The Seen and the Unseen: Clinical Guidelines and Cost-Effective Care

Monica Chang-Panesso and Benjamin D. Humphreys

Renal Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts

doi: 10.1681/ASN.2014050426

In the department of economy, an act, a habit, an institution, a law, gives birth not only to an effect, but to a series of effects. Of these effects, the first only is immediate; it manifests itself simultaneously with its cause—it is seen. The others unfold in succession—they are not seen: It is well for us, if they are foreseen.

Frédéric Bastiat (1850)

Clinical guidelines advise physicians on treatment choices in order to optimize outcomes and avoid costly or ineffective interventions. One aim is to reduce the waste that occurs because of the lack of adoption of proven best practices (estimated at >$100 billion in 2011). Healthcare-associated infections are a good example of a common (1.7 million cases in 2002), costly, and preventable complication for which guidelines with proven efficacy already exist in many cases.

However, clinical guidelines can also have unintended consequences. In this issue of *JASN*, Bell et al. explore the effects of a change in antibiotic prophylaxis designed to reduce the risk of *Clostridium difficile* infection (CDI) in surgical patients. In 2009, the Scottish Antimicrobial Group Prescribing Group (SAPG), a national clinical forum supported by the Scottish Government Health Directorate, issued a document with a set of principles to guide surgical antibiotic prophylaxis. The overall goal was to reduce the rate of healthcare-associated infections, principally CDI. A primary suggestion was to restrict the use of cephalosporins because they alter gut flora and increase the risk of CDI. Flucloxacillin (two doses of 1 g) was suggested as an alternative, with the addition of gentamicin (single dose of 4 mg/kg) when there was a risk of Gram-negative contamination of the surgical site.

An earlier small study by Challagundla et al. gave the first indication that the antibiotic change may be having unanticipated deleterious effects. The authors performed an observational study of 198 Scottish patients undergoing elective hip or knee surgery between September 2009 and September 2010. Patients who received high-dose flucloxacillin with gentamicin prophylaxis had an increased odds ratio for all severity AKI (14.5; 95% confidence interval [95% CI], 4.2 to 49.7) compared with patients that received cefuroxime alone.

Now, Bell et al. present a comprehensive population-based analysis of the consequences of this antibiotic policy change. The authors, who include members of the SAPG, aimed to evaluate postoperative AKI in surgical patients after the change in antibiotic prophylaxis recommendations. Their study population included 12,482 patients undergoing orthopedic, vascular, gastrointestinal, and gynecologic surgical procedures. Among orthopedic patients, there were 186 cases of AKI before the antibiotic policy change (Acute Kidney Injury Network criteria) and 361 cases after the change, resulting in a 94% increase in AKI in the orthopedic patient group (95% CI, 93.8 to 94.3). There was no significant change among other surgical groups. This association held after controlling for potential confounders including age, nephrotoxins, and Charlson comorbidity scores. Orthopedic patients who underwent repair for a fractured neck of femur did not receive the new antibiotic regimen (owing to surgeons concerns with using gentamicin) and did not experience an increase in AKI rate, supporting a causal role for the antibiotic change in increased AKI.

It is not entirely clear which antibiotic is at fault here but clinical experience would suggest that gentamicin is the culprit. Challagundla et al. speculated that flucloxacillin was at fault because six of the seven patients with severe AKI (RIFLE class F) were in a high-dose flucloxacillin group and there was a decrease in AKI after reducing the dose of flucloxacillin. In addition, two of three patients who required RRT underwent a kidney biopsy that showed acute tubulointerstitial nephritis, a pathology typical for penicillin-based antibiotics. However, these results are subject to selection bias. Gentamicin likely causes AKI much more commonly, whereas high-dose flucloxacillin may do so rarely but acute interstitial nephritis can be a more severe injury. Although gentamicin toxicity is usually cumulative, it is entirely conceivable that a single dose is sufficient to cause AKI in older postoperative patients with volume depletion who may have subclinical CKD.

Unsurprisingly, patients with AKI in the study by Bell et al. had worse long-term outcomes. The results showed that 21% of patients who underwent orthopedic surgery and developed AKI died within 1 year of surgery, in contrast with 8.2% mortality among patients that did not have AKI. The median length of hospital stay was increased by 1 day (8 days for patients with AKI versus 7 days for patients without AKI). CDI is
also associated with substantial morbidity and even mortality. The costs of a single case of hospital-acquired CDI are estimated at $5042–$7179.\textsuperscript{10} However, the costs of mild hospital-acquired AKI (increase in serum creatinine of $\geq 0.3$ mg/dl) are estimated at $4886 and the costs of moderate AKI (increase in serum creatinine of $\geq 0.5$ mg/dl) are estimated at $7499—almost exactly the same as the costs of CDI.\textsuperscript{11}

One important observation by Bell et al. is the lack of postoperative serum creatinine evaluation in approximately 50% of urology and gynecology patients, raising the question of whether postoperative AKI might have been missed in these populations. Relatively few studies have examined the utility of postoperative laboratory results, but recent investigations concluded that such testing is not necessary in all patients and should be guided by the patient’s medical history, citing potential cost savings.\textsuperscript{12,13} In a separate study of postoperative AKI after total joint arthroplasty in 9171 patients, 19% of patients did not have a serum creatinine measurement, suggesting that this is not an isolated issue.\textsuperscript{14} Given the adverse outcomes associated with AKI in this study and others, the suggestion by Bell et al. that any patient who receives gentamicin prophylaxis should have a serum creatinine determination both preoperatively and postoperatively is sound. The rate of CDI after antibiotic prophylaxis is not well defined, with frequencies ranging from 0.2% to 8%, depending on the type of surgery; however, most studies cite rates of 1%–2%. Importantly, Bell et al. report that patients with a fractured neck of femur, who received amoxicillin/clavulanic acid prophylaxis, experienced a similar reduction in the rate of CDI as surgical patients who received fluocoxacinil and gentamicin prophylaxis. Thus, reduced rates of CDI during the study period cannot be attributed to a switch to fluocoxacinil and gentamicin prophylaxis. Consequently, the increased rate of orthopedic postoperative AKI from 6.2% to 10.8% almost certainly affected a greater number of patients than might have been helped by preventing CDI. Appropriately, in its 2012 Good Practice Recommendations for Surgical and Procedural Antibiotic Prophylaxis in Adults in National Health Service for Scotland, the SAPG revised its antibiotic prophylaxis recommendations, removing fluocoxacinil and gentamicin as a suggested regimen and citing the risk of nephrotoxicity with aminoglycoside-based regimens.\textsuperscript{15}

Clinical guidelines will play an expanding role in our increasingly benchmarked and standardized clinical care environment. These guidelines must be based on solid data and a consensus of experts and stakeholders, but ultimately they are limited by the existing state of knowledge on which those guidelines are based. Guidelines should be revised when unanticipated complications occur, as was appropriately done in this case. When adverse outcomes may be envisioned (e.g., administration of a known nephrotoxin), evidence for such toxicities should be sought through active surveillance programs for example, routine post-operative labs. These policies should increase the chance that unforeseen complications are detected early so guidelines can be revised.

DISCLOSURES
None.

REFERENCES