Guidelines for Perioperative Blood Transfusion and Conservation in Cardiac Surgery: Lessons and Challenges

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In a recent issue of *Anesthesia & Analgesia*, Likosky et al.[1] reported the results of a survey designed to assess the penetration and effect on clinical practice of the 2007 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists (STS/SCA) Clinical Practice Guidelines[2] on perioperative blood transfusion and conservation in cardiac surgery. Their principal findings were that although three-quarters of the anesthesiologists surveyed and two-thirds of the perfusionists had read all or parts of the guidelines, unfortunately in only 20% of the institutions had the guidelines been discussed formally, and in only 14% had an institutional multidisciplinary group been established to monitor changes in practice. Overall, despite the wide variability in transfusion practices, many of the recommendations were practiced in fewer than 50% of the institutions, and only 3 recommended practices were followed by more than 75% of the respondents. Only 26% reported practice changes as a consequence of the guidelines, and only 4 of 37 guideline recommendations were reported by more than 5% of the respondents to have been changed. This would appear to be an unfortunate circumstance because, as pointed out by these authors, the adverse effects of bleeding and transfusion on outcomes after cardiac surgery are well known.[3,4]

Likosky et al.[1] accomplished a daunting task in designing, testing, distributing, and subsequently analyzing their survey, but unfortunately their report suffers from 2 major limitations, which the authors have acknowledged. The most obvious limitation is that cardiac surgeons did not participate in the survey and the second is the subjective nature and potential bias of surveys of this type. Also, this survey raises broader questions regarding the value and limitations of clinical guidelines in cardiac surgery and in other aspects of perioperative practice, and calls into question where we should concentrate our efforts in the future.

LACK OF INCLUSION OF CARDIAC SURGEONS IN THE SURVEY

The reasons surgeons declined to participate was not clear from the authors, nor have we been able to obtain an explanation from the STS despite many attempts. Their absence from this survey limits the validity and interpretation of the results.[1] Cardiac surgeons have an essential role in influencing transfusion practice associated with cardiac surgery based on technical considerations and decision making. Although anesthesiologists and perfusionists can help stimulate, organize, and implement blood management programs, without the "buy-in" and active support and leadership by the cardiac surgeons, these efforts will have minimal impact.

LIMITATIONS OF SUBJECTIVE SURVEYS

Although surveys of clinical practice are widely conducted, the results represent opinions that must be cautiously interpreted. These opinions are important, but they do not necessarily reflect evidence-based medical decision making. The limitations of subjective survey data are well known and were also addressed by Likosky et al.[1] Striking examples of these limitations were provided by their study. In many instances, there were significant differences in the answers reported by perfusionists as compared with anesthesiologists, and among practitioners in the same institution. Routine use of open venous reservoirs was reported by 81% of perfusionists and only 35% of anesthesiologists. Similar differences were reported about routine use of heparin-coated circuits (79% vs 65%), routine use of leukocyte reduction filters in the bypass circuit (14% vs 52%), routine use of acute normovolemic hemodilution (53% vs 39%), routine use of lowered pump prime volume (78% vs 64%), routine practice of retrograde autologous priming (57% vs 41%), and routine use of leuko-reduced red blood cell transfusion (78% vs 42%). The incidences of these practices should not depend on who is reporting them. Another example of problems with survey information illustrated in this article is that among the 30 institutions in which there were 5 or more responders, on several questions there was <75% agreement.[1] Finally, the survey

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Accepted for publication August 24, 2010.

Disclosure: The authors report no conflicts of interest.

Jerrold H. Levy is section Editor of Hemostasis and Transfusion Medicine for the Journal. The manuscript was handled by Charles W. Hogue, Jr., Associate Editor-in-Chief for Cardiovascular Anesthesiology, and Dr. Levy was not involved in any way with the editorial process or decision.

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DOI: 10.1213/ANE.0b013e3181fbb386

asked about the impact of changing practice on reducing overall transfusion rate and 9% responded that it was highly effective and 30% that it was somewhat effective. However, no information was provided regarding the evidence on which this assessment was to be made by the respondents.[1] Were objective data collected, and were the results adjusted for other variables affecting transfusion? Most likely the respondents used historical controls to reach their conclusion, despite limitations associated with their use. These limitations call into question whether such data belong in the scientific literature. Even though the authors highlight the limitations of their data, this does not prevent others from quoting their data as though they represent established facts.

Despite these limitations, Likosky et al.[1] provide several important observations. Although researchers report the adverse effects of blood transfusion in cardiac surgery, there continues to be a wide variation in transfusion practices. Second, the STS/SCA guidelines have had little impact on changing clinical practice. The authors have addressed the problem of limited impact of guidelines on clinical practice and have made important suggestions about how this can be improved, including the importance of team collaboration and institutional commitment.[1]

THE PROBLEM WITH CLINICAL GUIDELINES

Likosky et al.[1] emphasize the importance of guidelines in improving patient care and outcome and the obligation of various societies and other organizations in developing, promulgating, disseminating, and implementing guidelines. We question whether this is the proper response.

With the increasing emphasis on evidence-based medicine in the past 20 years, there has been a stimulus to develop clinical guidelines and as a result, many have appeared. Sniderman and Furberg[5] reported that in January 2009, the National Guideline Clearinghouse had registered 2373 guidelines (2462 as of July 9, 2010) produced by 285 organizations. Journals love guidelines because they are widely cited and thus helpful to their *impact factor*. Societies like them because they may increase their importance for clinical decision making. Authors like them because they often promulgate their opinions and biases and legitimize their personal research and publications. Medical industry likes them if they advocate use of their products and hence industry may provide financial support to underwrite the publication and promulgation of guidelines.[6] Practitioners like the simple rules guidelines offer to minimize the uncertainty or ambiguity of clinical decision making. Hospitals and health care systems like guidelines because they can reduce practice variability and grade physicians. Third-party carriers like them because they provide a basis for reimbursement, or better yet, to withhold payment (even for the management of complications if they are construed to be preventable per guidelines). Plaintiff lawyers like them because it makes their case when bad outcomes occur and guidelines were not followed. Thus, there is extensive secondary gain in producing guidelines other than simply the laudable aim of improving medical care and practice. Unfortunately, the popularity of evidence-based medicine and the demand for guidelines has induced those who develop guidelines to, more often than not, base them on lower levels of evidence or even "expert" opinion because of the lack of high-level evidence. This is addressed further below.

The report by Likosky et al.[1] also notes the low and slow adoption rate of guidelines and suggested ways in which this can be improved. However, we also question whether clinical guidelines consistently improve patient care if they are adopted and followed. There are a number examples in which guidelines have not improved outcome, or may have led to worse outcomes. Examples include hormonal replacement in postmenopausal women to decrease cardiovascular risk, the use of encainide and flecainide to reduce sudden death in patients with asymptomatic ventricular arrhythmias,[7] and, more familiar to anesthesiologists, tight glucose control and prophylactic β-blockade. This is largely because the levels of evidence on which guidelines are developed are often low, or the high-level evidence (e.g., fairly large randomized controlled clinical trials [RCTs]) is flawed or not applicable.

Guidelines are only as good as the data on which they are based.[8] Kurup et al.,[a] conducting a systematic review of the 4 American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for perioperative management of cardiac patients for noncardiac surgery, found that only 10% of the recommendations were based on Class A evidence, whereas 57% were based on Class B evidence and 33% were based on low-level evidence including consensus opinion. Although Likosky et al. highlight AHA guidelines as models for promoting evidence-based medicine, in a review of the scientific evidence underlying all 53 ACC/AHA clinical practice guidelines issued between 1984 and 2008, Tricoci et al.[8] reported that only 11% were supported by level A evidence, whereas 48% were only supported by level C evidence. Even the strongest class of recommendation (Class I) was only supported by level A evidence 19% of the time.[8] Despite an increased number of recommendations, the level of evidence supporting them seemed to be decreasing over time. They concluded that clinicians need to exercise caution when considering recommendations not supported by solid evidence.[8]

Often, because of the lack of definitive evidence from multiple large prospective RCTs, meta-analysis of multiple smaller studies or statistical manipulation of data from large observational studies (e.g., propensity scores) is used instead. In fact, the ACC/AHA considers results of meta-analyses as level A evidence. The limitations of the use of meta-analyses have been emphasized by others.[9–11] In a significant number of instances, results of meta-analyses have not been substantiated by subsequent large RCTs.[9,12–14] Hennekens and DeMets[10] argue that meta-analyses are useful to formulate hypotheses but not test hypotheses. Nuttall and Houle[15] have pointed out the limitations of use of propensity analysis.

Unfortunately, even single, large, well-conducted RCTs can lead to erroneous conclusions and recommendations, as demonstrated with the tight glucose control controversy. In 2001, van den Berghe et al.[16] published the results of a

[a]Kurup V, Myslajek T, Skhtar S, Barash PG. Quo-Vadis? A review of perioperative practice guidelines from the ACC-AHA (1996–2009) [abstract]. Denver: Association of University Anesthesiologists, April 2010.

large RCT (but unblinded), which showed that tight glucose control improved outcome of critically ill surgical patients. Tight glucose control was subsequently widely adopted and advocated in a consensus statement from the American Association of Clinical Endocrinologists and American Diabetes Association and even proposed and used to assess quality of care by hospitals and physicians. However, 5 subsequent RCTs failed to replicate these findings and the largest one actually demonstrated harm.[17] This led to a revision of the consensus statement from the American Association of Clinical Endocrinologists and American Diabetes Association.[18]

Another example of a well-intended guideline that had to be modified because of a subsequent large RCT that detected harm from its implementation is the recommendation for the prophylactic administration of β-blocking drugs to patients at risk for coronary artery disease undergoing noncardiac surgery. Based largely on the results of a small RCT reported in 1996,[19] in 1997 the American College of Physicians recommended the perioperative use of atenolol in patients with coronary artery disease or risk factors for coronary artery disease[20] and these recommendation were largely included (based on the results of additional trials) in the ACC/AHA 2002 and 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery.[21,22] However, the guidelines had to be revised in 2009[23] because of the results of a large RCT ("POISE") that showed an increased risk of stroke and death in patients receiving (high-dose) metoprolol.[24] Although the final place of these therapeutic approaches (e.g., glucose control and prophylactic β-blockade) in clinical care is yet to be defined, these examples emphasize the need for caution in adopting and following guidelines.

One of the authors of this commentary (EAH) has reviewed the guidelines on glucose control during adult cardiac surgery issued by the STS in 2009.[25] The document claims that keeping glucose <180 mg/dL improves patient outcomes. This is based largely on observations of 1 group that used historical controls or comparisons with other databases. Of the 4 relatively small RCTs that examined intraoperative tight glucose control, 2 were positive and 2 were not, with 1 even suggesting a greater risk for adverse events.[26] Other reviewers have recommended keeping the glucose between 120 and 150 mg/dL,[27] <150 mg/dL,[28] or <180 mg/dL,[29] but without providing high-level clinical evidence to support their recommendation. Another well-known guideline for managing septic patients has been criticized because major elements in the "bundle" are not supported by sound evidence.[30]

Detsky[31] has pointed out the sources of bias for authors of clinical practice guidelines and Sniderman and Furberg[5] have indicated why they believe guideline making requires reform. These limitations are further addressed by Shaneyfelt and Centor[32] in their editorial accompanying the aforementioned report of the scientific evidence underlying the ACC/AHA clinical practice guidelines.[8] They reached the harsh conclusion that "if all that can be produced are biased, minimally applicable consensus statements, perhaps guidelines should be avoided completely. Unless there is evidence of appropriate changes in the guideline process, clinicians and policy makers must reject calls for adherence to guidelines."[32] Guyatt et al.[33] have addressed the vexing problem of guidelines and conflict of interest, emphasizing, among others, the problem of *intellectual conflict of interest*, and have outlined the innovative strategies that the American College of Chest Physicians has developed to manage conflicts of interest in developing the ninth iteration of the antithrombotic guidelines(AT9). Another effort at improving guideline development and promulgation is the implementation of the GRADE system for rating the quality of evidence and strength of the recommendations.[7]

CONSENSUS STATEMENTS AND SYSTEMATIC REVIEWS

Consensus statements are similar to clinical guidelines, but are even more dependent on quality and the integrity and biases of the authors.[34] An example is that published by Shann et al.[35] on the practice of cardiopulmonary bypass. Unfortunately, most of the data supporting their conclusions are supported by lower-level (B) evidence, or the effects on surrogate variables of unproven clinical significance. Their strong advocacy of α-stat pH management ("level A evidence") is difficult to accept in view of the evidence reviewed by Hogue et al.[36] Their support of cell processing of field blood is suspect in the face of 2 relatively small RCTs, 1 that observed better outcome and 1 worse outcome with the use of cell processing.[37,38] Systematic reviews are other methods of summarizing evidence supporting medical practice. Articles in this journal present a review of the advantages and limitations of this approach.[39–41]

These critiques of the limitations of some guidelines and consensus statements are not to deny that some appear to have improved patient outcome. The evidence that the guidelines for placement of central venous lines have reduced catheter-related bloodstream infection and early bundled management of severe sepsis have improved outcome are but 2 examples.[42,43]

WHAT ARE THE ALTERNATIVES?

Whether we should continue to develop clinical practice guidelines, promulgate them, and facilitate their implementation, or desist in these efforts and instead concentrate our collaborative efforts on designing and conducting large-scale well-conceived RCTs to provide more valid evidence to guide clinical care is an important question.[10,32] Based on their study of the evidence underlying the ACC/AHA guidelines, Tricoci et al.[8] recommended that the medical research community streamline clinical trials, focus on areas of deficient evidence, and expand funding for clinical research. In a review of optimal perfusion during cardiopulmonary bypass, Murphy et al.[44] concluded that there were limited data upon which to confidently make strong recommendations, and although development of "evidence-based" guidelines are helpful they are of uncertain reliability. They emphasized the "critical need for high quality studies (i.e., large well conducted randomized controlled trials)." We believe the key phrase in the introductory statement by Likosky et al.[1] regarding the potential for well-developed guidelines to improve clinical practice is "based upon a high level of evidence."

Therefore, contrary to the conclusions reached by Likosky et al., we believe the emphasis should *not* be on improving implementation of guidelines, which are more

often than not supported by weak evidence, but rather *obtaining more high-level evidence* that includes large appropriate RCTs to better develop guidelines that we can enthusiastically endorse. This will not be easy, and will obviously require the commitment and collaboration of all groups and societies involved in managing patients undergoing cardiac surgery.

Again, this is not to deny that there are some benefits from developing guidelines and that some have resulted in improved patient outcomes. However, we suggest that the pendulum has swung too far toward developing and promulgating guidelines. There is such a strong drive to produce a plethora of guidelines that developers are forced to base them on less than high-level/quality of supporting data. It is not the development of guidelines that we object to, but the promulgation of guidelines that are based on low-level evidence that sometimes proves to be wrong and gives the whole process a bad reputation that leads to skepticism, lack of trust, and poor adoption by medical practitioners. Thus, we believe we should concentrate more of our collaborative efforts on generating reliable data upon which we can then develop reputable guidelines.

If we do persist in developing guidelines (e.g., the STS/SCA guidelines on blood conservation are currently undergoing an update), then we have an obligation to improve their quality (e.g., use of the GRADE system and other recommendations mentioned above) and then do a better job of implementing their adoption into practice. The latter requires collaboration of our 3 professional groups (i.e., cardiac surgeons, anesthesiologists, and perfusionists) and we must work together to obtain the support of our institutions. We hope that the STS will take note of the lessons provided by Likosky et al. and will work with us in improving implementation of our mutually developed guidelines.

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