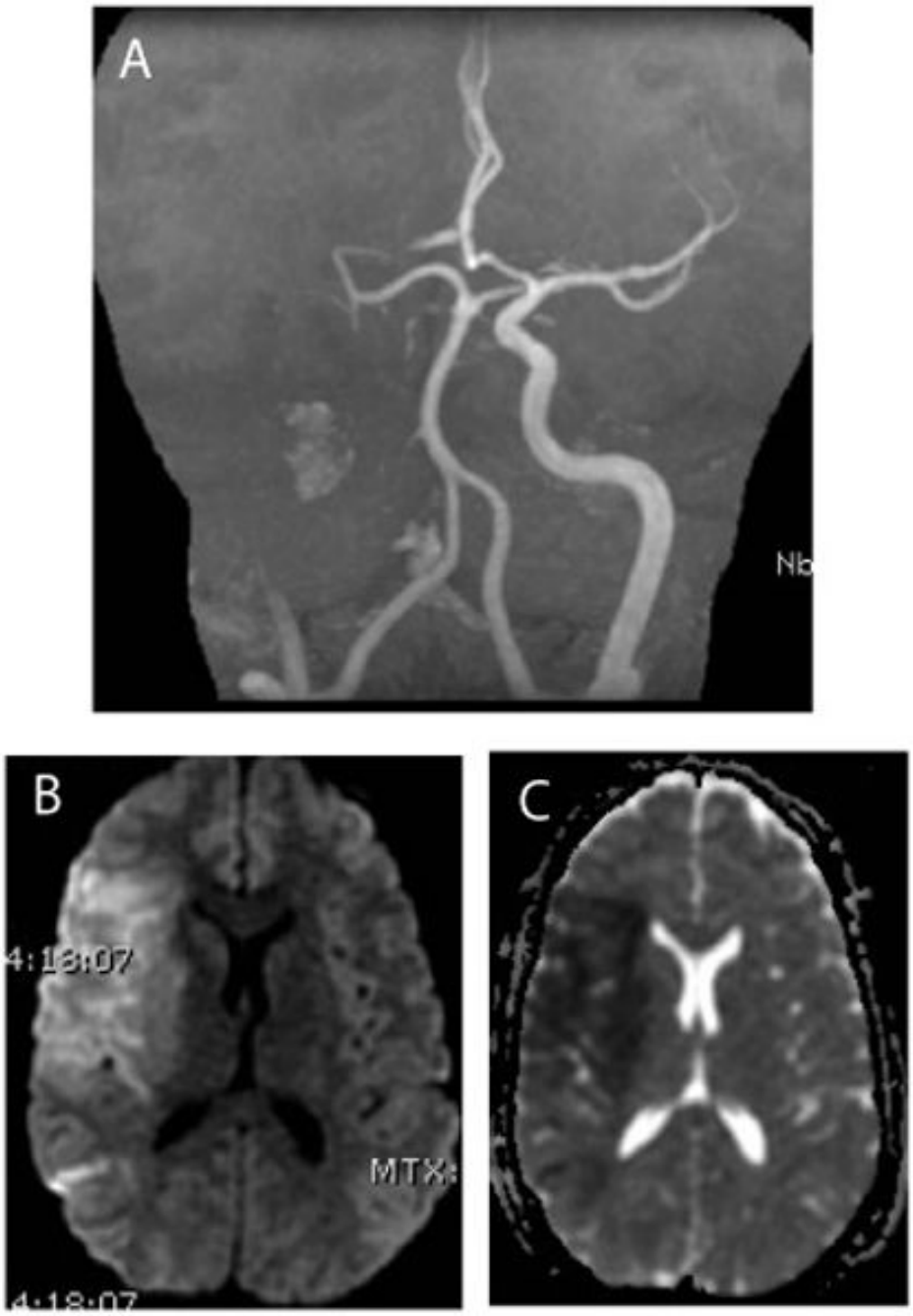

Figure 1. MRI and MRA Scans

Images were made 3.5 hours after symptom onset, and 1 hour after the completion of intravenous rt-PA therapy. In Panel A, the left internal carotid and middle cerebral arteries do not appear, consistent with occlusion. In Panel B, a diffusion-weighted image from a mid-parietal section, a large area of diffusion restriction is seen in the territory of the right middle cerebral artery. In Panel C, an Apparent Diffusion Coefficient image at the same level as in Panel C confirms that the diffusion restriction seen in Panel B is consistent with a very acute ischemic event.

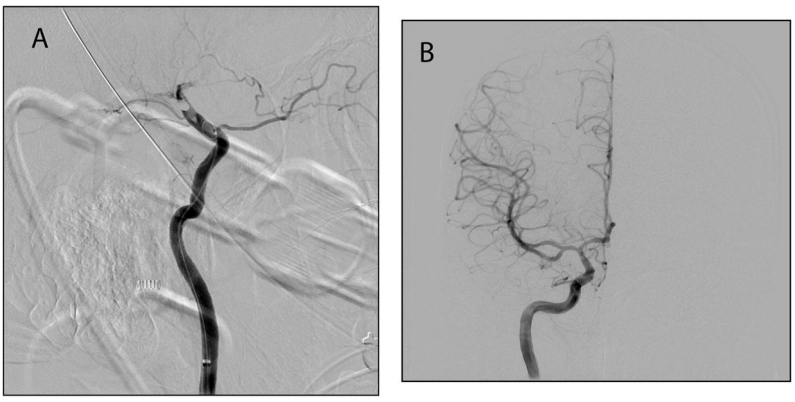

Figure 2. Intervention

Following intravenous rt-PA, the patient was studied with digital subtraction angiography. Panel A confirms that the right middle cerebral artery remains occluded at 7 hours following onset of symptoms. In Panel B,, successful recanalization of the middle cerebral artery is demonstrated, although reperfusion is not complete in the microcirculation.

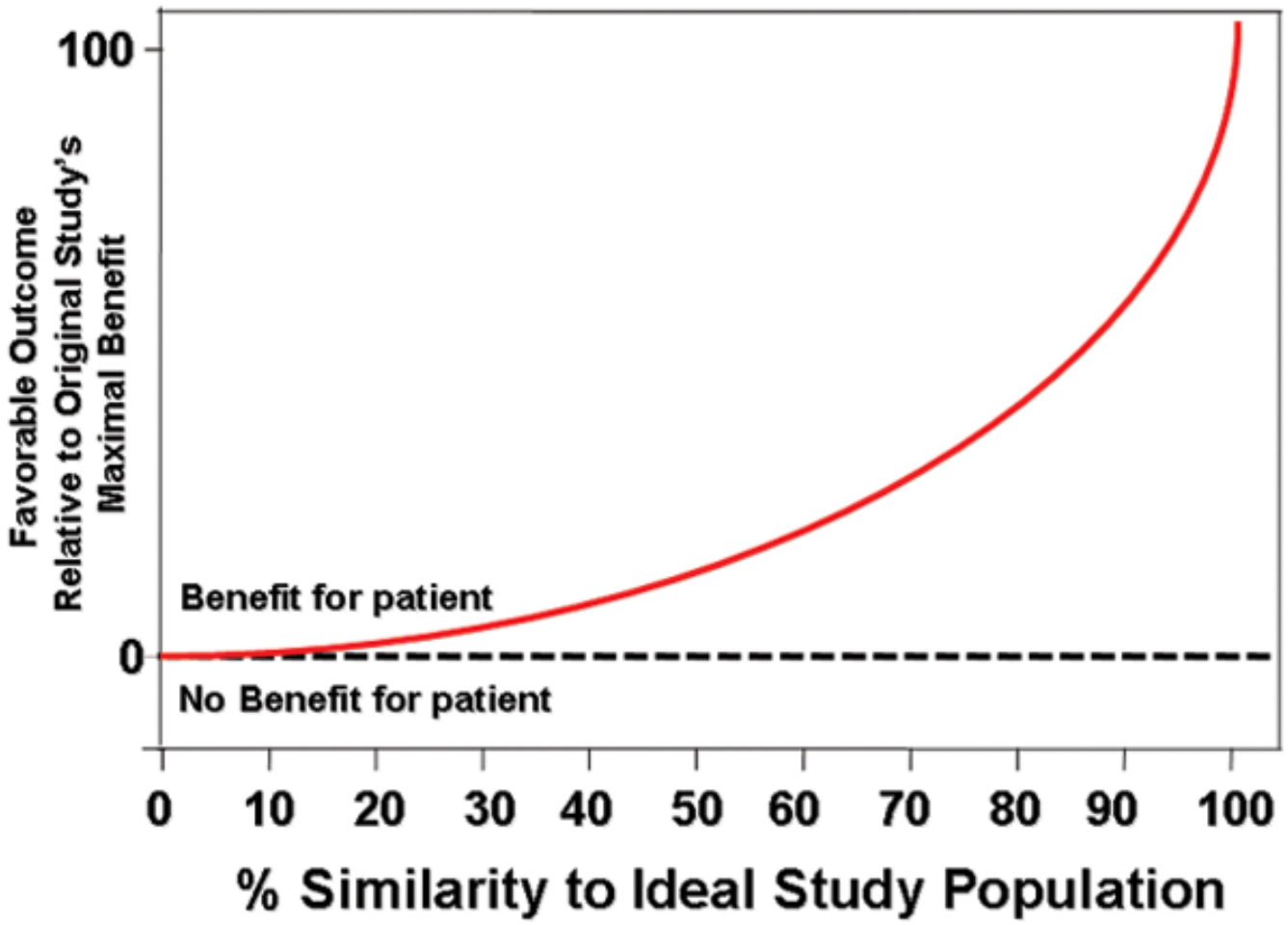

Figure 3. Hypothetical Scheme for Applying Clinical Trial Data to Individual Patients

The curve is a speculative representation of the relationship between study criteria and the individual patient. Conceptually, the further the patient is from the sample population contained in the clinical trial, the lower the likelihood of benefit.

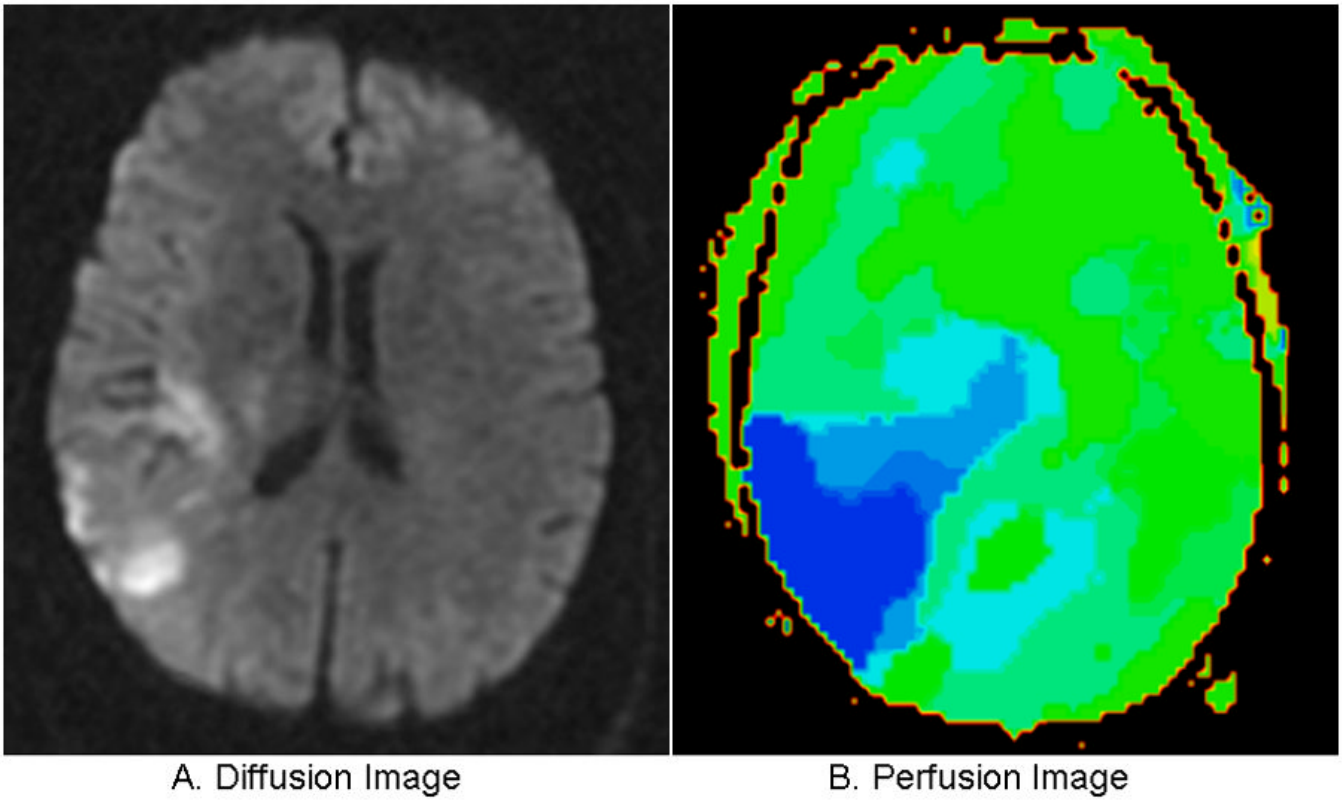

Figure 4. Example of Diffusion-Perfusion Mismatch

In Panel A, there are multiple areas of restricted water diffusion, interpreted as small regions of irreversible injury. In Panel B, a perfusion image shows an area of diminished perfusion much larger than the area of diffusion restriction. The hypothesis to be tested is that the brain with reduced perfusion showing minimal diffusion restriction remains salvageable. To date, the mismatch hypothesis has not been proven conclusively.

Table

Ethical Hierarchy for Decision Making during Medical Emergencies

Step 1 includes standard therapy supported by evidence, preferably from randomized controlled clinical trials. Also included in this category would be recommendations from specialty practice societies supported by top-level evidence. Step 2 involves enrollment into randomized controlled clinical trials. Such trials should be registered, including an approval from a regulatory agency such as FDA or EMEA; should include proper blinding and randomization; and should be properly powered. Step 3 includes published consensus statement from specialty clinical societies, and enrollment into registries. Step 4 includes “best judgment” therapy devised empirically and tailored to the individual patient.

1.	Standard Care
2.	Randomized Clinical Trials
3.	Consensus Statements/Registries
4.	Empiric Therapy/Best Judgment