Antibiotic Combinations with Redundant Antimicrobial Spectra: Clinical Epidemiology and Pilot Intervention of Computer-Assisted Surveillance

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Redundant antibiotic combinations are a potentially remediability source of antibiotic overuse. At a public teaching hospital, we determined the incidence, cost, and indications for such combinations and measured the effects of a pharmacist-based intervention. Of 1189 inpatients receiving ≥2 antibiotics, computer-assisted screening identified 192 patients (16.1%) receiving potentially redundant combinations. Chart reviews showed that 137 episodes (71%) were inappropriate. Physician overprescribing errors were found in 77 episodes (56%); most involved redundant coverage for gram-positive or anaerobic organisms. In 76 episodes (55%), lapses in the medication ordering and distribution system led to the persistence in the pharmacy records of regimens no longer active according to the patient charts. The incidence of redundant antibiotic combinations was significantly higher in the intensive care unit and surgery services, compared with medical services. Interventions to discontinue redundant agents were successful in 134 (98%) of the 137 episodes. Potential drug cost savings and reduction in redundant antibiotic combination days were $10,800 and 584 days, respectively; pharmacist time for patient review and intervention cost $2880. Use of redundant antibiotic combinations was common, and a pharmacist-based intervention was feasible, with a potential annualized cost savings of $48,000.

Excessive antimicrobial use is an important contributor to drug resistance, treatment costs, and adverse effects [1–4]. Although many approaches for controlling antibiotic use among inpatients have been recommended [2], little attention has been paid to redundant antibiotic combinations as a potentially remediability problem. Several studies have included redundant combinations in broader surveys of prescribing errors and have noted up to a 15% incidence of such errors [5–8]. However, relevant details, such as cost, specific combinations that were deemed inappropriate, reasons for redundant prescribing, or the effects of efforts at remediation, if any, were not reported. In a point prevalence survey based on computerized pharmacy records, we found that, for 19% of patients receiving ≥2 antibiotics, the combinations were redundant [9]. Therefore, we performed a prospective survey for potentially redundant antibiotic combinations among hospitalized patients to better describe the epidemiology of this phenomenon and to assess the impact of a pharmacist-based intervention.
METHODS

We designed a cross-tabulation table of all 39 systemically administered antibacterial drugs (hereafter referred to as “antibiotics”) on our formulary and designated those combinations that were potentially redundant. Potentially redundant antibiotic combinations were defined as those in which the antimicrobial spectrum of one drug is largely or wholly subsumed within that of the other (e.g., metronidazole and piperacillin-tazobactam) and for which we were unaware of evidence of effectiveness for treating individual indications. However, because such combinations may be appropriate for dual indications (e.g., metronidazole for treatment of diarrhea caused by Clostridium difficile combined with piperacillin-tazobactam for treatment of hospital-acquired pneumonia), ascertaining of the clinical indications for each episode was necessary to determine the appropriateness of the potentially redundant antibiotic combination.

To facilitate surveillance for potentially redundant antibiotic combinations, we designed and implemented a computer program. Data from the inpatient pharmacy computer system were downloaded to our infectious diseases server on a daily basis at midnight [10], and a computer query was written to identify adult inpatients at our 600-bed public teaching hospital who were receiving ≥2 antibiotics. A clinical pharmacist who specializes in infectious diseases (R.C.G.) then manually applied the table of potentially redundant antibiotic combinations to these patients to identify cases eligible for chart review. Patients were excluded if they were on the labor and delivery ward or were on the HIV ward and were receiving trimethoprim-sulfamethoxazole (for treatment of or prophylaxis for Pneumocystis pneumonia) or clarithromycin or azithromycin (for treatment or prophylaxis of Mycobacterium avium complex infection) as part of the potentially redundant antibiotic combination. Patients were also excluded from review if they no longer had an active drug order for both antibiotics in the pharmacy system at the time of the review (e.g., when an order to discontinue one of the antibiotics had been entered into the pharmacy computer since the report was generated). Finally, informed by previous experience [9], we excluded patients on the obstetrics/gynecology ward who were receiving erythromycin (for premature rupture of membranes) and ampicillin (for treatment or prevention of infection with Streptococcus agalactiae) [11].

The infectious diseases clinical pharmacist (R.C.G.) reviewed the charts and medication administration records of patients identified by this surveillance program who were receiving potentially redundant antibiotic combinations and, if necessary, contacted the prescribing physician to determine the indications of such combinations. If the clinical indications for the regimen were appropriate, no action was taken. However, the clinical pharmacist recommended modification of the antimicrobial regimen in all cases in which inappropriate combinations were being administered because of unintentional or intentional overprescribing by physicians. Unintentional prescribing errors by physicians included inadvertent ordering of multiple antibiotics or incomplete knowledge of the patient’s antimicrobial regimen (e.g., multiple physicians writing orders for the same patient). Intentional prescribing errors by physicians were defined as antibiotic combinations prescribed with intended overlap but which, in our judgment, lacked proven or likely clinical benefit. An infectious diseases physician (D.N.S.) was consulted when the appropriateness of the antimicrobial regimen was ambiguous or when the ordering physician disagreed with the pharmacist’s recommendations.

Orders for antimicrobials and other medications in our hospital are handwritten by physicians on triplicate order forms and transcribed to a paper-based medication administration record by the patient’s nurse. A pharmacy technician who makes hourly rounds transports copies of these orders to the inpatient pharmacy where they are entered into patient-specific computerized pharmacy records. Time lags between order changes and their subsequent entry into the pharmacy files have been shown previously to result occasionally in persistent mismatches between ward and pharmacy records [12]. When manual chart review demonstrated that such delays had caused the false appearance of potentially redundant antibiotic combinations in a patient’s computerized pharmacy file (e.g., orders in the inpatient pharmacy computer system that were no longer active on the ward), the infectious diseases clinical pharmacist corrected the computerized pharmacy record to prevent the continued preparation, dispensing, and potentially inadvertent administration of these drugs. These episodes were defined as medication ordering and distribution system errors.

Confirmed episodes of administering redundant antibiotic combinations were stratified by medical service and the source of error. Medical services were classified as medicine, surgery, or intensive care unit (ICU), to allow statistically meaningful comparisons. Rates (with 95% CIs) were calculated as confirmed redundant antibiotic combinations per 100 adult inpatient–antibiotic days (i.e., the number of days on which a patient received ≥1 antibiotic) and were compared between the different services using Epi Info, version 6 (Centers for Disease Control and Prevention).

Acquisition costs of redundant drugs were calculated using the Public Health System unit drug cost. Cost for intentional and unintentional overprescribing was determined by multiplying the cost of the redundant antibiotic by the number of days it was administered. Potential cost savings were estimated by multiplying the cost of the redundant agent by the number of days that therapy with the other antibiotic was continued, as...
Figure 1. Flow diagram of inpatient antibiotic recipients during 23 surveillance days. The distribution of cases of potentially redundant regimens, their appropriateness, sources of confirmed redundancies, and intervention acceptance rate are shown. Patients were excluded because there was no active order at time of review (174 patients), they were being treated by the HIV service (44 patients), or they were on the labor and delivery ward (21 patients).

summing that therapy with the redundant antibiotic would also have been continued. Potential cost savings achieved through correction of medication ordering and distribution system errors were estimated by multiplying the cost of the redundant antibiotic by the number of days that therapy with the other antibiotic was continued, assuming that the doses of redundant agents were dispensed and not reused. The cost of the pharmacist's time for review and intervention were calculated by multiplying hourly salary by the time spent reviewing cases; the costs of medication administration equipment (e.g., tubing) and wasted ward and inpatient pharmacy personnel time were not calculated. This study was reviewed and approved by the Institutional Review Board of Cook County Hospital (Chicago, IL).

RESULTS

On 23 nonconsecutive weekdays during January through March 2001, there were 6969 adult inpatients; 1189 were receiving ≥2 antibiotics, of whom 431 (36.2%) were identified as receiving potentially redundant antibiotic combinations (figure 1). One hundred ninety-two patients (16.1%) who were receiving ≥2 antibiotics met inclusion criteria. After reviewing the charts of these patients, the combinations were considered redundant for 137 (71%), representing 11.5% of patients receiving ≥2 antibiotics. Dual clinical indications (table 1) or potential synergy were judged to have justified the potentially redundant antibiotic combinations for the other 55 episodes (29%) re-
are not listed.

Table 1. Examples of acceptable indications for use of a second antimicrobial in the situation of concurrent administration of another antibiotic with overlapping spectra.

<table>
<thead>
<tr>
<th>Indication in a situation involving a second infection</th>
<th>Antibiotic</th>
<th>No. of episodes[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em>-associated diarrhea</td>
<td>Metronidazole</td>
<td>11</td>
</tr>
<tr>
<td><em>Pneumocystis pneumonia</em>[b]</td>
<td>TMP-SMX</td>
<td>11</td>
</tr>
<tr>
<td><em>Mycobacterium avium complex</em>[b]</td>
<td>Azithromycin</td>
<td>6</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>Amoxicillin</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. TMP-SMX, trimethoprim-sulfamethoxazole.

a Twenty-four episodes of accepted indications that occurred once or twice are not listed.

b Patients were being treated on wards other than the HIV service.

viewed. The redundant episodes were caused by a total of 153 physician prescribing errors and/or by lapses in the medication ordering and distribution system; 16 episodes involved both physician overprescribing and medication ordering and distribution system errors (figure 1). Of the 77 episodes caused wholly or in part by physician prescribing errors, 58 (75%) involved redundant coverage for gram-positive or anaerobic organisms, and 19 (25%) involved redundant coverage for gram-negative organisms (table 2); 38 (49%) resulted from intentional overprescribing, and 39 (51%) reflected unintentional prescribing errors. The other 76 errors were the result of medication ordering and distribution system errors.

The incidence of confirmed redundant antibiotic combinations was significantly higher in ICUs and on surgical floors than on medicine wards (table 3), although the proportion of episodes involving physician overprescribing did not vary significantly between these groupings. Clinical pharmacist recommendations to physician prescribers and interventions to correct distribution errors were successful in 134 (97.8%) of 137 redundant episodes; only 3 (2.2%) required adjudication by an infectious diseases physician.

Redundant antibiotic combinations resulting from physician prescribing errors were administered on 173 inpatient antibiotic-days (2.2 days per episode), at a total drug cost of $2800 (approximately $36 per episode). Continuation of the redundant drug therapy until discontinuation of the agent with which it was combined (i.e., as might have occurred in the absence of the pharmacists’ intervention) would have resulted in an additional 105 unnecessary antibiotic-days, at a cost of $1700. The cost of redundant antibiotic combinations caused by medication ordering and distribution system errors was estimated to be $6300 for 306 inpatient antibiotic-days (approximately $83 per episode). Overall potential total cost savings and days of redundant antibiotic combinations that could have been avoided were $10,800 and 584 days, respectively. An annualized savings estimate would be $60,000, and approximately 3500 redundant inpatient antibiotic days would be avoided. The clinical pharmacist spent 0.33 h per case for review and interventions, at a total cost of $2880 for this cohort. This would provide an estimated net cost savings of $48,000 per year.

DISCUSSION

We found that redundant antibiotic combinations constituted a substantial proportion (11.5%) of multiple-antimicrobial regimens given to adult inpatients, that both physician over-prescribing and hospital medication ordering and distribution system errors contributed to this problem, and that pharmacist-based recommendations and interventions were widely accepted and cost-effective. Because we accepted commonly used combinations that have theoretical benefit (e.g., in 6 cases, “double gram-negative coverage” consisting of a β-lactam combined with an aminoglycoside or fluoroquinolone), 11.5% is probably a conservative estimate of the prevalence of redundant antibiotic combinations.

Combination therapy has become popular as a means of providing broader coverage and potential antimicrobial synergy [13, 14]. However, our findings suggest that such combinations were often prescribed inappropriately. A substantial proportion of prescribing errors were unintentional and resulted from physicians not knowing which antibiotics their patients were receiving or which were ordered by a colleague. An increased frequency of redundant antibiotic combinations might be anticipated in ICUs, given the greater intensity of antimicrobial use in that setting [15], but we found that, after adjustment for patient-days for antibiotics, the incidence of administration of redundant combinations was significantly higher in both ICUs and surgical services than in medical services. This suggests that additional and as-yet-unidentified factors must be contributory. The high rate of physician acceptance of our recommendations may reflect the facts that clinical pharmacists

Table 2. Most common redundant antibiotic combinations associated with intentional or unintentional physician prescribing errors.

<table>
<thead>
<tr>
<th>Antibiotic combination</th>
<th>No. (%) of times redundant regimen prescribed[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin-tazobactam and cefazolin</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Vancomycin and cefazolin</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Clindamycin and cefazolin</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Levofloxacin and erythromycin</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Clindamycin and penicillin</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Cefoxitin and metronidazole</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Clindamycin and piperacillin-tazobactam</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Ceftriaxone and amoxicillin–clavulanic acid</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam and ceftazidime</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

a Thirty-nine episodes of administration of redundant antibiotic combinations that occurred once or twice are not listed.
are well integrated into clinical care at our institution and that physicians routinely utilize their expertise.

Our findings and prior experiences [6–8] suggest that unnecessary administration of redundant antibiotic combinations may be readily identified in other hospitals. Although approximately one-half of our cases reflected medication ordering and distribution system errors (e.g., patient transfer or discharge or an order to discontinue the antibiotic prescription not yet processed by the pharmacy), other hospitals have reported similar problems, suggesting that such lapses are not unique to our institution [16, 17]. The likelihood that implementing our program will produce cost benefits for other hospitals depends on the local prevalence of redundant antibiotic combinations [18]. Nevertheless, correcting these redundant combinations should also yield reductions in selection pressure for antimicrobial resistance and, possibly, reductions in adverse events.

Our cost estimates are conservative because they do not take into account costs for unnecessary use of equipment or personnel time. However, they assume that therapy with the redundant antibiotic combination would have been continued as long as the longest-administered antibiotic was given. Moreover, we assume that unused antibiotic doses dispensed by the pharmacy as a result of medication ordering and distribution errors were not reused and, therefore, were wasted. However, because antibiotic doses dispensed in intravenous piggyback form can often be reused [19], and because we did not attempt to measure how often this occurred, the cost savings associated with rectification of medication ordering and distribution errors must remain speculative. Nonetheless, we feel that the results of this study are sufficiently compelling to warrant routine implementation of computer-assisted surveillance for redundant antibiotic combinations at our institution, and to facilitate this, we have programmed our table of potentially redundant antibiotic combinations to automatically identify suspect episodes for review.

To further address intended but unnecessary prescribing of redundant antimicrobial combinations, it will be important to educate clinicians about indications for combination therapy [13, 14]. In addition, improvements in clinical information and medication ordering systems have the potential to reduce errors caused both by the medication ordering and distribution system and inadvertent physician prescribing. The wider availability of provider computerized order entry with links to the results of microbiological testing and clinical indications should make it possible to alert clinicians at the time that redundant antibiotic combinations are being ordered [20].

### References


