

Review

Rational use of computerized protocols in the intensive care unit

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Abstract

Excess information in complex ICU environments exceeds human decision making limits, increasing the likelihood of clinical errors. Explicit decision-support tools have favorable effects on clinician and patient outcomes and can reduce the variation in clinical practice that persists even when guidelines based on reputable evidence are available. Computerized protocols used for complex clinical problems generate, at the point-of-care, patient-specific evidence-based therapy instructions that can be carried out by different clinicians with almost no inter-clinician variability. Individualization of patient therapy is preserved by these explicit protocols since they are driven by patient data. Computerized protocols that aid ICU decision-makers should be more widely distributed.

Keywords decision-support, intensive care, protocols, research, safety

Critical care decision-support tools can focus on diagnostic [1], administrative [2], or therapeutic needs. Decision-support tools have been functionally categorized as 'reminders,' 'consultants,' or 'educational' [3]. These three categories do not embrace the intensive care unit (ICU) treatment management or titration protocols used to apply explicit methods of mechanical ventilation [4-6] and fluid and hemodynamic support [7,8] in patients with acute lung injury or acute respiratory distress syndrome (ARDS). In this review I focus on these management or titration protocols and consider several rationales for the use of such explicit detailed computerized protocols in the ICU. I discuss the features of computerized ICU protocols that distinguish them from other decision-support tools such as guidelines, paper protocols, and clinical or nursing or critical paths. These protocols complement, but do not replace, the ICU decision-maker.

Varieties of decision-support tools

Thousands of decision-support tools with different names, foci, and outputs are available but they often lack specific instructions for many of the situations encountered in clinical practice [9]. Most are useful only in a conceptual sense [10-16]. They neither standardize clinical decisions nor lead to a uniform implementation of clinical interventions, although

standardization and uniformity are their goals [14,16,17]. For example, it would be difficult to reduce variability with a protocol that required the clinician to determine whether the patient 'looked septic,' unless the state 'looked septic' were explicitly defined. Computerized protocols used for complex clinical problems can contain much more detail than is possible with textual guidelines or with paper-based flow diagrams [16]. The increased detail allows the generation, at the point of care, of patient-specific therapy instructions that can be performed by different clinicians with almost no inter-clinician variability [18]. This can make both formal clinical inquiries (for example, randomized trials) and informal clinical inquiries (for example, some continuous quality improvement efforts, or clinical practice evaluations) more robust [9,18].

Reducing clinician variability might seem to challenge the importance that clinicians assign to individualized (patient-specific) therapy. Unexpectedly, individualization of patient therapy is preserved when clinical decisions are standardized with explicit, detailed, patient-data-driven, computerized protocols [9,19]. An essential element in achieving this unexpected result is the use of patient data (that is, the patient's unique expression of the disease) to drive the decision-support tool (protocol) rules. Unlike these specific patient-

data-driven explicit methods [4,5,20–25], time-driven decision-support tools (for example a clinical path that requires discharge of the patient after 3 days of care) raise legitimate concerns about patient-invariant ('cookbook') care. Individualizing patient care while standardizing clinical decisions with an explicit method is, in my opinion, one of the most attractive attributes of the point-of-care use of computerized protocols.

Why is there need for protocols in the ICU?

Clinical error rates are common (about 1–50%) [26–53]. This is an expression of the general problem: that human error and injury are unavoidable [27,35,54,55]. Even when ICU errors represent only 1% of clinical decisions [53] and therefore indicate little room for personal improvement (in that 99% of decisions are correct), clinical ICU errors and injuries that threaten patient safety occur with distressing frequency [44,53].

Variation in clinical practice persists even when guidelines based on reputable evidence are available [28,29], and patients can be harmed when clinicians do not comply with standard practice [9,30,31]. Widespread distribution of evidence-based guidelines [35,36] and education programs [24,37–40] has had only a limited effect on low compliance by clinicians. Variability is fostered by incorrect perceptions. The perceptions of physicians in their use of physiological data and the actual use of such data in decision-making for cardiac problems in the ICU are internally inconsistent (within-decision-maker inconsistency) [56]. This is in part due to the use of ill-defined terms or statements such as '...caution should be exercised when PAOP [pulmonary artery occlusion pressure] becomes increased to the extent that pulmonary edema is a risk' [57]. This particular inconsistency appeared in a journal issue containing three articles that presented mutually contradictory sets of recommendations about hemodynamic monitoring (between-decision-maker inconsistency) [58].

Variation in practices with ICU fluids and electrolytes illustrates the confusion propagated by the imprecise use of words and concepts in medicine. An analytical scheme addressing three major factors in fluid and electrolyte evaluation (1, effectiveness of the arterial circulation; 2, extracellular fluid volume [ECF]; and 3, state of hydration [59]) is compatible with widely taught precepts [60–67]. Evaluating these three concepts separately is important for clarifying problems with fluids and electrolytes and thereby for reducing unnecessary variation. Use of fluid and electrolyte terms in a nonstandardized manner leads to confusion. An American Medical Association Council report cites isotonic, hypertonic, and hypotonic dehydration, thereby confusing the evaluation of the state of the ECF and the state of hydration [68]. Cardiovascular evaluation is also (inappropriately) included in the evaluation of hydration, thereby confusing the evaluation of the effectiveness of the arterial circulation (cardiovascular evaluation) with the evaluation of the state of hydration. Hypernatremic dehydration (a tautology if standard definitions

are used) was used to describe both dehydration (hypernatremia) and ECF contraction [69]. For patients with traumatic brain injury, dehydration was used in two contradictory ways [70]. First, the authors *recommended inducing dehydration* with mannitol (producing dehydration or underhydration according to the standard terminology) because it was *effective* in reducing intracranial pressure. They then *recommended avoiding dehydration* with diuretics (producing ECF contraction due to negative fluid balance) because it was *ineffective* in reducing intracranial pressure [70]. The use and the teaching of terms in such contradictory ways probably contribute to the uncertainty surrounding fluid and electrolyte therapy for sepsis [71], shock [72–74] and ARDS [75]. Fluid and electrolyte therapy is an important and uncontrolled co-intervention that can influence patient outcome and obscure the effects of therapeutic interventions in clinical trials.

Protocols enhance efficiency, safety, and efficacy of care

Efficiency is the term assigned to the evaluation of resource consumption for a clinical intervention accepted as part of routine practice. At the individual patient level, standardization enhances efficiency by making the clinical plan explicit to all providers dealing with that patient. Nurses, therapist, and physicians thereby achieve a level of uniformity of approach and goals for the specific patient. This reduces within-patient variability of decision-making. However, this does not reduce unnecessary variation between patients and between physicians. Standardized clinical decisions are important at several levels within the healthcare delivery system.

Human decision-making limitations, perceptual inaccuracies, and variation in the use and in the interpretation of important clinical variables all make clinicians unable to consistently generate therapeutic decisions that are coherent, that consider all appropriate options, and that are based on the relevant scientific evidence [27,34,35,43,44,46,76–79]. For example, adverse drug events are common, costly, and largely preventable causes of excess morbidity and mortality in ICU patients [25,80–82]. Estimates of the annual national cost of adverse drug events in the USA run as high as US \$79 billion to US \$136 billion [25,83]. Unfortunately, adverse drug events are generally undetected. Traditional screening for in-hospital adverse drug events detects only 1% and voluntary reporting only 12% of the adverse drug events detected by automated computerized screening of an integrated electronic clinical database [84].

Even when the healthcare community understands the proper approach, compliance of physicians with evidence-based treatments or guidelines is low across a broad range of healthcare topics [20,85–89]. Patient [90] and hospital [91] compliance is approximately as low. Only about 50% of patients with chronic diseases receive effective delivery of their therapy [90]. Like low compliance by clinicians, this seems to be a feature of our human condition. In contrast,

both paper-based and computerized decision-support tools that provide explicit, point-of-care (point-of-decision-making) instructions to clinicians have overcome many problems and have achieved clinician compliance rates of 90–95% [5,19,92]. However, the absence of requisite infrastructure in the ICU environment is an important obstacle to the adoption of clinical decision-support tools such as those demonstrated to produce a favorable clinical outcome in a multicenter randomized clinical trial [5,6].

Protocols enable rigorous clinical research

Modern medicine has fostered the development of undoubted advances. In spite of these and other obvious benefits, only a small fraction of current clinical practice has been shown to produce more good than harm [18,32–34]. Some important problems in critical care have long resisted resolution. While our understanding of underlying mechanisms of injury and inflammation in sepsis and ARDS has blossomed, our understanding of clinical management of sepsis and ARDS has not. Several clinical trials of promising therapeutic agents have consistently failed to identify the promised advances in therapy [21,93–98]. The absence of a clear benefit from this broad spectrum of tested interventions suggests that the clinical problems are insoluble and cannot be improved, or that the needed interventions have not yet been tested, or that our clinical investigative strategy is not sound. We have all been encouraged by recent advances in the treatment of patients needing mechanical ventilation [92] and those with sepsis [99], but our success rate with clinical trials that produce important clinical advances is disappointingly low.

Standardization of clinical decisions is needed not only for clinical practice but also for rigorous clinical research [49]. Many interventions of clinical value have relatively small effects, with odds ratios of 3.0 or less [50]. Systematically conducted clinical trials are necessary for these small effects to be recognized and for ineffective clinical care elements to be identified [50,51]. However, without explicit methods the fundamental scientific requirement of replicability of results [48,49] cannot be achieved. An explicit method, driven by patient data, contains enough detail to generate specific instructions (patient-specific orders) without requiring judgments by a clinician. Any form of guideline or protocol can theoretically contain enough detail to constitute an explicit method. In practice, however, paper-based versions of any protocols except the simplest (for example, vaccination schedules or treatment of hypokalemia in a patient receiving digitalis and diuretics) cannot be made explicit and therefore remain dependent on the judgment of a clinician.

Protocols enhance education

If explicit computerized protocols lead clinical trainees to abandon critical thinking, they might contribute to the production of clinicians less prepared for the rigorous intellectual challenge of healthcare delivery. For those afraid of demeaning the clinical training of students and house officers, I

respond that an explicit method, when used wisely, can be an effective tool for teaching students the principles both of decision-making and of clinical practice. Unlike much traditional clinical teaching, explicit decision-support tools articulate both the variables considered and the decision rules. In an environment dedicated to training, explicit methods can be an asset. In an environment that pays little heed to training, they could be a disadvantage. Like any tool, guidelines can be misused. Finally, many physicians are concerned about a reduction of their role in medical practice and of the potential disenchantment of physicians with medicine that could follow the widespread mandatory use of guidelines and protocols [15]. Standardization might be perceived as an attack on clinicians' assumption that they possess special and ineffable wisdom in clinical matters and on its corollary that patients receive the best outcome when physicians independently use their best clinical judgment [100,101]. It is this belief, namely that expert ICU physicians possess special and ineffable wisdom, that interferes with the education of young physicians, by avoiding the challenge of articulating precisely how decisions should be made.

Summary

The excess information in complex ICU environments exceeds human decision-making limits, increasing the likelihood of clinical errors. Explicit decision-support tools have favorable effects on the clinician and on patient outcomes. They have been implemented in diverse clinical environments and have been successfully transferred and used in geographically dispersed ICUs that were not involved in their initial development. However, various human factors and the paucity of distributed electronic clinical databases impede the widespread distribution of clinical decision-support tools. Notwithstanding these challenges, the documented benefit of the application of decision-support tools in the ICU and the rapid expansion of electronic ICU databases promise an increasingly favorable environment for the development, implementation, and use of computerized protocols to aid clinical decision-makers in the ICU.

Competing interests

None declared.

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References

- Squara P, Journois D, Formela JF, Schremmer B, Dhainaut JF, Bleichner G: **Value of elementary, combined, and modeled hemodynamic variables.** *J Crit Care* 1994, **9**:223-235.
- Berenholtz S, Pronovost P, Lipsett P, Dawson P, Dorman T: **Assessing the effectiveness of critical pathways on reducing resource utilization in the surgical intensive care unit.** *Intensive Care Med* 2001, **27**:1029-1036.
- Miller R, Goodman K: **Ethical challenges in the use of decision-support software in clinical practice.** In *Ethics, Computing, and Medicine: Informatics and the Transformation of Health Care*. Edited by Goodman K. Cambridge, UK: Cambridge University Press; 1998:102-115.
- East TD, Böhm SH, Wallace CJ, Clemmer TP, Weaver LK, Orme JF, Jr, Morris AH: **A successful computerized protocol for clinical management of pressure control inverse ratio ventilation in ARDS patients.** *Chest* 1992, **101**:697-710.
- East T, Heermann L, Bradshaw R, Lugo A, Sailors R, Ershler L, Wallace C, Morris A, McKinley G, Marquez A, Tonnesen A, Parmley L, Shoemaker W, Meade P, Taut P, Hill T, Young M, Baughman J, Olterman M, Goode V, Quinn J, Summer W, Valentine V, Carlson J, Bonnell B, deBoisblanc B, McClarity Z, Cachere J, Kovitz K, Gallagher E, Pinsky M, Angus D, Cohen J, Hudson L, Steinberg K: **Efficacy of computerized decision support for mechanical ventilation: results of a prospective multi-center randomized trial.** *Proc AMIA Symp.* 1999:251-255.
- McKinley BA, Moore FA, Sailors RM, Cocanour CS, Marquez A, Wright RK, Tonnesen AS, Wallace CJ, Morris AH, East TD: **Computerized decision support for mechanical ventilation of trauma induced ARDS: results of a randomized clinical trial.** *J Trauma* 2001, **50**:415-424; discussion 425.
- Morris A: **Evaluating and refining a hemodynamic protocol for use in a multicenter ARDS clinical trial [abstract].** *Am J Resp Crit Care Med* (ATS Proceedings Abstracts) 2000, **161**:A378.
- East T, Morris A: **A report instrument for refining computerized protocols [abstract].** *Am J Resp Crit Care Med* (ATS Proceedings Abstracts) 2001, **163**:A259.
- Morris A: **Algorithm-based decision making.** In *Principles and Practice of Intensive Care Monitoring*. Edited by Tobin M. New York: McGraw-Hill, Inc.; 1998:1355-1381.
- Audet A-M, Greenfield S, Field M: **Medical practice guidelines: current activities and future directions.** *Ann Intern Med* 1990, **113**:709-714.
- Fletcher R, Fletcher S: **Clinical practice guidelines.** *Ann Intern Med* 1990, **113**:645-646.
- Hadorn D, McCormick K, Diokno A: **An annotated algorithm approach to clinical guideline development.** *JAMA* 1992, **267**:3311-3314.
- Miller P, Frawly S: **Trade-offs in producing patient-specific recommendations from a computer-based clinical guideline: a case study.** *J Am Med Informatics Assoc* 1995, **2**:238-242.
- Fridsma D, Gennari J, Musen M: **Making generic guidelines site-specific.** In *Proceedings of the 1996 AMIA Annual Fall Symposium*. Edited by Cimino J. Washington, DC: Hanley & Belfus, Inc.; 1996:597-601.
- Tierney WM, Overhage JM, McDonald CJ: **Computerizing guidelines: factors for success.** In *Proceedings 1996 AMIA Annual Fall Symposium*. Edited by Cimino J. Washington, DC: Hanley & Belfus, Inc.; 1996:459-462.
- Tierney WM, Overhage JM, Takesue BY, Harris LE, Murray MD, Vargo DL, McDonald CJ: **Computerizing guidelines to improve care and patient outcomes: the example of heart failure.** *J Am Med Informatics Assoc* 1995, **2**:316-322.
- Field M, Lohr K (Eds): **Clinical practice guidelines: directions for a new program (summary).** Washington, DC: National Academy Press; 1990.
- Morris A, Cook D: **Mechanical ventilation clinical trial issues.** In *Physiologic Basis of Ventilatory Support*. Edited by Marini J, Slutsky A. New York: Marcel Dekker, Inc.; 1998:1359-1398.
- Morris A: **Developing and implementing computerized protocols for standardization of clinical decisions.** *Ann Intern Med* 2000, **132**:373-383.
- Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF Jr, Lloyd JF, Burke JP: **A computer-assisted management program for antibiotics and other anti-infective agents.** *N Engl J Med* 1998, **338**:232-238.
- Morris A, Wallace C, Menlove R, Clemmer T, Orme JJ, Weaver L, Dean N, Thomas F, East T, Suchyta M, Beck E, Bombino M, Sittig D, Böhm S, Hoffmann B, Becks H, Pace N, Butler S, Pearl J, Rasmussen B: **Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for ARDS.** *Am J Respir Crit Care Med* 1994, **149**:295-305. (Erratum, 1994, **149**:838.)
- East T: **Role of the computer in the delivery of mechanical ventilation.** In *Principles and Practice of Mechanical Ventilation*. Edited by Tobin M. New York: McGraw-Hill, Inc.; 1994:1005-1038.
- Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP: **The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection.** *N Engl J Med* 1992, **326**:281-286.
- Pestotnik S, Classen D, Evans R, Burke J: **Implementing antibiotic practice guidelines through computer-assisted decision support: clinical and financial outcomes.** *Ann Intern Med* 1996, **124**:884-890.
- Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP: **Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality.** *JAMA* 1997, **277**:301-306.
- Williamson J, Goldschmidt P, Jillson I: *Medical Practice Information Demonstration Project—Final Report (Contract #282-77-0068GS)*. Baltimore, MD: Office of the Assistant Secretary of Health, DHEW; 1979.
- Abramson NS, Wald KS, Grenvik ANA, Robinson D, Snyder JV: **Adverse occurrences in intensive care units.** *JAMA* 1980, **244**:1582-1584.
- McDonald CJ, Wilson GA, McCabe G Jr: **Physician response to computer reminders.** *JAMA* 1980, **244**:1579-1581.
- West J: **An autopsy method for evaluating trauma care.** *J Trauma* 1981, **21**:32-34.
- Morris AH, Chapman RH, Gardner RM: **Frequency of technical problems encountered in the measurement of pulmonary artery wedge pressure.** *Crit Care Med* 1984, **12**:164-170.
- Morris AH: **Elimination of pulmonary wedge pressure errors commonly encountered in the ICU.** *Cardiologia (Italy)* 1985, **30**:941-943.
- Browner W, Newman T: **The analogy between diagnostic tests and clinical research.** *JAMA* 1987, **257**:2459-2463.
- Physicians ACo: **Working conditions and supervision for residents in internal medicine programs: recommendations.** *Ann Intern Med* 1989, **110**:657-663.
- Iberty T, Fischer E, Leibowitz M, Panacek E, Silverstein J, Albertson T, Group PACS: **A multicenter study of physician's knowledge of the pulmonary artery catheter.** *JAMA* 1990, **264**:2928-2932.
- Wu A, Folkman S, McPhee S, Lo B: **Do house officers learn from their mistakes?** *JAMA* 1991, **265**:2089-2094.
- Brook R: **Using scientific information to improve quality of health care.** In *Doing More Good than Harm: the Evaluation of Health Care Interventions*. Edited by Warren K, Mosteller F. New York: The New York Academy of Sciences; 1993:74-85.
- Chalmers T, Lau J: **Randomized controlled trials and meta-analyses in gastroenterology: major achievements and future potential.** In *Doing More Good than Harm: the Evaluation of Health Care Interventions*. Edited by Warren K, Mosteller F. New York: The New York Academy of Sciences; 1993:96-106.
- Chan L, Schonfeld N: **How much information is lost during processing: a case study of emergency department records.** *Comput Biomed Res* 1993, **26**:582-591.
- McNeil B: **Use of claims data to monitor patients over time: acute myocardial infarction as a case study.** In *Doing More Good than Harm: the Evaluation of Health Care Interventions*. Edited by Warren K, Mosteller F. New York: The New York Academy of Sciences; 1993:63-73.
- O'Connor G, Plume S, Wennberg J: **Regional organization for outcomes research.** In *Doing More Good than Harm: the Evaluation of Health Care Interventions*. Edited by Warren K, Mosteller F. New York: The New York Academy of Sciences; 1993:44-51.
- Warren K, Mosteller F (Ed): *Doing More Good than Harm: the Evaluation of Health Care Interventions*. New York: The New York Academy of Sciences; 1993.
- Wennberg J, Barry M, Fowler F, Mulley A: **Outcomes research, PORTS, and health care reform.** In *Doing More Good than Harm: the Evaluation of Health Care Interventions*. Edited by

- Warren K, Mosteller F. New York: The New York Academy of Sciences; 1993:52-62.
43. Iberti TJ, Daily EK, Leibowitz AB, Schechter CB, Fischer EP, Silverstein JH: **Assessment of critical care nurses' knowledge of the pulmonary artery catheter. The Pulmonary Artery Catheter Study Group.** *Crit Care Med* 1994, **22**:1674-1678.
 44. Leape L: **Error in medicine.** *JAMA* 1994, **272**:1851-1857.
 45. Tyson NdG: **Signal versus noise.** *Nat Hist* 1996, **105**:72-76.
 46. Gnaegi A, Feihl F, Perret C: **Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act?** *Crit Care Med* 1997, **25**:213-220.
 47. Schulz E, Barrett J, Price C: **Read Code quality assurance: from simple syntax to semantic stability.** *J Am Med Inform Assoc* 1998, **5**:337-346.
 48. Sudeep N, Anuradha L, Obasanjo O, Chaisson R: **Errors in the treatment of tuberculosis in Baltimore.** *Chest* 2000, **117**:734-737.
 49. Palevsky PM, Bhagrath R, Greenberg A: **Hypernatremia in hospitalized patients.** *Ann Intern Med* 1996, **124**:197-203.
 50. Kohn L, Corrigan J, Donaldson M (Ed): *To Err is Human—Building a Safer Health System.* Washington, DC: National Academy Press; 1999.
 51. Nakhleh RE, Zarbo RJ: **Amended reports in surgical pathology and implications for diagnostic error detection and avoidance: a College of American Pathologists Q-probes study of 1,667,547 accessioned cases in 359 laboratories.** *Arch Pathol Lab Med* 1998, **122**:303-309.
 52. Krizek TJ: **Surgical error: ethical issues of adverse events.** *Arch Surg* 2000, **135**:1359-1366.
 53. Gopher D, Olin M, Badihi Y, Cohen G, Donchin Y, Sieski M, Cotev S: **The nature and causes of human errors in a medical intensive care unit.** In *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 1989:956-960.
 54. Reason J: *Human Error.* Cambridge, UK: Cambridge University Press; 1990.
 55. Reason J: **Human error: models and management.** *Br Med J* 2000, **320**:768-770.
 56. Ontario Intensive Care Study Group: **Evaluation of right heart catheterization in critically ill patients.** *Crit Care Med* 1992, **20**:928-933.
 57. Guidelines Committee Society of Critical Care Medicine: **Guidelines for the care of patients with hemodynamic instability associated with sepsis.** *Crit Care Med* 1992, **20**:1057-1059.
 58. Morris A: **Hemodynamic guidelines.** *Crit Care Med* 1993, **21**:1096.
 59. Palevsky P, Bhagrath R, Greenberg A: **Hypernatremia in hospitalized patients.** *Ann Intern Med* 1996, **124**:197-203.
 60. Feig P, McCurdy D: **The hypertonic state.** *N Engl J Med* 1977, **297**:1444-1454.
 61. Windus D: **Fluids and electrolyte management.** In *Manual of Medical Therapeutics*, edn 25. Edited by Orland M, Saltman R. Boston: Little, Brown and Company; 1986:40-56.
 62. Levinsky N: **Fluids and electrolytes.** In *Harrison's Principles of Internal Medicine*, edn 12. Edited by Wilson J, Braunwald E, Isselbacher K, Petersdorf R, Martin J, Fauci A, Root R. New York: McGraw-Hill, Inc.; 1991:278-283.
 63. DeVita M, Michelis M: **Perturbations in sodium balance.** *Clin Lab Med* 1993, **13**:135-148.
 64. Rose B: *Clinical physiology of Acid-Base and electrolyte disorders*, edn 4. New York: McGraw-Hill, Inc.; 1994.
 65. Mange K, Matsuura D, Cizman B, Soto H, Ziyadeh FN, Goldfarb S, Neilson EG: **Language guiding therapy: the case of dehydration versus volume depletion.** *Ann Intern Med* 1997, **197**:848-852.
 66. Vanatta J, Fogelman M: *Moyer's Fluid Balance—a Clinical Manual*, edn 4. Chicago: Year Book Medical Publishers, Inc.; 1988.
 67. Weaver L, Hopkins R, Churchill S, Chan K, Morris AH, Clemmer T, Elliott C, Orme J, Thomas F, Haberstock D: **Outcome of acute carbon monoxide poisoning treated with hyperbaric or normobaric oxygen (double-blind) [abstract].** *Am J Resp Crit Care Med* (ATS Proceedings Abstracts) 2001, **163**:A16.
 68. Weinberg A, Minaker K: **Dehydration.** Evaluation and management in older adults. *JAMA* 1995, **274**:1552-1556.
 69. Chilton L: **Prevention and management of hypernatremic dehydration in breast-fed infants.** *West J Med* 1995, **163**:74-76.
 70. Zornow M, Prough D: **Fluid management in patients with traumatic brain injury.** *New Horizons* 1995, **3**:488-498.
 71. Thijs L: **Fluid therapy in septic shock.** In *Clinical Trials for the Treatment of Sepsis.* Edited by Sibbald W, Vincent J-L. Berlin: Springer-Verlag; 1995:167-190.
 72. Shoemaker W, Appel P, Kram H: **Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients.** *Chest* 1988, **94**:1176-1186.
 73. Tuchschildt J, Fried J, Astiz M, Rackow E: **Supranormal oxygen delivery improves mortality in septic shock patients.** *Crit Care Med* 1991, **19**:S66.
 74. Shoemaker W, Appel P, Kram H, Bishop M, Abraham E: **Temporal hemodynamic and oxygen transport patterns in medical patients: septic shock.** *Chest* 1993, **104**:1529-1536.
 75. Mitchell J, Schuller D, Calandrino F, Schuster D: **Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization.** *Am Rev Resp Dis* 1992, **145**:990-998.
 76. Tversky A, Kahneman D: **Availability: A heuristic for judging frequency and probability.** In *Judgment Under Uncertainty: Heuristics and Biases.* Edited by Kahneman D, Slovic P, Tversky A. Cambridge, UK: Cambridge University Press; 1982:163-178.
 77. Jennings D, Amabile T, Ross L: **Informal covariation assessment: data-based versus theory-based judgments.** In *Judgment Under Uncertainty: Heuristics and Biases.* Edited by Kahneman D, Slovic P, Tversky A. Cambridge, UK: Cambridge University Press; 1982:211-230.
 78. McDonald CJ: **Protocol-based computer reminders, the quality of care and the non-perfectability of man.** *N Engl J Med* 1976, **295**:1351-1355.
 79. Pocock SJ: *Clinical Trials: A Practical Approach.* New York, NY: John Wiley & Sons; 1983.
 80. Avorn J: **Putting adverse drug events into perspective (Editorial).** *JAMA* 1997, **277**:341-342.
 81. Bates D, Spell N, Cullen D, et al: **The costs of adverse drug events in hospitalized patients.** *JAMA* 1997, **277**:307-311.
 82. Lesar T, Briceland L, Stein D: **Factors related to error in medication prescribing.** *JAMA* 1997, **277**:312-317.
 83. Johnson J, Bootman J: **Drug-related morbidity and mortality; a cost of illness model.** *Arch Int Med* 1995, **155**:1949-1956.
 84. Classen DC, Pestotnik SL, Evans RS, Burke JP: **Computerized surveillance of adverse drug events in hospital patients.** *JAMA* 1991, **266**:2847-2851.
 85. Nelson E, Splaine M, Bataalden P, Plume S: **Building measurement and data collection into medical practice.** *Ann Intern Med* 1998, **128**:460-466.
 86. Schacker T, Collier AC, Hughes J, Shea T, Corey L: **Clinical and epidemiologic features of primary HIV infection.** *Ann Intern Med* 1996, **125**:257-264. (Erratum, 1997, **126**:174.)
 87. Kiernan M, King AC, Kraemer HC, Stefanick ML, Killen JD: **Characteristics of successful and unsuccessful dieters: an application of signal detection methodology.** *Ann Behav Med* 1998, **20**:1-6.
 88. Galuska DA, Will JC, Serdula MK, Ford ES: **Are health care professionals advising obese patients to lose weight?.** *JAMA* 1999, **282**:1576-1578.
 89. Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ: **Optimisation of antihypertensive treatment by crossover rotation of four major classes.** *Lancet* 1999, **353**:2008-2013.
 90. Marinker M: **The current status of compliance.** *Eur Respir Rev* 1998, **8**:235-238.
 91. Prevention CfDcA: **Adoption of hospital policies for prevention of perinatal group B streptococcal disease—United States 1997.** *JAMA* 1998, **280**:958-959.
 92. The Acute Respiratory Distress Syndrome Network: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome.** *N Engl J Med* 2000, **342**:1301-1308.
 93. Bernard G: **Sepsis trials. Intersection of investigation, regulation, funding, and practice.** *Am Rev Respir Crit Care Med* 1995, **152**:4-10.
 94. Bone R: **Sepsis and controlled clinical trials: the odyssey continues.** *Crit Care Med* 1995, **23**:1313-1315.
 95. Bone R: **Sepsis and controlled clinical trials: the odyssey.** *Crit Care Med* 1995, **23**:1165-1166.
 96. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MA, Fisher CJ Jr: **Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature.** *Crit Care Med* 1995, **23**:1430-1439.

97. Eidelman L, Sprung C: **Why have new effective therapies for sepsis not been developed?** *Crit Care Med* 1994, **22**:1330-1334.
98. Lefering R, Neugebauer EA: **Steroid controversy in sepsis and septic shock: a meta-analysis.** *Crit Care Med* 1995, **23**:1294-1303.
99. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr: **Efficacy and safety of recombinant human activated protein C for severe sepsis.** *N Engl J Med* 2001, **344**:699-709.
100. Matthews J: *Quantification and the Quest for Medical Certainty.* Princeton: Princeton University Press; 1995.
101. Gigerenza G, Swijtink Z, Porter T, Daston L, Beatty J, Krüger L: *The Empire of Chance.* Cambridge: Cambridge University Press; 1989.