Cefuroxime Utilization Evaluation: Impact of Physician Education on Prescribing Patterns

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Abstract

Background: Cefuroxime is a second-generation cephalosporin antibiotic used widely for the treatment of various infections.

Objectives: To assess the appropriateness of cefuroxime usage as well as the long-term impact of re-feeding the results to prescribing physicians.

Methods: Drug utilization evaluation involved three data-collecting periods, each comprising 6 weeks, during which all patients receiving cefuroxime were evaluated. Results of phase I were distributed to all physicians in a newsletter and departmental lectures; phase II was announced and conducted 6 months later. An identical phase III was unannounced and conducted one year after phase II. The study included all patients receiving cefuroxime during the three phases. The main outcome measure was appropriateness of initiation, and continuation beyond 3 days, of empirical treatment. Appropriateness was determined according to a prepared list of indications based on the literature and the hospital's protocols.

Results: Cefuroxime was initiated appropriately in 104 of 134 patients (78%) in phase I, in 85 of 100 (85%) in phase II, and in 93 of 100 (93%) in phase III ($P<0.001$). Cefuroxime was continued appropriately after 3 days in 58/134 (43%), 57/100 (57%) and 70/100 (70%) respectively ($P<0.001$). The total number of appropriate treatment days out of all treatment days increased from 516 of 635 (81%) in phase I, to 450 of 510 (88%) in phase II, to 485 of 509 (95%) in phase III ($P<0.001$). The principal reason for cefuroxime usage was community-acquired respiratory tract infection.

Conclusion: Drug utilization evaluation may provide valuable data on the usage of a particular drug. This information, once re-fed to physicians, may improve utilization of the particular drug. This positive effect may be prolonged beyond the immediate period of observation.

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Drug utilization evaluation is an established tool to assess the appropriateness of usage of different medications [1–3]. The purpose of DUE is to detect possible problems with, and improve, drug use [1]. DUE has focused on drugs with frequent side effects, for example, digoxin; with high price tags, e.g., antimicrobial agents [4,5]; or with complicated dosing regimens, like aminoglycosides [6].

Most hospitals control the prescribing of the newer broad-spectrum antimicrobials in order to control costs and delay emergence of bacterial resistance [7–9]. In our medical center it was recently decided to discontinue supervision of cefuroxime usage. This second-generation cephalosporin is widely used for various community-acquired infections as well as for some nosocomial infections, usually in conjunction with an aminoglycoside. Because of concern about possible misuse of the drug once supervision by infectious disease physicians was removed, a prospective DUE was conducted.

Patients and Methods

This study was performed in a 550-bed university-affiliated medical center. It was precipitated by the decision to discontinue supervision of the prescribing of cefuroxime; the first phase of the study was performed 6 months later. This consisted of a 6 week data-collecting period, conducted by one physician who daily reviewed the drug cardexes of all admitted patients. When cefuroxime was prescribed, the survey physician reviewed the patient's medical record to ascertain the diagnosis for which the antibiotic was used. No attempt was made to confirm or refute the diagnoses, and no intervention was made during the data-collecting stage. The initiation of cefuroxime, as well as the continuation beyond 3 days after initiation, was classified as appropriate or inappropriate according to a prepared list of indications for cefuroxime usage [Appendix 1]. This list, distributed previously to all physicians, was based on the hospital's protocols for antimicrobial usage in infections commonly

DUE = drug utilization evaluation

Table 1. Appropriateness of therapy with cefuroxime

Variable	Phase 1 No. (%) (n=134)	Phase 2 No. (%) (n=100)	Phase 3 No. (%) (n=100)	*P**	*P***	*P****
Initiation of treatment was appropriate/ all patients receiving drug	104 (78)	85 (85)	93 (93)	NS	0.05	<0.001
Discontinued ≤3 days	60 (45)	34 (34)	25 (25)	NS	NS	<0.001
Continued >3 days appropriately	58 (43)	57 (57)	70 (70)	<0.01	0.05	<0.001
Continued >3 days inappropriately	16 (12)	9 (9)	5 (5)	NS	NS	<0.05
Total duration of appropriate treatment days/all treatment days	516/635 (81%)	450/510 (88%)	485/509 (95%)	NS	0.05	<0.001

* Difference between phases 1 and 2.
** Difference between phases 2 and 3.
*** Difference between phases 1 and 3.

encountered in the hospital. These protocols in turn are based upon the literature, the antimicrobials available in the hospital, and the results of the local microbiology laboratory, including susceptibility patterns.

The results of the first phase of the study were analyzed and distributed to all the hospital's physicians. This was done in the form of a personal letter that included the overall results and the main reasons for inappropriate use. Attached was the list of appropriate indications for initiation and continuation of cefuroxime, and an announcement of a repeat survey to be conducted several months later. In addition, the infectious diseases consultants lectured on the topic of appropriate antimicrobial therapy in general and cefuroxime in particular in all major departments. The second phase of the study was conducted by the same physician 6 months after completion of the described educational efforts. One year after completion of the second phase of data collecting, an unannounced third survey, identical to the earlier surveys, was carried out. However, this survey excluded those departments whose usage of the study drug was insignificant; in addition, pediatrics, which was included in phase 1 and 2, was not included in phase 3.

During the entire period no attempts were made to control or influence cefuroxime usage. The pharmacy's data on monthly usage of antimicrobial agents, by department, were used in order to detect possible changes in drug utilization of other antimicrobial agents during and after the survey periods. The hospital's committee on human experimentation permitted this study to be conducted; and it was not deemed necessary to obtain informed consent from the patients who were reviewed.

Data were computerized using the QuattroPro package (Borland Inc., USA). Results were analyzed with the analytical tools provided by the same program. Statistical analysis was performed with Student's *t*-test and Chi-square analysis [10]. Significance levels were set at $P<0.05$.

Results

During the first study period, cefuroxime was appropriate in 130 of 170 patients (76%) who received the drug; during the second period it was appropriate in 104 of 121 (86%) who received the drug ($P<0.05$). During the first period 625 of a total of 806 cefuroxime treatment days (77%) were considered appropriate, as compared to 514 of 604 (85%) in the second period ($P<0.001$). The principal departments that administered cefuroxime during the first two stages of the study were: medicine (43%), acute geriatrics (21%), pediatrics (19%), and urology (4%). The remaining treatment courses (13%) were in surgical departments, otorhinolaryngology, the intensive care unit, and the emergency department. The third phase of the study was carried out one year after completion of the second phase in order to assess the maintenance of high appropriateness of drug usage. As mentioned earlier (see Methods), this phase included only departments with high cefuroxime usage. Therefore, in the subsequent comparisons, departments not included in phase 3 were deleted from the list of departments in phase 1 and 2. Appropriateness of initiation, continuation after 3 days, and total duration of cefuroxime treatment in the three phases of the study are presented in Table 1. Mean duration of treatment (±SD) was 4.7±2.9 days in phase 1, 5.1±2.5 days in phase 2, and 5.1±2.0 in phase 3; differences were statistically insignificant.

Table 2. Indications for initiation of cefuroxime therapy

Indication	Phase 1 (n=134)	Phase 2 (n=100)	Phase 3 (n=100)
Pneumonia, community acquired	63 (47%)	47 (47%)	56 (56%)
Bronchitis	37 (27%)	28 (28%)	32 (32%)
Pneumonia, hospital acquired*	0 (0%)	6 (6%)	3 (3%)
Other	4 (3%)	4 (4%)	2 (2%)
Inappropriate	30 (22%)	15 (15%)	7 (7%)

* With aminoglycoside

The principal indications for initiation of cefuroxime therapy were respiratory tract infections [Table 2]. The main indication for continuation of cefuroxime beyond the initial empirical 3 days of treatment was an appropriate clinical indication (according to the list of indications) with relevant culture results being unavailable in 49 (36%) in the first phase of the study, 57 (57%) in the second phase, and 68 (68%) in the third phase. Sputum cultures had been sent in only 14%, 16% and 15% (P=NS) of patients with respiratory tract infections in the three phases of the study, respectively. The principal reasons for inappropriate use of cefuroxime were urinary tract infection: 13 of 29 patients (45%) in phase 1, 5 of 15 patients (33%) in phase 2, and none of 7 in phase 3

($P<0.001$ between phase 1 and 3); and empirical treatment of an otherwise undiagnosed febrile illness: 9 of 29 patients (31%) in phase 1, 6 of 15 (40%) in phase 2, and 3 of 7 (43%) in phase 3.

The appropriateness of cefuroxime usage, according to department, is presented in Figure 1. All departments showed improvement in appropriateness of utilization over time. This improvement reached statistical significance for all departments except for geriatrics, where the initial improvement did not continue until the third phase. In phase 3, the geriatric department utilized cefuroxime significantly less appropriately (76%) than other departments ($P<0.01$). The monthly drug use, expressed in defined daily doses, in the two years during which the study surveys were conducted was as follows: ampicillin 1,218±242, cefuroxime 486±69, gentamicin 517±77, ciprofloxacin 274±56, and ceftazidime 107±27. Despite small monthly fluctuations, no significant change in use of these agents was noted.

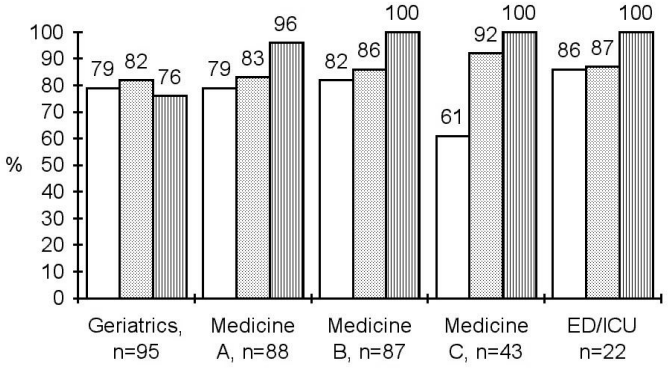

Figure 1. Appropriateness of cefuroxime treatment: breakdown by department (%). Phase 1 = open bars; phase 2 = light grey; phase 3 = dark grey. ED/ICU = Emergency Department/Intensive Care Unit. The differences respectively between phase 1 and 2, 2 and 3, and 1 and 3 were as follows: Geriatrics: NS, NS, NS; Medicine A: NS, <0.01, <0.001; Medicine B: NS, <0.001, <0.001; Medicine C: <0.001, <0.01, <0.001; ED/ICU: NS, <0.001, <0.001.

Discussion

Antimicrobial agents are among the most frequently prescribed drugs [11,12]. Many concerns have been voiced in recent years regarding the emergence of microbial resistance to commonly used antibiotics [13], the apparent overuse of these drugs [14], and the enormous expenses involved [9]. Therefore, since the early 1970s most hospitals have adopted policies to control the use of certain broad-spectrum antimicrobials [15]. These policies are usually formulated by infectious diseases physicians, microbiologists and pharmacists, and the application of these policies is often monitored by the same professionals, with or without computer programs [11,16,17] The efficacy of these efforts has recently been questioned [18]. Therefore, DUE may complement these controlling efforts [19–21].

The prescription of antimicrobial agents is typically governed by four major decisions [22]. Firstly, after diagnosis of an infectious process that is deemed to require antibiotic therapy, a decision needs to be made regarding empirical therapy. Many factors may influence this decision — namely, the more likely causative organisms, the susceptibility patterns of these organisms in the particular location or hospital, the available antimicrobial agents that would cover these organisms, specific host factors like concurrent immunodeficiency and renal function, pharmacokinetic factors, and cost. The second decision involves adaptation of antimicrobial therapy, usually 2 to 3 days after initiation of therapy. The principal reason for adaptation is a result from the microbiology laboratory regarding a relevant clinical specimen. The third decision concerning hospitalized patients on intravenous antimicrobial therapy involves the change to an oral drug. The final decision concerns the overall duration of antimicrobial treatment. The latter two decisions are very much influenced by clinical factors. Therefore, in this study we focused on the first two decisions, i.e., initiation of empirical therapy, and adaptation of therapy up to 3 days after commencement of treatment.

The predetermined list of indications for appropriate initiation of cefuroxime therapy used in this study was based on the hospital's guidelines for use of antimicrobial agents, distributed in the form of a pocket booklet to all physicians [23]. Many physicians and pharmacists would regard this list [Appendix 1] as excessively liberal. Nonetheless, in the first phase of the study, cefuroxime was found to be given appropriately in only 78% of the patients. During the second phase, performed after phase I results were distributed to all physicians and conducted approximately half a year later, the appropriateness of initiation had improved to 85%. No further attempts were made to influence cefuroxime utilization, and the third phase of the study was conducted one year later without prior announcement. In this phase, appropriateness of cefuroxime utilization had further increased to 93% ($P<0.001$). The same trends were observed for cefuroxime treatment days [Table 1]. As shown previously, one of the main reasons for what was considered inappropriate use of cefuroxime was empirical therapy for urinary tract infection. Our educational efforts were successful with regard to this particular reason for cefuroxime usage; we observed a decrease in inappropriate reasons for use of the study drug for urinary tract infection from 45% in phase 1 to 33% in phase 2 to 0% in phase 3 ($P<0.001$). We believe that *initial* treatment with cefuroxime in patients admitted for community-acquired urinary tract infection is inappropriate for two reasons; firstly, only 82% of associated strains of Enterobacteriaceae isolated in our laboratory are susceptible to cefuroxime, and, secondly, *Pseudomonas aeruginosa* appeared to be the causative organism in up to 10% of patients [24]. Isolation of a cefuroxime-susceptible organism allows for *adaptation of the initial* antibiotic regimen, which in our hospital — as elsewhere — consists of ampicillin and gentamicin.

This study also attempted to assess the appropriateness of continuation of treatment with the study drug after the initial 3 day empirical treatment period. We found that the main indication for continuation of cefuroxime beyond this point was an appropriate clinical indication (according to the list of indications) with relevant culture results being unavailable in 36% of patients in the first phase of the study, 57% in the second phase, and 68% in the third phase. Sputum cultures had been sent in only 15% of patients with respiratory tract infections in the three phases of the study. It seems highly likely therefore, that if sputum cultures were sent more frequently the results could lead to a substantial change from cefuroxime to penicillin if penicillin-susceptible strains of *Streptococcus pneumoniae* were isolated. We believe that *initial* therapy of patients with community-acquired respiratory tract infections requiring hospital admissions warrants a second-generation cephalosporin, and not penicillin, because of the 10–30% penicillin resistance rate of isolates of *Streptococcus pneumoniae* in this country [25,26] and the beta-lactamase production of at least 40% of strains of *Haemophilus influenzae* [24]. Isolation of a penicillin-susceptible strain from a relevant culture, i.e., sputum or blood sample, would allow for an antibiotic change to penicillin. However, the failure to obtain a sputum culture prior to initiation of antibiotic therapy in the majority of patients has led to a vast, and probably unnecessary continuation of cefuroxime beyond the initial empirical treatment period. Despite our efforts, we were evidently unable to influence physicians' behavior in this respect.

In summary, this study has confirmed that DUE provides important quantitative and qualitative data on the use of a particular drug. This information, once re-fed to the treating physicians, does improve prescribing habits and utilization of the drug. This positive effect may outlast the immediate period of surveillance. Although the reason for this effect is unclear, we believe that few circumscribed indications for drug usage play an important role. In addition, this study was able to identify a likely reason for inappropriate continuation of cefuroxime therapy beyond the initial 3 days of empirical therapy, namely, significant underutilization of the sputum culture. Unfortunately, this study did not show any improvement in ordering of this simple laboratory test.

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Appendix 1. List of indications for cefuroxime therapy

A. Initial, empiric therapy, up to 3 days, for patients under 6 years of age

1. Pneumonia, including community acquired, excluding strong evidence for viral (i.e., typical bronchiolitis) or atypical pneumonia.
2. Cellulitis.
3. Osteomyelitis, excluding hematogenic.
4. Septic arthritis.
5. Lymphadenitis.
6. Suspected bacteremia, excluding meningeal involvement and excluding infants up to 6 weeks of age.

B. Initial empiric therapy, up to 3 days, for patients of any age

1. Pneumonia, community acquired.
2. Pneumonia, hospital acquired, only if combined with an aminoglycoside.
3. Bronchitis.
4. Sinusitis.
5. Cholecystitis.
6. Any invasive infection caused by an organism susceptible to cefuroxime and not to a less advanced and broad spectrum antimicrobial.
7. Other indications, to be approved after consultation with an infectious disease consultant.

C. Continuation of cefuroxime beyond 3 days

1. Bronchitis and pneumonia in adults, or septic arthritis, bacteremia or other invasive infection at any age, when culture results indicate infection with an organism susceptible to cefuroxime but not to less advanced antibiotics.
2. Bronchitis and pneumonia in adults, or septic arthritis, bacteremia or other invasive infection at any age, when culture results are not available.
3. All other indications described under A and B, when clinically indicated according to the attending physician.