

Changes in the Use of Broad-Spectrum Antibiotics after Cefepime Shortage: a Time Series Analysis

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The original cefepime product was withdrawn from the Swiss market in January 2007 and replaced by a generic 10 months later. The goals of the study were to assess the impact of this cefepime shortage on the use and costs of alternative broad-spectrum antibiotics, on antibiotic policy, and on resistance of *Pseudomonas aeruginosa* toward carbapenems, ceftazidime, and piperacillin-tazobactam. A generalized regression-based interrupted time series model assessed how much the shortage changed the monthly use and costs of cefepime and of selected alternative broad-spectrum antibiotics (ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam) in 15 Swiss acute care hospitals from January 2005 to December 2008. Resistance of *P. aeruginosa* was compared before and after the cefepime shortage. There was a statistically significant increase in the consumption of piperacillin-tazobactam in hospitals with definitive interruption of cefepime supply and of meropenem in hospitals with transient interruption of cefepime supply. Consumption of each alternative antibiotic tended to increase during the cefepime shortage and to decrease when the cefepime generic was released. These shifts were associated with significantly higher overall costs. There was no significant change in hospitals with uninterrupted cefepime supply. The alternative antibiotics for which an increase in consumption showed the strongest association with a progression of resistance were the carbapenems. The use of alternative antibiotics after cefepime withdrawal was associated with a significant increase in piperacillin-tazobactam and meropenem use and in overall costs and with a decrease in susceptibility of *P. aeruginosa* in hospitals. This warrants caution with regard to shortages and withdrawals of antibiotics.

Shortages of antibacterial drugs have become a worldwide problem and threaten to be more frequent in the near future (9). The Study Group for Antibiotic Policies of the European Society for Clinical Microbiology and Infectious Diseases (ESGAP) drew attention to their increasing incidence in the member states of the European Union and beyond during the last 10 years. In a survey among 55 hospitals in 23 European countries, 69% reported antibacterial shortages within the last 12 months (12). Shortages give several causes for concern. They can affect patient care if therapy used for replacement is less effective or less well tolerated (1). In the case of some antibiotics, especially those with the broadest spectrum of activity, shortages will deprive patients of one of the already scarce therapeutic options against multiresistant bacteria. These problems and a possible higher acquisition cost of the alternative agents can result in higher health care costs (23). Finally, the shortage of an antibacterial drug will increase the selective pressure exerted on bacteria by substitute drugs or may even lead to the use of agents with a broader spectrum of activity, two consequences that contribute to the development of antimicrobial resistance.

In Switzerland, increasing frequency of drug shortages affects clinical practices as well (15). Cefepime—one of the 10 most frequently used antibiotics from 2004 to 2006 in a sentinel network of 60 Swiss acute care hospitals—was withdrawn from the Swiss market in January 2007 (21). Neither generic cefepime nor any other “fourth-generation” cephalosporin was on the market at that time. A generic was approved by the Swiss Agency for Therapeutic Products in October 2007.

We studied how hospitals adjusted to the withdrawal of

cefepime. The primary aim of the study was to evaluate the changes in the consumption of other broad-spectrum antibiotics after this withdrawal and after the subsequent release of the generic. The secondary aims were to assess the impact of these changes on hospital antibiotic policies, on overall costs of the broad-spectrum antibiotics, and on the proportion of *Pseudomonas aeruginosa* not susceptible to carbapenems, ceftazidime, and piperacillin-tazobactam. We chose *P. aeruginosa* because of its frequent isolation in the hospital setting and its rapidly changing susceptibility to carbapenems (22).

MATERIALS AND METHODS

Design and setting. This was an observational, retrospective, multicenter study conducted in Swiss hospitals of which the pharmacists volunteered to deliver monthly data on antibiotic consumption. The hospitals were classified in 3 groups: group A, without any cefepime supply since its withdrawal; group B, without any cefepime supply during the shortage and then supply of a generic as soon as it became available; and a control group C of hospitals with uninterrupted cefepime supply thanks to importation from abroad. The study period ran from January 2005 to December 2008. The drug shortage was defined as the time elapsed from the

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date when the manufacturer announced that cefepime was no longer available (January 2007) to the date when the first generic entered the market (October 2007).

Antibacterial consumption data. We collected data on the monthly consumption of broad-spectrum antibiotics with anti-*P. aeruginosa* activity that were most often used in Swiss hospitals—namely, cefepime, ceftazidime, piperacillin-tazobactam, imipenem-cilastatin, and meropenem. We obtained a yearly consumption for all antibiotics with ATC codes J01, J04AB, and P01AB.

Antibacterial consumption in grams was converted into defined daily doses (DDD) using the 2009 release of the DDD by the WHO Collaborative Centre for Drug Statistics Methodology (25) and then expressed in DDD per 100 occupied bed days per month (DDD/100BD/month).

Antibiotic policies. Participants were asked whether cefepime was on their hospital formulary before the withdrawal, if they had antibiotic policies that mentioned cefepime, and how they handled the situation.

Overall costs. We calculated the overall costs by summing up the drug costs based on their ex-factory prices (corresponding to the U.S. wholesale acquisition cost [WAC]) and the costs due to the personnel time and the materials required for drug preparation and administration. The costs were then expressed in U.S. dollars per 100 occupied bed days per month (USD/100BD/month).

Resistance in *P. aeruginosa* isolates. Yearly data were obtained from those study hospitals that were participating to a national surveillance program for antibacterial resistance (www.anresis.ch). The prevalences of nonsusceptibility to carbapenems (meropenem and imipenem-cilastatin), ceftazidime, and piperacillin-tazobactam among *P. aeruginosa* isolates were obtained by dividing the number of isolates either resistant or with intermediate susceptibility by the total number of clinical isolates. MICs were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Doubles, defined as the same microorganism with the same resistance profile in the same patient during the preceding year, were excluded from analysis.

Data analysis. The impact of cefepime shortage on antibiotic policy was estimated by the proportion of hospitals having recommended each one of the (nonexclusive) alternative solution. To estimate and assess the effect of cefepime withdrawal on the consumption of the broad-spectrum antibiotics over time, an interrupted time series (ITS) model was used. First, the Dickey-Fuller test was used to test the appropriateness of the ITS regression (test for trend stationarity in the data) (7). We then identified the presence of autocorrelation and chose a lag of three, according to the rule of $4(T/100)^{2/9}$, where T is the number of observations ($T = 48$) (19). The regressions were performed with Newey-West standard errors (24). For groups A and C, the statistical model included 3 independent variables: (i) a variable which codes for time (from 1 to the time point t), with a coefficient that may be interpreted as the slope of the increase (or decrease) of the consumption before the withdrawal; (ii) a variable “withdrawal” coded as a dichotomous dummy term (0 for prewithdrawal time points, 1 for postwithdrawal time points), with a coefficient corresponding to the change in level immediately after the withdrawal; (iii) an interaction term between “time” and “withdrawal” was coded 0 for all the prewithdrawal time points and then increased across the postwithdrawal time points. The coefficient of this variable corresponded to the change in the slope after the withdrawal. The model for group B had two more independent variables: (i) a variable for the change in level after introduction of the generic and (ii) an interaction term for estimating the change in slope after the end of the shortage. A similar model was used to assess the effect of the cefepime withdrawal on the overall costs of each antibiotic over time.

A paired Wilcoxon signed-rank test was performed to compare differences among means of costs as well as carbapenem susceptibility of *P. aeruginosa* before and after withdrawal of the original cefepime product. A P value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using Stata software 11.0 (Stata Corp., College Station, TX).

RESULTS

Fifteen acute care hospitals participated in the study. Group A (definitive interruption of cefepime supply) included 6 hospitals (from 95 to 365 beds), group B (transient interruption of supply) included 7 hospitals (from 122 to 1,118 beds), and two hospitals (94 and 123 beds) were in group C (no interruption of supply).

Impact of cefepime shortage on antibiotic policy. Before withdrawal, the original cefepime product was on the hospital formulary in all participating hospitals. Written information about the withdrawal was sent to prescribers by infectious disease specialists, pharmacists, or drug committees in all the hospitals that had to deal with the withdrawal. They recommended alternatives such as piperacillin-tazobactam (80% of these hospitals), imipenem-cilastatin (67%), ceftazidime (60%), meropenem (40%), or ciprofloxacin (13%). Some of them encouraged the consumption of other antibiotics, like amoxicillin-clavulanic acid (7%) or ertapenem (7%). The largest hospital reserved its cefepime stockpile for selected wards. Six months after withdrawal, 6/15 (40%) hospitals had officially replaced cefepime in their local guidelines by a substitute drug.

Impact of cefepime shortage on antibiotic consumption. Figure 1 shows the monthly consumption of the five antibiotics in the three groups over the study period.

In group A, the estimated underlying trend of cefepime consumption was already decreasing before the withdrawal by 0.05 DDD/100BD/month (95% confidence interval [CI], -0.07 to -0.03 ; $P < 0.001$) (Table 1). A significant increase in the already upward trend was observed after the withdrawal for piperacillin-tazobactam ($+0.03$ DDD/100BD/month [95% CI, 0.01 to 0.04]; $P < 0.01$), although there was a significant decrease in the level at the moment of the withdrawal (-0.28 [95% CI, -0.45 to -0.11]; $P < 0.01$). The use of imipenem-cilastatin increased until the withdrawal ($+0.03$ DDD/100BD/month [95% CI, 0.02 to 0.04]; $P < 0.001$) and then remained stable. The withdrawal did not have any impact on the low use of ceftazidime and meropenem in this group.

Group B also showed a decrease in cefepime consumption of 0.13 DDD/100BD/month (95% CI, -0.19 to -0.07 ; $P < 0.001$) before the withdrawal. We noted a statistically significant 0.14 DDD/100BD/month increase (95% CI, 0.04 to 0.23; $P < 0.01$) in the consumption of meropenem during the cefepime shortage followed by a new reverse change after the introduction of the generic (-0.17 [95% CI, -0.28 to -0.04]; $P < 0.01$). Each alternative antibiotic had increased its consumption during the shortage.

We observed no statistically significant change in the level and trend in the consumption of broad-spectrum antibiotics other than cefepime after its withdrawal in control group C.

Figure 2 shows the yearly global antibiotic consumption in the three groups from 2005 to 2008, expressed in defined daily doses per 100 bed days, and the proportion of broad-spectrum antibiotics (cefepime, ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam) and selected antibiotics with narrower spectrums (amoxicillin-clavulanic acid, cefuroxime, ceftriaxone, metronidazole, ciprofloxacin, and clarithromycin). We observed a slight decrease of use for the broad-spectrum antibiotics between 2007 and 2008 in groups A and B, where the proportions of narrower-spectrum antibiotics increased, respectively, by 2% and 1%.

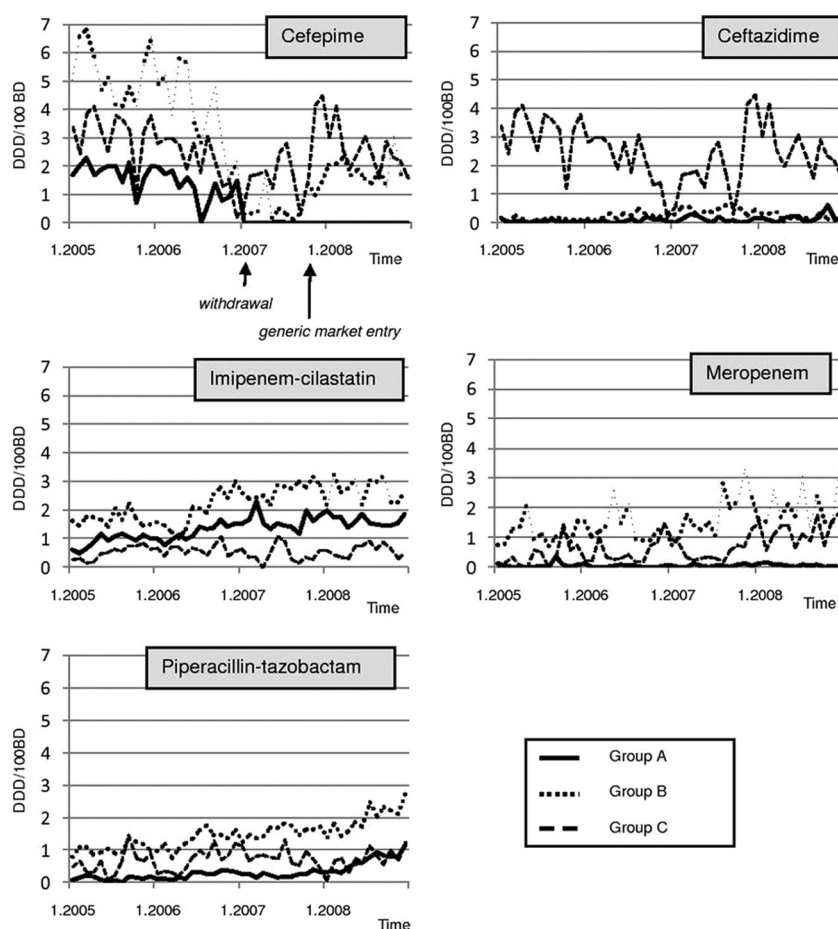


FIG 1 Changes in the monthly use of cefepime and other broad-spectrum antibiotics with anti-*Pseudomonas* activity, expressed in defined daily dose per 100 bed days (DDD/100BD) in group A (hospitals with definitive interruption of cefepime supply), group B (hospitals with transient interruption of supply), and group C (control hospitals without interruption of supply) from January 2005 to December 2008.

Impact on overall costs. In group A, the mean costs per 100 bed days for the five antibiotics was 259.1 USD before the withdrawal and 391.0 thereafter, a significant 51% increase ($P < 0.05$). Taking each antibiotic separately, the ITS analysis revealed a statistically significant increase in costs for piperacillin-tazobactam (+4.29 USD/100BD/month [95% CI, 2.25 to 6.33]; $P < 0.001$).

In group B, the mean costs per 100 bed days was 522.8 USD before the withdrawal and 727.5 thereafter, a significant 39% increase ($P < 0.05$). Taking each antibiotic separately, a significant increase in costs was found for imipenem-cilastatin (+7.79 USD/100BD/month [95% CI, 0.6 to 15.0]; $P < 0.05$) and meropenem (+3.63 USD/100BD/month [95% CI, 1.1 to 6.1]; $P < 0.01$). After the generic cefepime market entry, imipenem use decreased by 16.92 USD/100BD/month (95% CI, -23.5 to -10.4; $P < 0.05$) and meropenem by 5.56 (95% CI, -8.4 to -2.8; $P < 0.001$). The costs of ceftazidime increased during the shortage, although this was not statistically significant, but we noticed a statistically significant decrease in cost level (-9.64 USD/100BD/month [95% CI, -18.8 to -0.5]; $P < 0.05$) and trend (-4.38 USD/100BD/month [95% CI, -6.2 to -2.5]; $P < 0.001$) after the generic cefepime market entry. The control group had a mean cost of 328.0 USD before and 432.5 USD after the shortage, a 32% increase. The ITS analysis revealed no statistically significant change in use after the cefepime withdrawal.

Impact on susceptibility patterns of *Pseudomonas aeruginosa*. The proportion of nonsusceptible *P. aeruginosa* was 13.7% in 2006 (a total of 711 isolates from 8 hospitals) and 15.8% in 2008 (1,233 isolates) for carbapenems ($P = 0.26$), 8.9% (a total of 776 isolates from 8 hospitals) and 11.5% (1,240 isolates) for ceftazidime ($P = 0.12$), and 4.8% (a total 632 isolates from 7 hospitals) and 7.4% (1,065 isolates) for piperacillin-tazobactam ($P = 0.24$). Taking each hospital separately and ranking the hospitals according to the differences in proportion of carbapenem-nonsusceptible *P. aeruginosa*, we show in Fig. 3 that for 6/8 hospitals the difference was positive and that the 4 hospitals with a significant increase in level or trend in consumption of meropenem and/or imipenem are the 4 hospitals with the numerically largest change in proportion of carbapenem-nonsusceptible *P. aeruginosa*.

DISCUSSION

This study assessed the consequences of a shortage of cefepime on the consumption of other broad-spectrum antibiotics, the overall costs associated with the consumption of these antibiotics, and the susceptibility rates of one selected microorganism, i.e., *P. aeruginosa*, to some of the antibiotics that can be used instead of cefepime (carbapenems, ceftazidime, and piperacillin-tazobactam). A first finding was that cefepime withdrawal was associated with a statistically significant increase in the consumption of piperacillin-tazobactam in group A

TABLE 1 Changes in the use of cepfime and other broad-spectrum antibiotics in group A (hospitals with definitive interruption of cepfime supply), group B (hospitals with transient interruption of supply), and group C (control hospitals without interruption of supply)

Drug	Group A			Group B			Group C				
	Avg monthly use before cepfime withdrawal (Jan. 2005 to Dec. 2006)	Level immediately after the withdrawal	Trend after cepfime withdrawal (Jan. 2007 to Dec. 2008)	Avg monthly use before cepfime withdrawal (Jan. 2005 to Dec. 2006)	Level immediately after cepfime withdrawal	Trend during cepfime shortage (Jan. 2007 to Sept. 2007)	Level immediately after generic market entry	Trend after generic market entry (Oct. 2007 to Dec. 2008)	Avg monthly use before cepfime withdrawal (Jan. 2005 to Dec. 2006)	Level immediately after the withdrawal	Trend after cepfime withdrawal (Jan. 2007 to Dec. 2008)
Cepfime	-0.05 (<0.001*)	-0.95 (<0.001*)	0.05 (<0.001*)	-0.13 (<0.001*)	-2.53 (<0.001*)	0.11 (0.06)	1.17 (<0.001*)	0.05 (0.19)	-0.10 (0.001*)	0.17 (0.663)	0.13 (0.002*)
Ceftazidime	0.00 (0.45)	0.01 (0.85)	0.00 (0.57)	0.01 (<0.001*)	0.04 (0.58)	0.01 (0.27)	-0.15 (0.01*)	-0.04 (<0.001*)	0.00 (0.22)	0.00 (0.93)	0.00 (0.17)
Imipenem-cilastatin	0.03 (<0.001*)	0.21 (0.13)	-0.04 (<0.001*)	0.04 (0.04*)	0.05 (0.86)	0.03 (0.38)	0.04 (0.76)	-0.08 (<0.001*)	0.02 (0.11)	-0.40 (0.14)	-0.01 (0.53)
Meropenem	0.00 (0.58)	0.01 (0.57)	0.00 (0.53)	0.01 (0.38)	-0.68 (0.016*)	0.14 (0.001*)	-0.17 (0.002*)	-0.17 (0.009*)	0.04 (0.05)	-0.78 (0.05)	0.03 (0.29)
Piperacillin-tazobactam	0.01 (<0.01*)	-0.28 (0.004*)	0.03 (<0.01*)	0.03 (<0.001*)	-0.18 (0.16)	0.02 (0.34)	-0.38 (0.04*)	0.03 (0.09)	0.01 (0.014*)	-0.19 (0.06)	0.01 (0.44)

^a The coefficients of the time series analysis are expressed in defined daily doses per 100 bed days per month. P values are given in parentheses and are noted with an asterisk when statistically significant.

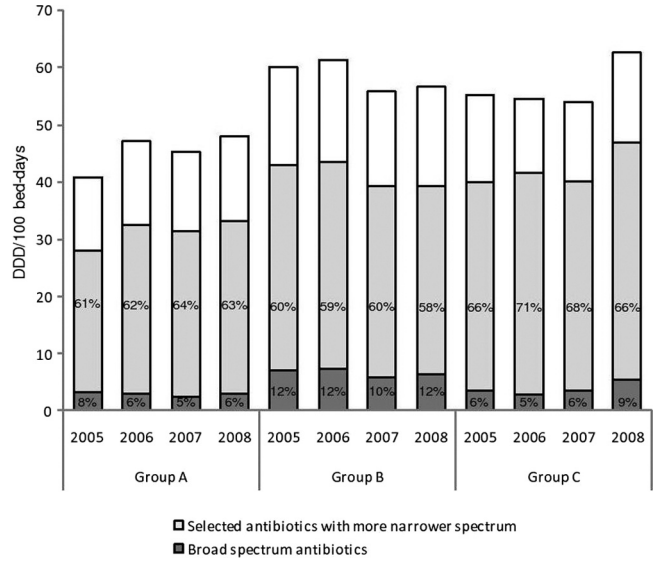


FIG 2 Global antibiotic consumption (ATC code, J01, J04AB, and P01AB) in groups A, B, and C from 2005 to 2008, expressed in defined daily doses (DDD) per 100 bed days, and proportion of broad-spectrum antibiotics (cefepime, ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam) and selected antibiotics with narrower spectrums (amoxicillin-clavulanic acid, cefturoxime, ceftriaxone, metronidazole, ciprofloxacin, and clarithromycin).

(hospitals with definitive interruption of cepfime) and of meropenem in group B (hospitals with transient interruption of cepfime supply). We observed in group B that the consumption of each alternative antibiotic increased during the cepfime shortage. Use of narrower-spectrum antibiotics slightly increased in groups A and B between the periods before and after withdrawal. This may be due to the fact that some hospitals encouraged their consumption in the information about cepfime withdrawal. Second, the shift toward more expensive broad-spectrum agents increased the overall costs significantly in groups A and B. The ITS analysis revealed an increase

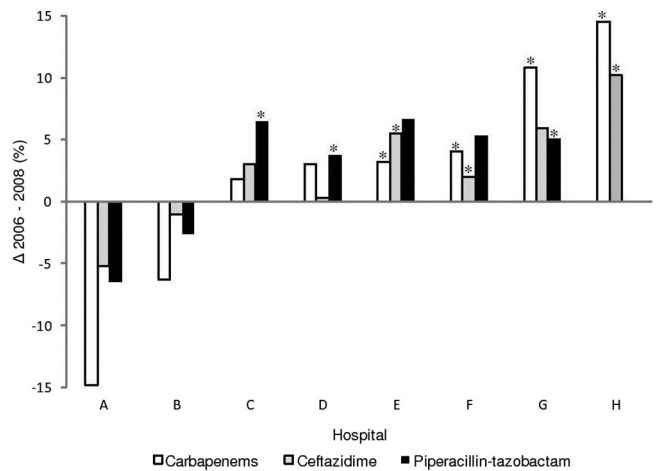


FIG 3 Difference in proportions of *Pseudomonas aeruginosa* not susceptible to carbapenems (imipenem-cilastatin and meropenem), ceftazidime, and piperacillin-tazobactam between 2006 and 2008 in 8 of 15 participating hospitals. The asterisks represent the statistically significant increase in consumption level or trend for imipenem-cilastatin and/or meropenem, ceftazidime, and piperacillin-tazobactam.

in expenses for piperacillin-tazobactam in group A and for imipenem-cilastatin and meropenem in group B. Third, the proportion of *P. aeruginosa* isolates nonsusceptible to carbapenems, ceftazidime, and piperacillin-tazobactam increased, although this trend did not reach statistical significance. We found that hospitals with a statistically significant increase in trend or level of carbapenem consumption showed the most important progression in carbapenem resistance. A progression of resistance was also observed, although to a lesser extent, when the use of ceftazidime and piperacillin-tazobactam statistically increased in trend or level. This suggested that hospitals had to adjust to a cefepime shortage at the price of an increase in resistance in *P. aeruginosa*.

Although the number of drug shortages or withdrawals has been increasing since the early 2000s, published studies of their consequences in the area of antimicrobials are scarce and have not been sufficiently considered. The impact of a piperacillin-tazobactam shortage was studied by Bosso and Kokko, who observed an increased consumption of cefepime, ticarcillin-clavulanate, and antibiotics with antianaerobic activity associated with cost reductions for the institution (2). Mendez et al. showed a significant increase of consumption of alternatives in antimicrobial prescribing in patients admitted 6 months before and during the shortage of piperacillin-tazobactam (16). The increase of overall costs was consistent with that reported in the study of Baumer et al., who found a significant negative impact of drug shortages on finances in hospitals (1). Harbarth et al. observed the effect of penicillin G shortage used for intrapartum prophylaxis of group B streptococcal disease in a tertiary care center (13). The consumption of penicillin G was replaced in obstetrics by ampicillin and in nonobstetric patients potentially eligible for penicillin G treatment by broad-spectrum antibiotics: 62% of patients received cephalosporins, 34% fluoroquinolones, and 25% ampicillin or ampicillin-sulbactam. They concluded that shortage-triggered treatment changes had a negative effect on prescribing patterns.

The relevance of these findings lies in the long-term consequences of antibacterial shortages and especially withdrawals. First, they reduce the therapeutic options available to treat a given bacterium or infection, while using a diversity of therapeutic options, in the context of a formal cycling or not, is one of the recommended strategies to minimize the spread of resistance (4, 5, 8). Shortages and withdrawals may even leave patients infected by multiresistant organisms without therapeutic options. Shortages would not be so worrisome if the absence of new antibiotics under development was not threatening public health (3, 10, 11). Second, shortages and withdrawals may compromise cost-effectiveness of antibiotic therapy. Cefepime, for instance, has been shown to be cost-effective compared to alternative therapies (17, 20). Of note, although ertapenem also has a broad spectrum of activity, it has not been analyzed in this study. Prescription data were observed for this antibiotic only since 2006, and this did not comply with the criteria of using time series analysis, which required data within a minimum of 12 months before the event. The consumption of ertapenem was low in comparison with that of imipenem and meropenem, and it did not correspond to our choice of comparing antibiotics with anti-*Pseudomonas* activity.

One strength of our study is the use of a generalized regression-based interrupted times series analysis, a statistical method more robust than the ones used in most previous studies. Nevertheless, we recognize several limitations. First, the impact on patients' outcomes has not been measured. Second, the DDD methodology

allows comparisons among hospitals, but it may inaccurately reflect the dosages chosen in some of them, thus limiting the qualitative appraisal of different prescribers' profiles (6, 18). Finally, our findings may have alternative explanations. For instance, the publication by Yahav et al. in May 2007 of a possible association between the consumption of cefepime and increased all-cause mortality, in particular in patients with febrile neutropenia, may also have led to a change in the prescription habits (26). This could indeed have contributed to the decreasing consumption of cefepime already observed before its withdrawal, even if the FDA invalidated this association thereafter through meta-analyses and confirmed the appropriateness of cefepime therapy (14).

In conclusion, our study demonstrated that the shortage of a widely used broad-spectrum antibiotic can affect hospital antibiotic policies and has an undesirable impact on costs and bacterial resistance. This pleads for actions that could improve the management of antibacterial shortages. For instance, manufacturers' commitment to the supply of their products could be a condition for drug approval by authorities, or it could be a criterion for the selection of drugs by hospitals, at least for a list of essential antibacterials based on resistance data.

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REFERENCES

- Baumer AM, et al. 2004. National survey of the impact of drug shortages in acute care hospitals. *Am. J. Health Syst. Pharm.* 61:2015–2022.
- Bosso JA, Kokko H. 2004. Assessment of the impact of an antibiotic shortage: patient outcomes and costs. *Hosp. Pharm.* 39:43–47.
- Boucher HW, et al. 2009. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin. Infect. Dis.* 48:1–12.
- Brown EM, Nathwani D. 2005. Antibiotic cycling or rotation: a systematic review of the evidence of efficacy. *J. Antimicrob. Chemother.* 55:6–9.
- Dellit TH, et al. 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin. Infect. Dis.* 44:159–177.
- de With K, Bestehorn H, Steib-Bauert M, Kern WV. 2009. Comparison of defined versus recommended versus prescribed daily doses for measuring hospital antibiotic consumption. *Infection* 37:349–352.
- Donnelly NJ. 2005. Ph.D. thesis. University of New South Wales, Sydney, Australia.
- Fishman N. 2006. Antimicrobial stewardship. *Am. J. Med.* 119:S53–S61.
- Fox ER, et al. 2009. ASHP guidelines on managing drug product shortages in hospitals and health systems. *Am. J. Health Syst. Pharm.* 66:1399–1406.
- Fox JL. 2006. The business of developing antibacterials. *Nat. Biotechnol.* 24:1521–1528.
- French GL. 2008. What's new and not so new on the antimicrobial horizon? *Clin. Microbiol. Infect.* 14(Suppl 6):19–29.
- Harbarth S, Filius PM, Natsch S, MacKenzie FM, Gyssens IC. 2007. Shortage of antimicrobial agents in Europe: results of an international survey, abstr P-1105. Abstr. 17th Euro. Cong. Clin. Microbiol. Infect. Dis., Munich, Germany.
- Harbarth S, Gundlapalli AV, Stockdale W, Samore MH. 2003. Shortage of penicillin G: impact on antibiotic prescribing at a US tertiary care centre. *Int. J. Antimicrob. Agents* 21:484–487.
- Kim P. 2009. Clinical review—cefepime. U.S. Food and Drug Adminis-

- tration, Washington, DC. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/UCM167313.pdf>.
15. Martinelli E. 2004. Versorgungsengpässe mit essentiellen Produkten für die Spitäler der Schweiz. GSASA, Bern, Switzerland. <http://www.spitapo-berner-oberland.ch/BAGVersorgung141204.pdf>.
 16. Mendez MN, et al. 2006. Impact of a piperacillin-tazobactam shortage on antimicrobial prescribing and the rate of vancomycin-resistant enterococci and *Clostridium difficile* infections. *Pharmacotherapy* 26:61–67.
 17. Montalar J, et al. 2002. Cefepime monotherapy as an empirical initial treatment of patients with febrile neutropenia. *Med. Oncol.* 19:161–166.
 18. Muller A, Monnet DL, Talon D, Henon T, Bertrand X. 2006. Discrepancies between prescribed daily doses and WHO defined daily doses of antibacterials at a university hospital. *Brit. J. Clin. Pharmacol.* 61:585–591.
 19. Newey WK, West KD. 1994. Automatic lag selection in covariance matrix estimation. *Rev. Econ. Studies* 61:631–653.
 20. Paladino JA. 1994. Cost-effectiveness comparison of cefepime and ceftazidime using decision analysis. *Pharmacoeconomics* 5:505–512.
 21. Plüss-Suard C, Pannatier A, Kronenberg A, Mühlemann K, Zanetti G. 2011. Hospital antibiotic consumption in Switzerland: comparison of a multicultural country with Europe. *J. Hosp. Infect.* 79:166–171.
 22. Rahal JJ, et al. 1998. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. *JAMA* 280:1233–1237.
 23. Sparling PF. 2001. Shortages of antibiotics, antivirals, and vaccines threaten the public health. *Clin. Infect. Dis.* 33:1502–1503.
 24. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. 2002. Segmented regression analysis of interrupted time series studies in medication use research. *J. Clin. Pharm. Ther.* 27:299–309.
 25. World Health Organization Collaboration Center for Drug Statistics Methodology. 2010. Guidelines for ATC classification and DDD assignment, 13th edition. World Health Organization, Oslo, Norway.
 26. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. 2007. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect. Dis.* 7:338–348.