Guidelines Have Done More Harm than Good

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Introduction

Practice guidelines are a recent fad in medicine [1]. They came from non-existence 20 years ago, to over 2,000 strong today, covering all aspects of medical care. Guidelines can be educational and resemble medical textbooks in certain ways. There are key differences, however. Textbook chapters are usually single or double authored and are as authoritative as the individual authors. Different textbooks exist covering more or less the same subjects, giving a spectrum of opinion. While many authors share their personal clinical experience and make suggestions regarding treatment, they shy away from being overly specific, leaving treatment decisions to the readers. Textbook entries can be updated until literally just pre-publication. Authors are free, indeed encouraged, to scan ahead and make predictions about where the field is going, based on as yet unpublished data. Textbooks are financed by publishers who then market the product in the hope of making a profit, or at least, recoup expenses.

In contrast, guidelines result from the deliberations and contributions of a ‘panel of experts’ formed into a ‘work group’. Panelists frequently have financial relationships with industry with actual or apparent conflicts of interest with the outcome of deliberations. Specific treatment recommendations are made, and with great authority. Literature to be reviewed by panelists is pre-selected by staffers. The process requires a strict cutoff date – articles published after this date cannot be considered (though they may be relevant). The upshot is that guidelines are hopelessly vulnerable to being out of date when
ultimately released. Guidelines are generally sponsored implicitly or explicitly by industry, via funding of specialty societies. These companies are not in the altruism business; they expect to recoup their investment through increased sales of their products, based on guideline recommendations (which are distributed for free).

Most of the comments in this paper will refer to guidelines produced by the National Kidney Foundation’s Kidney Disease Outcome and Quality Initiative (KDOQI), since this is our main area of expertise. We believe our critique is applicable to guidelines in general. It is no secret that clinical research is increasingly dominated by industry-supported studies, mostly of pharmaceutical products. It should not come as a surprise that most guidelines’ bottom line is a recommendation for pharmaceutical treatment of one type or another. It should be self-evident that changes in target levels for blood pressure, cholesterol, and glycosylated hemoglobin in diabetics, will have a profound effect on sales of medications used to achieve these targets. We note in passing the inexorable decline in guideline definitions of normal blood pressure and cholesterol, and optimal HbA1C in diabetics.

Have guidelines done more harm than good? It is impossible to answer this question with hard evidence. That guidelines have been accepted on faith should be troubling to scientists.

Impact of KDOQI Guidelines on the Practice of Nephrology

The KDOQI guidelines have almost certainly influenced the practice of nephrology. Increases in Kt/V (or URR), hemoglobin (Hb), fistula use, as well as reductions in Ca × Phos and PTH, have been seen and may be partially attributed to guidelines [2]. More patients are being diagnosed with chronic kidney disease (CKD) as a result of the classification system based on MDRD GFR. Since this equation has a built-in age bias, a significant number of otherwise healthy elderly folk now have a diagnosis of CKD.

We run into difficulty trying to divine the impact of guidelines, individually and collectively, on hard outcomes such as survival. The very modest improvement in survival in dialysis patients noted since the beginning of the guideline era does not make for a convincing case of a beneficial effect [2]. At best one could argue that some guidelines have led to improvements while others have had no impact, or caused harm. We will examine some of these more closely.

Kt/V or URR

80% of patients in 1993 had URR <70; it was down to 35% in 2004. We can remember the disappointment when this significant improvement in average URR was associated with such an unimpressive change in mortality [2]. There are several possible explanations: to the extent that the boost in average URR was due to increases above already acceptable numbers, this would not be expected to lead to improved survival. It may also reflect the inherent limitations of URR as a predictor of survival, or be due to unintended consequences of limiting dialysis time in patients with ‘adequate’ URR. Some of these will be small or malnourished, others will have unmet needs for phosphorous clearance or volume removal. Both groups have poorer survival. A last possibility is that a significant effect of improved clearance was masked by a deleterious effect elsewhere.

Fistula Use

A-V fistula use increased from under 30% to over 40% from 1998 to 2004. This was accompanied by a marked decline in the use of A-V grafts [2, 3]. The superiority of A-V fistulae is assumed based purely on observational data (of which there is a prodigious amount) [4]. However, A-V shunts increase cardiac output, work, and pulmonary arterial pressures [5]. Small, radiocephalic fistulae in younger patients with healthy hearts are generally well tolerated. Larger brachiocephalic shunts in older patients, or those with significant cardiac disease, are not. Indiscriminate or premature placement of A-V shunts could have a negative impact on survival.

Treatment of Anemia

None of the KDOQI guidelines or recommendations has caused more controversy than the recent anemia guidelines [6]. The tacit raising of the upper level of Hb to 13 g/dl came a few months before the publication of the CHOIR [7] and CREATE [8] studies in November 2007, both randomized, controlled trials which showed no benefit and probable harm in the groups of CKD patients treated to the upper Hb target levels. The National Kidney Foundation (NKF) was forced to reconvene the anemia work group under pressure from the community and in the face of impending action by the FDA and CMS (Center for Medicaid and Medicare Services), to recon-
sider their recommendations. Financial relationships between Amgen, Ortho Biotech and the NKF, as well as with various members of the anemia work group, were revealed in the medical and lay press [9]. The episode drew attention to many of the problems we have previously noted with guidelines, notably regarding conflicts of interest, and the absurdity of having to turn a blind eye to late-breaking, but significant new data [1]. Beyond this controversy surrounding the upper limit of Hb, the anemia guidelines merit some concern about the lower limit of recommended Hb, 11 g/dl. The tremendous importance of the lower limit is related to the normal distribution of Hb concentrations which will lead to a median Hb of ≥12 if the floor is set at 11. This will result in a significant proportion of patients with Hb >13 g/dl, where adverse effects and increased mortality is expected. The lower limit of 11 g/dl was based on ‘moderate strength’ evidence, to wit, an uncontrolled observational study [10] and two meta-analyses of observational studies [11, 12]. Most showed optimal survival associated with Hb ≥11 g/dl. But association does not equal causality; other factors could explain the observed findings. No controlled, prospective studies that we are aware of demonstrate superior results at Hb of 11 vs. 10 g/dl. A lower level of 10 g/dl implies a median closer to 10 and only a handful of patients will be >13 g/dl. There are also major implications for sales of erythropoiesis-stimulating agents and for dialysis unit profits in our current USA system of payment for dialysis. The guidelines also neglect the effect of volume removal on Hb levels. Plasma water removal from blood during hemodialysis raises the Hb to a level determined by the total blood volume and the amount removed. A Hb level of 12 or 13 pre-dialysis could be 15 or 16 post-dialysis. Few would consider this safe or desirable. Hemoconcentration may explain some of the excess mortality in the high Hb group in the Besarab normal hematocrit study, the only other prospective randomized trial of different levels of anemia treatment in CKD [13]. Thus the KDOQI anemia guidelines have contributed to raising the median Hb to >12 g/dl, with harm likely occurring in some portion of patients within the right-hand side of the bell curve [14].

Bone and Mineral Metabolism

These guidelines, released in 2003, were based on literature published by January 2001 [15]. Quite a lot of important studies have been published since then, yet these guidelines still hold sway and are used in pay-for-perfor-mance systems and to rank dialysis units within certain large chains. Three major advances since these guidelines were published have rendered them obsolete: the association between calcium ingestion and vascular calcification [16, 17]; the close alignment of adynamic bone with vascular calcification [18], and the discovery of a biologically active N-terminally truncated PTH hormone (7-84 PTH) secreted by the parathyroid gland [19, 20]. It was clear at that time from mass balance considerations alone that excessive calcium intake would result in a positive balance in CKD and dialysis patients. Yet the guidelines ‘allow’ up to 2 g of elemental calcium intake per day. Following this advice in our view is clearly harmful. London et al. [18], and others, have shown a strong inverse correlation between vascular calcification and low, not high bone turnover. This is an extremely important observation since the guidelines, and most current bone management protocols, are designed first and foremost to suppress bone turnover. It was also known that the intact PTH assay, which measures both 1-84 and 7-84 PTH, fails to predict bone turnover in the 100–600 pg/ml range [21]. In spite of this, the work group set targets for intact PTH at 150–300 pg/ml for CKD stage 5, and lower for CKD stages 3 and 4. Based on existing histological evidence we can safely say that anywhere from 30 to 60% of patients kept within this range will have adynamic bone, thus placing them at increased risk for vascular calcification and mortality [21]. We are in the midst of an epidemic of adynamic bone disease and vascular calcification that is, at least in part, due to adherence to the KDOQI bone guidelines.

Other Harmful Effects of Guidelines

Guidelines have other negative effects, beyond the examples outlined above. Once guidelines are published, we cannot prevent them from being used as performance measures by payers in various pay-for-performance schemes. These are nothing more than sophisticated rationing systems, similar in design and philosophy to managed care. In this way, guidelines become the means by which payers gain control of medical decision-making. We also run the risk of being accused of not providing ‘standard of care’ lest we ignore one or a few guidelines. This could have legal and licensing ramifications. Guidelines promote a ‘one-size-fits-all’ approach to care which we regard as the antithesis of good medicine. Guidelines undermine confidence in the medical profession due to actual and apparent conflicts of interest. By

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seeming to pronounce certain areas ‘settled’, guidelines inhibit research and dull inquisitive minds. Guidelines lend credence to the notion that medical care can be reduced to plugging a few numbers into an algorithm. Guidelines presume that information derived from large population studies supersedes the local knowledge of individual patients by their personal physician.

We do not need guidelines. They constitute an unnecessary burden whose net effect is deleterious to patients, and to the medical profession.

Conclusions

Practice guidelines are a recent phenomenon and have proliferated without much scrutiny. Though mostly opinion-based, they have been misused and overinterpreted. Because they have not themselves been subjected to rigorous scientific analysis regarding effects on hard endpoints, it is impossible to say with certainty whether or not they have done more harm than good. Based on the analysis presented in this essay, we feel the net result of guidelines has been negative. It should be incumbent on the guideline creators and advocates to demonstrate a positive effect by constructing randomized, controlled trials. Failing this, considering the potential for abuse and harm to medical autonomy presented by guidelines, they should be abandoned.

References