

Decreasing antibiotic overuse in neonatal intensive care units: quality improvement research

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Overutilization of antibiotics and emergence of resistant bacteria are important problems, particularly in intensive care units. To date, reproducible interventions to improve antibiotic utilization in hospitals have not been proven to be effective or safe. Evidence-based medicine, clinical practice guidelines, and health information technology are frequently promoted as means to cross the “quality chasm” described by the Institute of Medicine. This article outlines how these approaches intersect in a strategy for quality improvement research evaluating the safety and effectiveness of clinical practice guidelines designed to improve antibiotic use in neonatal intensive care units.

Considerable evidence suggests that antibiotic overuse selects for bacterial resistance (1), and several investigators have shown a close association between antibiotic use and the emergence of antibiotic-resistant bacteria (2–7). To address the growing problem of antibiotic resistance, the Centers for Disease Control and Prevention, the National Foundation for Infectious Diseases, the Society for Healthcare Epidemiology of America, and the Infectious Disease Society of America have all urged hospitals to develop systems to monitor antibiotic use and urged physicians to reduce inappropriate antibiotic use (8–10). Antibiotic stewardship is increasingly the subject of research, discussion, and debate (11).

Well-designed observational studies suggest that antibiotics are overused in hospitals. It is estimated that one third of hospitalized patients receive antibiotics and that 50% of this use is unnecessary (12). Overuse in intensive care units (ICUs) is of particular concern, as this environment contains a number of pressures promoting resistance (13). Antibiotic consumption in ICUs approaches 10 times that in general hospital wards (14, 15) and, while much of this use is dictated by ICU patients’ severity of illness, research suggests that overuse contributes substantially (16–18). In neonatal intensive care units (NICUs) much of the overuse involves vancomycin, as the frequency of coagulase-negative staphylococci infections makes it a common choice for empiric therapy (19). A study from the National Institute of Child Health and Human Development Neonatal Research Network found that 30% of infants without proven infection received vancomycin (20). In a survey of infection control professionals and neonatologists at 35 hospitals with NICUs, 80% estimated that infants with a single blood culture positive for coagulase-negative staphylococci were treated with a full course of antimicrobials in >50% of occurrences, and 60% estimated that such infants were treated in >75% of occurrences (21).

Baylor University Medical Center recently reviewed 124 consecutive courses of vancomycin administered in its NICU. Forty-seven percent of the 797 vancomycin days were used for patients with a blood culture positive for an organism justifying vancomycin use. Of these, 70% of the vancomycin days were for coagulase-negative staphylococci infections, with all but a few treatment courses initiated on the basis of one blood culture. In the 53% of vancomycin days used to treat patients without supporting microbiology culture results, 22% of the vancomycin days were used for empiric therapy only—i.e., treatment was discontinued when culture results became available. Seventy-eight percent of the vancomycin days in culture-negative patients were used beyond 3 days despite lack of supporting microbiology results.

The best way to decrease vancomycin overuse in NICUs remains unclear. Suggestions in the literature include obtaining two blood cultures before beginning vancomycin for suspected bloodstream infection to decrease the frequency of treatment initiated because of contaminated cultures, discontinuing vancomycin promptly if microbiology culture results do not support continuation of empiric therapy, and not using vancomycin routinely for empiric therapy of late-onset infection (21). As none of these guidelines are supported by results of randomized controlled trials (RCTs), the standard model for development of clinical practice guidelines (CPGs) calls for more and better RCTs addressing indications for vancomycin therapy in the NICU population. However, it is unlikely that traditional RCTs—randomizing patients to treatment and control groups—would resolve the controversies or be acceptable to patients’ families or institutional review boards. That is not to say that CPGs in this setting are not needed or that their safety and effectiveness should not be evaluated.

Although many studies claiming improved antibiotic use in hospitals appear in the literature, their credibility has been called into question. Ramsay et al, in a systematic review of interventions to improve hospital antibiotic prescribing, found that only 91 of 306 studies published since 1980 (30%) met the minimum methodologic and analytic criteria for review by the Cochrane Collaboration’s Effective Practice and Organisation of

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Table. Support strategies for implementing clinical practice guidelines: effectiveness and potential information technology support

Support strategy	Effectiveness	Potential information technology support
Provider education	Usually not sufficient to effect meaningful change	Point-of-care connection to relevant literature promising
Prompts and reminders	Most reliable support strategy	Difficult to achieve without health information technology
Audit and feedback	Effectiveness varies depending on perceived credibility of the data	Reliable capture of relevant data is the biggest challenge
Multidisciplinary collaboration	Most effective when specified responsibilities are shared/redistributed	Can promote collaboration—e.g., between clinical pharmacists and physicians
Multiinstitutional collaboration	Feedback of data allowing comparison of performance may be effective	Sharing data is a significant challenge
Active management	More effective when oversight is provided by someone other than primary care providers	Audit and feedback reports could be delivered to managers/supervisors when appropriate

Care (EPOC) group (23). In addition to engaging in independent research, the EPOC group reviews the evidence base for organizational or systems interventions designed to improve professional practice and the delivery of effective health services. Ramsay et al concluded that there are “fundamental methodological flaws in the design and/or execution and/or the analysis of the results of the majority of published evaluations of interventions to improve antibiotic prescribing in hospitals” and that these flaws have in some cases led investigators to unwarranted or incorrect conclusions about the efficacies of interventions (23). Because of the poor quality of the studies, the authors did not feel they could make recommendations regarding interventions to improve antibiotic use. They urged that future studies of interventions should be more rigorously designed and evaluated.

This article addresses the issue of next steps. The hypothesis is that the problem of antibiotic overuse, in general and in the NICU, is best understood as a quality improvement problem and can be best addressed by using quality improvement research methods.

QUALITY IMPROVEMENT RESEARCH

Clinical quality improvement (QI) interventions are based on therapies or tests known to be safe and effective in target populations in controlled settings. Quality improvement research, in turn, can be thought of as the evaluation of the safety and effectiveness of reproducible clinical quality improvement interventions. From these definitions it follows that at least two conditions should be met to warrant a quality improvement research project:

- There should be convincing evidence of a gap between knowledge and practice in the targeted area to justify an intervention; this gap can be overuse, underuse, or misuse of therapies or tests.
- Evidence supporting safe and effective quality improvement interventions targeting the overuse, underuse, or misuse is lacking. Otherwise, the interventions should be implemented, not studied.

The case for a quality improvement research study is particularly strong if there is reason to believe that the gap in question is not easily breached, as with overuse of antibiotics in ICUs. Unfortunately, much of the QI research published to date has

been of questionable quality. Systematic reviews of QI strategies have consistently identified weak study designs (24). For example, a review of QI studies published in major US medical journals reported that 75% relied on simple before-and-after designs, often at single institutions at single sites, which makes it difficult to attribute any observed benefits to the QI interventions.

Before discussing study designs appropriate for QI research, it is useful to consider important insights recently offered by members of the EPOC group and others. Systematic reviews show that translating clinical research findings into daily practice is difficult (23, 25, 26). It has also become clear that in clinical settings successful QI interventions typically require support strategies to be effective: combinations of education, point-of-care prompts or reminders, audit and feedback, and project management, among others (Table) (24, 25, 27). This seemingly obvious observation has important implications for QI research and evaluation of CPGs. First, research reports need to describe support strategies in sufficient detail for them to be replicated in similar settings. Second, it is useful to conceptualize QI interventions designed to improve professional practice and the delivery of effective health services as taking place at the organizational or systems level rather than strictly at the provider-patient interface (28, 29). It follows that QI interventions are best evaluated by comparing patients nested in organizational units—groups of patients exposed to the organizational intervention versus groups of patients receiving standard care. For RCTs of organizational interventions, it is more appropriate to randomize groups of patients than individual patients (30).

The traditional RCT, where patients are randomized to intervention and control arms, is usually not suitable for evaluation of organizational interventions; awareness of this fact has likely contributed to the paucity of RCTs evaluating QI interventions. Shojania and Grimshaw note that a better case can be made for permitting well-designed observational studies to provide adequate evidence for major policy decisions in clinical research than in QI research. RCTs offer protection from the effects of unknown predictors of treatment outcome by balancing their prevalence between control and experimental groups. In clinical research, we usually understand many of these risk factors and can therefore adjust for imbalances in observational studies. By contrast, we generally have very limited understanding of the

factors that determine the success of a QI intervention, making randomized designs even more important if one wants to avoid wasting resources on ineffective interventions (24). The issue of resources becomes more important as QI support strategies increasingly rely on expensive information technology.

CLINICAL PRACTICE GUIDELINES TO IMPROVE ANTIBIOTIC USE

The Institute of Medicine defines clinical practice guidelines as “systematically developed statements that assist practitioner and patient decisions about appropriate health care for specific conditions” (31). Using this definition, it is difficult to conceive a reproducible QI intervention to improve antibiotic utilization that does not involve CPGs. As there is uniform agreement that CPGs should be based on therapies or tests known to be safe and effective in target populations in controlled settings (32–34), there is a rationale for thinking about CPGs as a type of QI intervention.

Failure to recognize CPGs’ dependence on organizational support may explain why CPGs have had relatively little impact on the overall quality of health care. In most settings, guidelines are yet one more input to the already overburdened health professional; they are either ignored or not read (35). Implementation of CPGs with carefully planned support strategies has been the exception rather than the rule. Berg proposed that CPGs must be embedded in the material and organizational environment in which clinicians work, using structured supports such as prompts, order sets, and checklists of medication options, in order to be successfully implemented (35).

Implemented with support strategies, CPGs, like other QI interventions, are most appropriately evaluated at the organizational level. In some instances, it may be possible to compare groups of physicians that use or do not use CPGs. However, this implies that the CPG is applied exclusively at the physician-patient interface. In hospitals and ICUs, effective CPGs typically involve multiple physicians as well as nonphysician members of the health care team. All members of the team need to be able to identify patients potentially in the target population (29). This requires that the target population be explicitly identified in the CPGs—which in turn allows the design of organizational or systems-level support for CPGs. Whether the quality of health care is measurably improved in organizations that implement specific organizational support strategies is a legitimate subject of research.

In ideal circumstances, organizational supports set processes in motion that lead to CPG adherence unless a health care provider or patient intervenes, based on clinical judgment or values. Berg used the term “flexible standardization” (35), and James described this scenario as “making it easy to do the right thing” (36). In regard to CPGs, making it easy to do the right thing is largely about identifying patients potentially in the target population so that health care professionals can deliver optimal care at appropriate times. Given that it is not possible to identify patients in CPG target populations with enough confidence to allow treatment or testing to proceed without clinical judgment, the organizational goal is to highlight the need for clinical decisions. If the algorithm for identifying CPG target patients works well, a large majority of identified patients can be set on a standardized trajectory. However, if the algorithm includes too many patients for whom the standard is judged not to be appropriate or fails to

identify too many patients for whom it is, the CPG will be not be useful. No matter how sound the logic behind the algorithm used to identify patients in the target population for CPGs, operationally the challenge is to implement an information system that provides clinicians with the right information at the right time and place.

HEALTH INFORMATION TECHNOLOGY

It is widely believed that health information technology will play a critical role in taking western health care delivery systems across the quality chasm described by the Institute of Medicine report (37). However, it is also generally acknowledged that to date such technology has had a very limited impact on the quality of health care. Berg argued that many of the failures occur because the designs impose a level of standardization inconsistent with the flexibility necessary in health care (35).

Another factor that has limited the impact of health information technology is that most clinicians do not interface with the technology in the course of routine documentation and order writing. In settings where clinicians document and order electronically, systems designed to support antibiotic prescribing have shown a great deal of promise (38–42). When health care professionals, including physicians, are engaged with an electronic medical record, health information technology will be able to deliver key QI support strategies—point-of-care decision support and audit and feedback. With properly designed systems, CPGs can be embedded in the form of prompts and order sets, making them more accessible and likely to be used than if stored on a shelf or in a database (24, 25). Another advantage of using information technology to deliver support strategies is reproducibility. Even if software cannot be modified to work in similar settings, key data elements, definitions, and algorithms can be replicated. Finally, where the safety of CPGs is of concern, health information technology can be used to create surveillance systems to provide the equivalent of “postmarketing” monitoring.

SAFETY CONCERNS

While the effectiveness of CPGs aimed at reducing antibiotic utilization can be measured in units such as defined daily doses, antibiotic days, and cost, safety should be measured in terms of mortality and morbidity. Much of the literature on methods to improve antibiotic utilization fails to address clinicians’ legitimate concerns that patients may suffer if interventions are overzealous or misguided. The concern regarding patient safety is a compelling reason to rigorously evaluate CPGs aimed at decreasing overutilization of therapies that have strong indications in an imperfectly defined population of patients. For vancomycin, this will involve establishing that patients not treated with vancomycin have clinical outcomes equivalent to those who are treated. It is not reasonable to expect patients who are not treated to have superior clinical outcomes, nor is it possible to demonstrate no difference between these groups. Studies can and should be designed to establish that differences in clinical outcomes may be small. However, the inability to prove no difference in clinical outcomes makes ongoing surveillance all the more important. Embedding CPG supports in operational electronic information systems creates the opportunity for ongoing surveillance of antibiotic use, microbial resistance patterns, mortality, and morbidity—unlike

typical RCTs, in which the research information system disappears when the project ends.

MODIFICATION OF CPGs

CPGs should be updated as new knowledge or new therapies become available. In the case of CPGs directing antibiotic therapy, changes in the prevalence or virulence of resistant organisms might necessitate revision of CPGs. To evaluate the safety and effectiveness of modified CPGs, well-designed interrupted time series studies may be an acceptable alternative to group randomized trials (23). In contrast to simple pre-post comparisons, rigorous interrupted time series studies rely on large numbers of baseline as well as postintervention observations to minimize the chances that differences were due to random variation or regression to the mean. Including control sites can address another factor that commonly confounds simple pre-post studies: secular trends in health care delivery. The practical limitation of interrupted time series studies is the large number of baseline observations required—many more than is typically practical to obtain. Additionally, the information system used to capture outcome data needs to be equivalent if not the same in both the pre and post periods for valid comparison (43). Well-designed interrupted time series studies will become practical with surveillance systems designed to capture baseline outcome data necessary to evaluate future interventions.

PEDIATRIX NETWORK

Based on the principles outlined, the safety and effectiveness of CPGs should be evaluated in group-randomized RCTs where the CPGs are implemented with recognized support strategies embedded in electronic information systems used by clinicians in routine daily work, with post-study surveillance included in the study design. The practical challenges of developing a network of comparable groups of patients and the rarity of clinically functional electronic information systems explains the current lack of such studies. For NICUs, the network of Pediatrix-staffed NICUs affords a unique laboratory in which to evaluate CPGs and other QI interventions.

Pediatrix Medical Group is the nation's largest neonatal physician group, employing more than 630 neonatologists and advanced practitioners in 180 NICUs with total daily admissions and census typically exceeding 120 and 2500, respectively. Pediatrix physicians and nurse practitioners use a common electronic documentation system for history and physicals, daily progress notes, and discharge summaries. In collaboration with Baylor Health Care System's Institute for Health Care Research and Improvement, Pediatrix is seeking external funding to support a multiphase project culminating in a cluster RCT to evaluate a set of CPGs aimed at improving antibiotic utilization in NICUs. Pilot work to develop a standard batch interface between Pediatrix's electronic documentation system and the hospitals' pharmacy and microbiology information systems is under way. The resulting information system will also allow participating NICUs to measure hospital-acquired infection rates with much greater accuracy and ease than before. Many aspects of this system should be applicable to adult ICUs when physicians begin using electronic documentation systems and computerized order entry more commonly.

DISCUSSION

It is important that all parties engaged in implementing and evaluating CPGs have a common understanding of the term. In this article, CPGs have been discussed in the framework of flexible standardization as described by James and Berg (35, 36). This framework fits with Plesk's model of complex adaptive systems in health care delivery, recognizing the interpretive, interactional, and pragmatic nature of health care (44). The practical implication of this model is that the goal for compliance with CPGs is explicitly less than 100%. This is in contrast to the Six Sigma model, where noncompliance is expected to be rare (45). In health care, the Six Sigma model is more appropriate for standardizing how a process is carried out rather than which patients are or are not treated or tested.

The approach to the development and evaluation of CPGs outlined in this paper differs somewhat from the standard paradigm. Most discussions focus on the evidence base supporting the treatment or test employed in the CPG rather than the safety and effectiveness of the CPG itself. Although there is no question that CPGs should be based on therapies or tests known to be safe and effective, patient-level RCTs of some therapies appear to be unwarranted and/or not feasible. What is needed is a direct evaluation of the safety and effectiveness of the CPG, based on clinical outcomes. That a CPG incorporates evidence-based therapies does not guarantee either safety or effectiveness. Using this logic, group-randomized trials are not a second-best option when patient-randomized trials are not feasible; they are preferable. Also different from the standard model of CPG evaluation, the model put forward in this paper requires that CPGs be evaluated in conjunction with reproducible support strategies. The model proposes that health information technology and some version of the electronic medical record are the optimal media for delivering reproducible support strategies for CPGs: point-of-care prompts and audit and feedback. The Pediatrix network offers the opportunity to develop and evaluate the safety and effectiveness of CPGs supported by information technology.

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