Impact of a Computerized Integrated Antibiotic Authorization System

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ABSTRACT: **Background:** Overuse and abuse of antibiotics is a major cause of microbial resistance. Within the hospital setting such overuse necessitates real-time supervision by infectious diseases (ID) specialists.

Objectives: To evaluate the impact of a recently introduced computerized antibiotic authorization system on the pharmacy budget.

Methods: The study was performed in a 400 bed university hospital. With the new system, antibiotic requests are entered electronically by the ward physician and reviewed within minutes to hours by ID specialists. The feedbacks are seen in the wards and pharmacy. Successive years, one before and the other after introduction of the system, were compared.

Results: During the first year with the new system 7167 antibiotic requests were entered; 20% of them were rejected, mainly for improper indication (43% of the rejections). During that year the antibiotic expenditure was reduced by 17%, compared to the previous year (~equal to 200,000 US$), and was against the trend of the last 5 years. Of the 35 antibiotics under the control of the ID team, the use of 7 was probably curtailed by the supervision. Pareto analysis revealed that four drugs constituted › 50% of the pharmacy's expenses. The mortality rate (per 1000 hospitalization days) during those 2 years fell from 4.0 to 3.8.

Conclusions: Computerized antibiotic control by ID specialists is a feasible cost-saving new modality that may help reduce unnecessary antibiotic prescriptions.

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KEY WORDS: antibiotic, antimicrobial, computerized system, antibiotic control, management, health care costs

The assumption that antibiotics are generally safe has fostered overuse and has led to an increase in bacterial resistance [1]. Overuse and abuse of antibiotics cannot be overemphasized [2-5]. These problematic practices have been noticed in both the community and the hospital setting [4,6,7]. In hospitals, antibiotics constitute a non-negligible proportion of the pharmacy's budget.

In the past decade patients' charts and laboratory tests in our hospital became computerized, unlike antibiotic control that continued by means of cumbersome paper work. It became clear that proper control of the prescription practices is possible solely by an online real-time computerized system. We evaluated the impact of the introduction of such a system in a medium-size hospital.

METHODS

SYSTEM OUTLINE

The Bnai Zion Medical Center is a government 400 bed acute-care referral hospital located in Haifa and is affiliated with the Faculty of Medicine of the Technion. The computerized antimicrobial management program was designed as a tool to provide the hospital in general and the pharmacy in particular with better control over the use of antimicrobial agents. The system comprises three key players: the attending physician, the infectious diseases specialist, and the pharmacist. The program is integrated into the computer-based patient records at Bnai Zion and makes available as much patient-specific information as possible. The program can be accessed on computer terminals throughout the hospital. The program is also available for inspection by the ID physicians by remote access from their homes. Most antimicrobials available on the hospital's formulary (except for penicillin G, ampicillin, amoxicillin-clavulanate, cefazolin, ceftriaxone and gentamicin) require authorization by an ID physician (controlled antibiotics). At the time of this writing, the system covers

Table 1. Hospitalization data

	1 July 2009-30 June 2010	1 July 2010-30 June 2011
Hospitalizations	40,306	39,765
Excluding newborns	36,795	36,280
Hospitalization days	151,228	162,060
Hospitalization days (not newborns)	140,718	146,365
Percent occupancy	93.3%	91.5%
No newborns	94.5%	96.1%
Annual deaths	609	623
Mortality/1000 hospital days	4.0	3.8

Table 2. Major antibiotic consumption change at Bnai Zion Medical Center, 2010/11 vs. 2009/10

Antibiotic (all IV)	% change of unit price	% change of total consumption*	% change in total expenditure*	Probable reason for change
Amikacin	102.6	221.4	227.1	Lack of gentamicin
Amphotericin (liposomal)	100.3	-4.5	-4.6	Return of product to distributor
Amphotericin	123.3	78.9	97.3	
Ampicillin	103.5	97.3	100.7	
Ampicillin-sulbactam	99.5	103.9	103.4	
Amoxicillin-clavulan	89.3	103.7	92.6	
Anidulafungin	96.6	221.1	213.5	New drug
Azithromycin	99.8	82.1	81.9	ID control
Cefamycin	118.5	84.6	100.2	
Ceftazidime	93.3	130.8	122	Policy change + patient mix
Ceftriaxone	82.1	104.6	85.9	Price change
Cefuroxime	94.3	107.7	101.6	
Ciprofloxacin	92.6	101.3	93.8	
Clindamycin	99.8	73.4	73.2	ID control
Cloxacillin 0.5 g	108.9	106.2	115.7	
Cloxacillin 2 g	99.7	44.8	44.6	
Colistin	98.8	101.3	100.1	
Daptomycin	101.2	50	50.6	Patient mix
Ertapenem	99.8	81	80.8	ID control
Fluconazole	79.2	99.6	78.9	Price change
Gentamicin	103.4	56.1	58	Shortage
Imipenem	99.8	76.7	76.6	ID control
Levofloxacin	92.7	86.7	80.3	ID control
Linezolid	99.7	130.5	130.1	Patient mix
Meropenem 0.5 g	102.6	269	276	
Meropenem 1 g	99.8	80.4	80.2	
Ofloxacin	99.8	21.4	21.3	ID control
Penicillin G	99.8	89.4	89.2	
Piperacillin-Tazobactam	85.7	88.5	75.8	ID control + price change
Ticarc-Clavulan	83.6	60.6	50.6	Change in policy
Tigecycline	95	35.9	34.1	Change in policy
Vancomycin 1	91.3	88.3	80.7	
Vancomycin 0.5 g	92	113.4	104.3	
Voriconazole	99.6	165.1	164.4	Patient mix
Tab. Voricon 200 mg	98.8	146.7	144.9	
Tab. Linezolid 600 mg	124.5	260	323.6	

Antibiotics with a total expense of < 500 NIS were excluded from this list
* Compared to the previous year

the entire hospital, except for the intensive care unit which requires daily rounds by the ID team.

FLOW OF DATA

Once the attending physician has chosen the required antibiotic(s), a message is displayed on both the pharmacy and the ID unit computers. Response by the ID team is given within 0–2 hours during working hours, within 2–4 hours in the afternoons, and the next morning for requests placed at night. Since the patients' well being is the top priority, permission to provide the antibiotic is given for the first 24 hours, even if an ID consult is not available. Beyond these 24 hours, nurses are not allowed to dispense the antibiotic and the ID consultant is contacted by phone. The ward nurses have a real-time picture of which antibiotics have not yet been approved and can alert the residents.

THE DECISION TOOL

The display on the ID consultant's desktop contains a summary of the patient's chart, which includes the admission diagnoses, latest kidney function, antibiotic allergies (if any), and the reason for the requested drug. Additional information – such as admission history, concurrent drugs taken by the patient, and laboratory tests (hematology, chemistry, microbiology) – is available through the computer-based medical record. If the data are adequate a decision is made to approve (usually for 3 days) or reject the regimen. The system also allows for the addition of teaching remarks or requests for clarification. When critical information needed for reaching a decision is missing the patient is seen by the ID team; alternatively, the attending physician is contacted by phone. When the allocated time (3 days) is over, the request is renewed automatically but requires reapproval.

MEASURES

The period under investigation was from July 2010 (implementation of the new system) to June 2011. This period was compared to the preceding year in terms of total expenditure of the pharmacy and expenditure on the antibiotics under control. Comparisons were made by antibiotic type and by ward. To control for confounding factors such as change in volume of patients, or price changes, the admission and discharge data as well as the absolute volume of dispensed drugs were examined. For each observed change in total consumption/price, we tried to determine the cause (computerized ID control, price change, change of policy, shortage). In order to evaluate the impact of the different antibiotics on the budget, we performed a Pareto analysis of the entire list of antibiotics. There have been no noticeable infectious outbreaks in our hospital during the period under study. The number of antibiotic requests, the rejec-

tions by the ID team and the reason for the rejections were also analyzed.

The study, which was retrospective in nature, was granted an exemption by the local Helsinki committee. There were no changes in antibiotic prescription policies during the study period.

RESULTS

Expenditure for antibiotics at the Bnai Zion Medical Center during the first period under observation was 15.6% of the pharmacy drug budget, which decreased to 13.6% during the second period. During these successive periods the number of hospitalizations (excluding newborns) at Bnai Zion had decreased by 1.4%, but the number of hospitalization days had increased by 4.0% [Table 1]. Thus, it is remarkable that during the same period the total antibiotic expenditure was curtailed by 17% (4.1 million NIS, down to 3.4 million NIS). There was no increase in the total mortality rate during the year under observation. In fact, a slight decrease (4.0 to 3.8/1000 hospitalization days) was noted.

During both periods the antibiotic expenditure in the intensive care unit (six beds) constituted roughly 12.5% of the pharmacy's antibiotic budget. Notably, the ICU was not controlled by the computerized system and thus could serve as an internal control. During the successive years, the antibiotic expenditure in the ICU dropped by only 5.7%; this rate confirms the impact of the computerized system.

Analysis of the entire spectrum of antibiotics (those under control and those without control) revealed some interesting findings [Table 2]. First, the hospital formulary contains at least 35 different antibiotics. Second, the prices in the two periods remained generally stable (except for five exclusions). Third, while the consumption (units) of some drugs remained stable, others have shown a remarkable change (amikacin, linezolid). This change could be attributed to various factors: price change, antibiotic control by the ID team, shortage, change in policy, and patient mix. Both the total consumption and the expenditure of seven different drugs were curtailed as a result of the ID team control. The combined savings attributed to the curtailed use of these seven drugs totaled 542,322 NIS* (78% of the total savings). Notably, a single drug, piperacillin-tazobactam, constituted 31.2% of these savings. These savings were due to a significant drop in both the cost and the quantity dispensed. It is noteworthy that with the new system the price of piperacillin-tazobactam dropped by 39% during the last quarter. However, by this time point, 75% of this drug had already been dispensed. Thus, most of the savings were due to savings in quantity.

*NIS = new Israeli shekels. At the time of writing one U.S. dollar = 3.8 shekels
ICU = intensive care unit

Table 3. "Pareto" – major contributors to total expense

Rank in 2010/11	Antibiotic (all IV)	Relative contribution 2010/11 (%)	Relative contribution 2009/10 (%)
I	Ertapenem	20.4	21.0
II	Piperacillin-tazobactam	20.0	21.9
III	Azithromycin	6.1	6.1
IV	Imipenem	4.1	4.5
V	Linezolid	3.6	2.3
VI	Clindamycin	3.4	3.9
VII	Amoxy-Clavulanate	3.2	2.9
VIII	Voriconazole	2.8	1.4

Table 4. Infectious diseases and antibiotic consultations 1 July 2010 to 30 June 2011

	No.	%
Antibiotic consults		
Approved	5731	
Rejected	1436	
Reasons for rejection*		
Improper indication#	215	42.5
Prolonged	107	21.2
Dosage (high/low)	81	16.0
Resistant organism	37	7.3
Allergy	8	1.6
Other	57	11.3
ID consults	1851	
Total	9018	

*Based on a convenience sample of the last 505 rejects
Most commonly improper use of wide-spectrum antibiotics

To determine the most costly item in the antibiotic budget, the impact (relative contribution, "Pareto analysis") of the top eight antibiotics (in terms of expense) was tabulated [Table 3]. Two antibiotics, intravenous ertapenem and intravenous piperacillin-tazobactam, constituted > 40% of the total expenditure. Surprisingly, intravenous azithromycin ranked third on this list.

The infectious diseases team has received more than 9000 computerized requests during the first year of implementation (in addition to curbside and telephone consults). Of the requests, 20.5% were pure ID consults and the rest were antibiotic approval requests [Table 4]. Of the 7167 antibiotic requests, 20% were rejected, mainly because of improper indication.

DISCUSSION

This study shows that computerized antibiotic control is both feasible and a considerable cost saver. During the first year of the program's implementation we observed a drop of 694,000 NIS (currently about US$ 181,000) in antibiotic

expenditure (or 17% of the pharmacy's expenditure on antibiotics). Furthermore, 78% of these savings were attributed directly to the intervention of the ID physicians.

Antimicrobial management can be carried out by two basic strategies: clinical decision support and direct antimicrobial approval [8-11]. In the former, decisions are taken by any physician, while in the latter the decisions are made solely by ID physicians. Both strategies have advantages and disadvantages, but both can be financially self-supporting and may improve patient care [12-14]. We chose to apply the second system and found that the savings could easily support more than one full-time ID physician [15]. Extrapolation from our results to the entire State of Israel (population 7.8 million) implies a total saving of ~28 million NIS (US$ 8million) for the health care system. Remarkably, a recent study surveying antibiotic policy measures in 977 acute French hospitals found that information technology support was the least commonly applied measure [16].

A computerized antibiotic control system has many advantages over simple paper surveillance. A computerized system operates in real-time, and decisions are sometimes made within minutes of the original request. It thus prevents unnecessary doses or inaccurate dosages of antibiotics, and permits immediate feedback to the attending physicians. With our 'old' paper system the pharmacy was visited only once a day; this routine was clearly of limited efficacy. An important example of the benefits of the new system was the implementation of stop orders for drugs such as azithromycin. The long tissue half-life of azithromycin (2–4 days) enables a short course of 3–5 days for most cases of pneumonia. Before institution of the computerized system, stop orders were not implemented vigorously at our hospital. Azithromycin was sometimes prescribed for 7–10 days. Additionally, the immediate feedback to the attending physicians has a clear educational benefit. When the indication for a specific antibiotic is inappropriate the elements of the decision process are discussed with the physician in real-time. It is clear that a system that provides a full platform for seeing the patients' data and is accessible remotely (Intra- and Internet) is advantageous. A computerized system also allows immediate control by the pharmacy of the ward supplies and real-time output of reports by the pharmacy or ID team.

Analysis of the rejections of antibiotic requests revealed an opportunity for educational effort in terms of antibiotic stewardship. More than 40% of the rejections were for improper indication. These included selection of third-line drugs such as ertapenem for community-acquired infections, or the choice of antibiotics for non-infectious cases. Although uncommon, some patients received an antibiotic to which they were allergic (e.g., piperacillin-tazobactam for a patient allergic to penicillin). This point is worrisome due to its highly adverse potential. Although educational efforts may prove useful here, implementation of an internal computerized control order seems necessary.

Despite the overall benefit, the system described here may have some drawbacks. For example, the system allows requests to be placed even by inexperienced interns. This is a factor that can be changed by permits. We felt that a non-negligible percentage of the rejects could have been prevented had a senior physician overviewed the process. In addition, this study describes only one year of experience. Thus, we could not control for inter-year fluctuations. Another component that was not explored in depth was the impact of antimicrobial management on patient outcome. Towards this end we examined the overall mortality rate at the Bnai Zion Medical Center and found an actual drop per 1000 hospital days. Last but not least, the results in a 400 bed hospital shown here may not be generalizable to larger hospitals where the patient mix may be considerably different.

In conclusion, computerized antibiotic control is a feasible, educational, cost-saving new modality that may help reduce the number of unnecessary antibiotic prescriptions. Other medical centers should consider implementing this beneficial instrument.

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Capsule

Selection of IgA-secreting cells in the gut

The gut needs to keep its trillions of microbial inhabitants contained. The immune system has evolved a multifaceted approach to this problem, which includes the production of large quantities of immunoglobulin A (IgA) in the intestinal mucosa. In a process that is not well understood, plasma cells that produce IgA specific for the gut microflora are selected in Peyer's patches in the gut. Kawamoto et al. used genetically manipulated mice to show that the inhibitory co-receptor, programmed cell death-1 (PD-1), is required for the proper selection of IgA-secreting cells in the gut. The effect of PD-1 deletion, however, was not intrinsic to the B cells that produce IgA. Instead, the absence of PD-1 affected the differentiation of T follicular helper cells, which provide important signals to B cells that help guide them as they develop the capacity to produce microflora-specific IgA. Mice deficient in PD-1 exhibited alterations in the composition in their microflora, which suggests that defective selection of IgA can perturb the careful balance that exists between the immune system and resident bacteria.

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Capsule

The American College of Rheumatology issues guidelines for management of lupus nephritis

To establish the 2012 lupus nephritis guidelines, investigators reviewed the medical literature from 1966 through 2010 for all evidence pertaining to "lupus kidney disease." Three panels of researchers were involved with reviewing the data and producing the recommendations, which include:

- Advising renal biopsy (in previously untreated patients with active nephritis)
- Adjunctive treatment (background therapy with hydroxychloroquine, ACE inhibitors, control of blood pressure to goal of 130/80 or lower for almost all SLE patients with nephritis)
- Induction of improvement in patients

with ISN Class III/IV lupus glomerulonephritis
with Class IV or IV/V plus cellular crescents
with Class V "pure membranous" lupus nephritis

- Maintaining improvement in patients responsive to induction therapy (with azathioprine or mycophenolate mofetil)
- Changing therapies in patients not adequately responsive to induction therapy
- Identifying vascular disease in SLE patients with renal abnormalities
- Treating nephritis in pregnant patients

Despite the availability of new therapeutics, studies have shown an increase in the incidence of end-stage renal disease from lupus over the past twenty years, with specific increases in young patients, African Americans, and in the southern U.S. "We look forward to seeing a reduction in these trends with implementation of these guidelines as part of high-quality, comprehensive care for SLE patients," said Dr. Hahn. The authors acknowledge that the guidelines are limited by the absence of agreed terms for remission, flare and response, and limited data to inform recommendations for steroid dosing and tapering of immunosuppressive therapies. Dr. Hahn concludes, "Ongoing evaluation and expansion of the guidelines is necessary to further improve outcomes for patients with SLE and nephritis."

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