Maximizing Appropriate Antibiotic Prophylaxis for Surgical Patients: An Update from LDS Hospital, Salt Lake City

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Errors in antimicrobial prophylaxis for surgical patients remain one of the most frequent types of medication errors in hospitals. Failure to administer the first dose of antimicrobial prophylaxis within the 2-h window of time before incision is associated with 2- to 6-fold increases in rates of surgical site infection. Optimal use of antimicrobial prophylaxis includes proper case selection; use of appropriate agents; proper dosing, route of administration, timing, and duration; and intraoperative dosing when appropriate. Effective use of antimicrobial prophylaxis also requires monitoring of and feedback on patterns of use. Programs to improve antimicrobial prophylaxis should be multidisciplinary and should aim to improve use of medications, not simply to change physician practice patterns. The LDS Hospital experience demonstrates the clinical and financial benefits of such a program and also shows the pitfalls of and great difficulties associated with changing systems of care.

For >30 years, researchers have reported that as much as 50% of all use of antibiotics in hospitals is inappropriate, and yet little tangible improvement has occurred despite the potential benefits of reduced costs and selection pressure for drug-resistant bacteria [1]. The proper use of antimicrobial agents is a goal that has new urgency because of the impending crisis with regard to antibiotic resistance. Moreover, complacency with regard to the status quo is no longer acceptable in view of the intense interest aroused by the recent Institute of Medicine report on the importance of medical errors [2]. This report targeted medication errors as the most frequent and preventable type of error.

BACKGROUND

Use of antimicrobials in the treatment of surgical patients mirrors the larger problems associated with use of antibiotics for hospitalized patients; the important difference is that prophylaxis, rather than treatment of infection, is more common. The concept of preoperative use of antimicrobials to prevent postoperative infection in surgical patients was introduced before the modern era of antibiotics [3]. Nonetheless, for many years, antibiotic prophylaxis for surgical patients was considered ineffective, even though classic experiments by Miles et al. [4] in the 1950s demonstrated that skin infections in guinea pigs could be suppressed by iv antibiotics given during the “decisive period” (i.e., within 3 h after wound contamination). Burke [5] then proposed that the failure of prophylactic antibiotics in surgical patients was due to the common practice of starting administration of antibiotics after the operation. The clinical validity of these observations, which was established in the 1960s by Bernard and Cole [6] and Polk and Lopez-Mayor [7], was further supported by Stone et al. [8]. However, controversy continued well into the 1970s. For instance, the incidence of infections was the same in orthopedic patients who received antibiotics prophylactically and in those who did not [9]. Antimicrobial prophylaxis for certain types of op-
erations designated as “clean contaminated” (i.e., those that involve entry into a hollow viscus under controlled conditions and without unusual contamination) and for specified “clean” procedures (those that involve placement of prosthetic material or those for which an infection would be catastrophic) became well established in the 1980s on the basis of controlled clinical trials. Use of antibiotics during “contaminated” or “dirty” procedures is considered therapy rather than prophylaxis. However, as controversy about the efficacy of antimicrobial prophylaxis subsided, interest shifted to reducing the unnecessary duration of prolonged antimicrobial prophylaxis beyond the perioperative period. Many studies showed no value in continuing antimicrobial prophylaxis beyond the 24-h period after surgery and will not be reviewed here. A population-based study of patterns of antimicrobial-drug use at 20 randomly selected hospitals in Pennsylvania in 1975 found that an important determinant for discontinuing antimicrobial prophylaxis was hospital discharge and that the mean duration of antimicrobial prophylaxis was 4.6 days; the timing of the initial administration of antimicrobial prophylaxis was not studied [10]. However, in 1979, a survey of 27 metropolitan hospitals in Minnesota found that only 41% of patients received initial administration of antibiotics during the 4 h preceding the start of surgery [11].

The reason for belaboring this history of antimicrobial prophylaxis is to underscore the all-too-familiar pattern of long intervals between the recognition of an important principle and its uniform application in clinical practice, perhaps in part because of confusion between efficacy and effectiveness. Shapiro, a pioneer hospital epidemiologist who appreciated this distinction, not only confirmed the experiments of Miles et al. in an animal model of synergistic infection [12] but also introduced protocols for antimicrobial prophylaxis in a university hospital in Israel in the late 1970s, placing special emphasis on the correct timing of the first parenteral dose. He noted, in a small observational study, that even though the proportion of patients who received antimicrobial prophylaxis increased, there was a concomitant decrease in antibiotic usage as a result of markedly decreased rates of infection and a decreased need for antibiotics for the treatment of infections [13].

Similar data were accumulated by the Utah Peer Review Organization in 1979; among 21 hospitals, only 38% of patients received antimicrobial prophylaxis immediately before or during the operation, and of 4753 days of use of prophylactic antibiotics, 3789 were considered excessive [14]. Educational mailings to surgeons, followed by concurrent reminders placed in the charts of postoperative patients, were minimally successful in changing practices [15]. These studies were hampered by the lack of outcome measures, such as rates of infection, and by the emphasis on changing physician practices rather than the systems of care. Moreover, placing blame for inappropriate antimicrobial prophylaxis on the surgeon has created barriers to constructive approaches [16], a theme echoed throughout the Institute of Medicine’s report on errors.

In retrospect, it is astonishing that proper timing of perioperative antimicrobial prophylaxis, a procedure capable of reducing rates of surgical site infections, received far less attention than did efforts to limit the duration of postoperative courses of antibiotics, which have little effect on postoperative rates of infection. Use of antibiotics was seen more as a target for cost savings than as a means of improving quality of care. A further problem has been the assumption that guidelines alone are capable of changing practice. At the Second International Conference on Nosocomial Infections in 1980, Nichols [17] relegated the faulty timing of initial administration of antimicrobial prophylaxis to the historic dustbin and claimed that the most common error that remained was continuation of the agents beyond the time necessary for maximal benefit.

**LDS HOSPITAL STUDIES**

Periodic prevalence surveys of infections and use of antibiotics at LDS Hospital, Salt Lake City, in 1971, 1979, 1984, and 1990, have shown marked serial decreases in the duration of antimicrobial prophylaxis [18]. However, even in 1990, more than half of the overall use of antibiotics was inappropriate, and 78% of the inappropriate use involved antimicrobial prophylaxis.

The evolving computerized patient-record system at LDS Hospital has enabled more detailed assessment of the problems associated with the use of antibiotics. Infectious diseases surveillance and therapeutics was the first medical domain to use the decision-support features of the system on a widespread basis [19]. Real-time assessment of surgical site infections identified by computer screening of electronic information sources and confirmed by bedside review by infection control practitioners, in use since 1985, has proved an efficient, sensitive, and reliable method of surveillance [20].

During a 6-month study in 1985, multiple errors in antimicrobial prophylaxis were identified; these involved errors of both omission and commission [21]. Antimicrobial prophylaxis was not given in 345 (21%) of 1621 operations in which prophylaxis is generally indicated (table 1) and was given unnecessarily in 822 (50%) of 1642 in which it is of unproven value. Antimicrobial prophylaxis was continued beyond 48 h for 1088 (40%) of 2691 patients [22]. Moreover, it was not given preoperatively (within 2 h before the surgical incision, except for patients undergoing cesarean sections) in 983 (60%) of 1621 operations in which prophylaxis is indicated.

From the institution’s perspective, the complexity of antimicrobial prophylaxis unfolds from the large number of prescribers and procedures involved; in the 1985–1986 study at
LDS Hospital, >300 different kinds of operative procedures were performed by 241 surgeons [21]. After the baseline study in 1985, the infectious diseases team sought consensus from each of the various surgical subspecialty divisions with regard to guidelines for case selection, acceptable antimicrobial agents, optimal delivery time, intraoperative dosing, and duration of antibiotic prophylaxis for surgical patients. Decision-support algorithms that were based on data elements in the computerized hospital-information system were then developed to identify patients who were to undergo a surgical procedure for which antimicrobial prophylaxis was indicated and, separately, for patients receiving antimicrobial prophylaxis beyond 48 h after surgery. These duration guidelines screened individual patient records to identify patients who were afebrile, who had no positive or pending microbiology cultures, who had surgical procedures that were not classified as “contaminated” or “dirty,” and who were not isolated for an infectious process. The criteria were soon changed to recognize the growing consensus that antimicrobial prophylaxis should be ended within 24 h. The computer programs then generated alerts for intervention by the epidemiology team.

As in previous efforts by others, our initial efforts at improvement were directed toward the surgeons themselves. In 1986, a clinical pharmacist placed a reminder sticker in the paper charts of patients for whom computer analysis had determined that antimicrobial prophylaxis was indicated; a stop order was placed in the charts of patients receiving prolonged antimicrobial prophylaxis. Whereas both of these interventions were associated with significant reductions in rates of surgical site infection and reduced antibiotic costs, the gains were modest and disappointing [21, 22]. The frequency of optimal timing of antibiotics (defined as administration within the 2-h window of time before the incision is made) increased from 40% to 58% in 1986 (table 1), the incidence of surgical site infections decreased from 1.8% to 0.9%, and the proportion of patients who received antimicrobial prophylaxis for >48 h decreased from 40% to 35%.

In 1986, the concepts of continuous quality improvement and holding the gains had not yet gained currency in health care. Despite the elegant computer technology at LDS Hospital, our results met with initial resistance and indifference. A more comprehensive analysis of the 1985–1986 study population, performed by use of stepwise logistic regression methods, confirmed that administration of antimicrobial prophylaxis during the preoperative period was independently associated with the lowest risk of surgical site infection [23]. Moreover, the relative risk of infection correlated with the time of administration of the first dose and ranged from a 2-fold to nearly 6-fold greater risk, depending on the timing of antimicrobial prophylaxis. The rate of infection increased on either side of the optimal window of time (figure 1). This analysis of the effects of practice variation on clinical outcomes, facilitated by the computerized capture of important clinical variables from a large population of 2847 patients, paralleled the results of earlier experiments in animals and clinical trials in humans and has helped to convince hospital leadership to support further initiatives.

In 1987, while these studies were in progress, we convened a multidisciplinary team of hospital department leaders from nursing, the operating rooms, anesthesiology, surgery, the pharmacy, and infectious diseases to examine the processes for antimicrobial prophylaxis. Administering the first dose of antimicrobial prophylaxis “on call” in the patient’s room was the most frequent practice associated with errors in timing. (The recently issued Hospital Infection Control Practices Advisory Committee Guideline for Prevention of Surgical Site Infection, 1999 [24] states, “Clearly, the concept of ‘on-call’ infusion of antimicrobial prophylaxis is flawed simply because delays in transport or schedule changes can mean that suboptimal tissue and serum levels may be present when the operation starts.”) In addition, multiple persons (floor nurses, operating room nurses, recovery room nurses, and anesthesiologists) had responsibilities for administering antimicrobial prophylaxis. Nurses in the holding room volunteered to take primary responsibility for giving the first dose according to a checklist placed in the patient’s chart. When this process was put into place, the proportion of patients who were given antimicrobial

Table 1. Perioperative use of antibiotics at LDS Hospital, Salt Lake City, for patients undergoing procedures for which antibiotic prophylaxis was indicated: 1985–1991 and 1992–1998.

<table>
<thead>
<tr>
<th>Timing of administration of antibiotics</th>
<th>Percentage of patients who received antibiotic prophylaxis during study year(s)</th>
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<tbody>
<tr>
<td>Early</td>
<td>12</td>
</tr>
<tr>
<td>Optimal</td>
<td>40</td>
</tr>
<tr>
<td>Late</td>
<td>27</td>
</tr>
<tr>
<td>Never</td>
<td>21</td>
</tr>
</tbody>
</table>

NOTE. During 1985–1991, study periods ranged from 3 to 6 months. During 1992–1998, study periods consisted of 3 months per year. Early, administration 2–24 h before incision; late, administration after time of incision; optimal, administration within a 2-h window of time before the surgical incision was made.
Figure 1. Rates of surgical wound infection corresponding to the temporal association between administration of antibiotics and the start of surgery. Numbers shown above the intervals are the number of infections/number of patients for each interval. Numbers shown to the left of the arrow (time of incision) on the X-axis denote hours before the time of surgical incision. Trend toward higher rates of infection for each hour of delay in administration of antibiotics after surgical incision was significant ($Z$ score = 2.00; $P < .05$ by Wilcoxon test). Adapted from [23] (used with permission).

prophylaxis within the 0- to 2-h window of time before surgery increased from 58% in 1986 to 72% in 1988 (table 1).

However, the nurses still had no way to identify patients for whom antimicrobial prophylaxis was indicated. Further improvement was achieved by use of the decision-support capabilities of the Health Evaluation through Logical Processing [19] information system to target patients for whom antimicrobial prophylaxis was indicated by placing a standing order (with the agreement of the surgeons) on the computer-generated operating room schedule. With this innovation, correct timing increased to 96% in 1991. Because of the objections of some surgeons to potential liability, notwithstanding the gains, the program was discontinued in 1992, and the percentage of patients who received antimicrobial prophylaxis 0–2 h before the incision decreased from 96% to 80% (table 1). When this evidence was reviewed, the program was reinstated. From 1993 through 1998, the timing was optimal for 97%–99% of the patients who required antimicrobial prophylaxis, as determined from the results of 3-month study periods each year.

Pharmacists have continued to review postoperative antibiotic therapies on the basis of the decision-support alerts and have always been the human intermediaries between the computer suggestions and the surgeons. With continual feedback about the data and quarterly analyses of postoperative use of antibiotics from 1988 to 1998, the percentage of patients who received antimicrobial prophylaxis for >24 h decreased from 29.8% to 5.8%, and the average number of doses of antibiotics given per patient decreased from 10 to 4.2. Although the overall proportion of patients who received antibiotics at LDS Hospital increased during the past decade, the proportion that used antibiotics for surgical prophylaxis remained stable [25]. More remarkable was a 38% reduction in inflation-adjusted costs of antibiotics and a 64% reduction in rates of antibiotic-associated adverse drug events, as well as relatively stable antibiotic resistance patterns.

One lesson of this long history of what is now seen as an example of quality improvement [26] is the great difficulty in changing systems of care, even in an institution with an advanced computerized information system. Documenting the adherence to common guidelines and the relevance of these guidelines to the clinical outcomes would have been a formidable, if not impossible, task even in our system. The message, however, can be applied in any health care facility, regardless of its information infrastructure. Indeed, the Joint Commission on Accreditation of Healthcare Organizations has adopted timing of antimicrobial prophylaxis as a core comparative performance measure, and a consensus statement from a workshop convened by the Centers for Disease Control and Prevention and the National Foundation for Infectious Diseases has listed optimization of antimicrobial prophylaxis for operative procedures as the first strategic goal for the prevention of the emergence and spread of antimicrobial-resistant microorganisms in hospitals [1].

THE ERRORS AGENDA

The LDS Hospital experience documented that, at least in one hospital, there was considerable variation in the timing of antimicrobial prophylaxis and that administration of such prophylaxis in the 2 h before surgery reduces the risk of wound...
infection. Lee and Olson [27] proposed an alternative strategy for assessing the problem at the Minneapolis Veterans Administration Medical Center by retrospectively reviewing 104 patients with surgical site infections that complicated 8480 low-risk cases; they reported that 89 practice flaws were found in these 104 cases, of which 23 were errors in the use of antibiotics. This insight suggested another means to assess other dimensions of antimicrobial prophylaxis in addition to timing, as well as a practical method to identify errors in accord with the Institute of Medicine’s mandate (i.e., surveillance of adverse outcomes in the tradition of health care epidemiology).

To identify further opportunities for improving antimicrobial prophylaxis, we reviewed all patients who had deep sternal or mediastinal infections that complicated open heart surgery at LDS Hospital in 1996. Although the rate of sternal infections was acceptably low (17 [1.7%] in 976 operations), we found that errors associated with antimicrobial prophylaxis occurred in 6 (35%) of the 17 infected patients. These errors were most often failures of intraoperative dosing in prolonged operations, but occasional charting problems led to lack of documentation of the patients having received any antimicrobial prophylaxis. Continuing efforts to address such problems led to steady improvement so that, by 1999, no errors were found for 16 patients who developed sternal infections (table 2). The improvement was not reflected in the gross measure of overall rates of wound infection and demonstrates that, even for high-volume procedures, rates of infection are an insensitive indicator of important problems [28].

A GLOBAL PROBLEM

In the past decade, many investigators have reported rates of errors in the timing of antimicrobial prophylaxis similar to the problem described at LDS Hospital. For example, the Health Care Quality Improvement Project of New York State reported that 27%–54% of all patients did not receive antimicrobial prophylaxis in a timely fashion in a retrospective review of 2651 specified surgical procedures (aortic grafts, hip replacements, or colon resections) performed during 1993 at 44 hospitals [29]. There were no major differences between teaching and nonteaching hospitals with regard to the optimal use of antimicrobial prophylaxis, but premature timing was more frequent for operations with start times that occurred later in the day. Many similar studies have been reported from the United States, The Netherlands, Spain, Israel, Canada, India, and Brazil [30–39].

At the Society for Healthcare Epidemiology of America’s annual meetings from 1993 through 1999, 19 abstracts described studies that reported errors in the timing of administration of antimicrobial prophylaxis. However, only approximately half of these studies were designed to determine whether the errors were associated with increased rates of surgical site infections, and even fewer documented successful efforts to improve timing and to subsequently show that improved timing was followed by reduced rates of infection. Systematic approaches to ensure that antibiotics are used at the optimal time are clearly the turf of health care epidemiology; the role that publication bias may have played in discouraging similar reports simply because they report nothing new is unknown.

Errors in antimicrobial prophylaxis are unlikely to stir public interest in the same way as the headline-grabbing Institute of Medicine report. However, given the high cost of surgical site infections [40, 41] and the strong evidence that lower rates of infection can be achieved with programs to optimize antimicrobial prophylaxis, the health care epidemiology community should accord this problem its highest priority. A focus on the root causes of errors in the systems of care, rather than on the mistakes of individual surgeons, offers the greatest potential.

Table 2. Perioperative use of antibiotics among patients who developed sternal infections at LDS Hospital, Salt Lake City: 1996–1999.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of operations</th>
<th>With infection</th>
<th>Who received inappropriate prophylaxis</th>
</tr>
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<tbody>
<tr>
<td>1996</td>
<td>976</td>
<td>17 (1.7)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>1997</td>
<td>1035</td>
<td>30 (2.9)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1998</td>
<td>963</td>
<td>12 (1.2)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>1999</td>
<td>932</td>
<td>16 (1.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

References

15. Improved prophylactic antibiotic use through an educational and concurrent reminder program. Utah Peer Review Organization/UlPSRO Update 1981; 4(1).