DOI:10.1111/j.1365-2125.2005.02370.x

Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: Cohort study using data from the UK General Practice Research Database

Stefan Russmann, James A. Kaye, Susan S. Jick & Hershel Jick
Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, MA, 02421, USA

Correspondence
Dr Stefan Russmann, Boston Collaborative Drug Surveillance Program, 11 Muzzey Street, Lexington, MA 02421, USA.
Tel: +1 781 862 6660
Fax: +1 781 862 1680
E-mail: russmann@bu.edu

Keywords
cholestasis, flucloxacillin, GPRD, liver disease, oxytetracycline, population-based cohort study

Received
21 September 2004
Accepted
17 November 2004

Aims
To provide additional quantification of the risk of flucloxacillin-related liver disease and to describe time trends in flucloxacillin prescribing in the UK.

Methods
This was a cohort study using data from the UK General Practice Research Database. We identified patients with a first-time prescription for flucloxacillin or, for comparison, oxytetracycline from 1992 to 2002 and cases who developed clinically documented cholestatic liver disease of uncertain origin after first-time use of these drugs. We also determined the annual frequency of first-time use of flucloxacillin from 1991 to 2000.

Results
We identified 283 097 and 131 189 first-time users of flucloxacillin and oxytetracycline, respectively. The risk of cholestatic liver disease per 100 000 first-time users was 8.5 (95% CI 5.4, 12.6) in the 1–45 days and 1.8 (95% CI 0.6, 4.1) in the 46–90 days after starting flucloxacillin, and 0.8 (95% CI 0.02, 4.3) in the 1–45 days after starting oxytetracycline. The frequency of first-time use of flucloxacillin remained stable between 1991 and 2000.

Conclusions
Flucloxacillin is now established as an important cause of cholestatic liver disease. Warnings about the risk have not had an impact on prescribing practices in the UK, where it remains the predominantly prescribed antistaphylococcal oral antibiotic. This situation in the UK is in sharp contrast to regulatory actions and changes in prescribing habits in Australia after identification of the risk of cholestasis associated with flucloxacillin, and to the predominant use of the alternative drug dicloxacillin in the USA.

Introduction

Flucloxacillin is a penicillinase-resistant halogenated semisynthetic isoxazolyl penicillin used for the oral antibiotic treatment of soft tissue infections caused by *Staphylococcus aureus* (*S. aureus*). Initial case reports from the Netherlands and Scandinavia in the 1980s reported cholestatic liver disease of unknown origin occurring in flucloxacillin users, and subsequently numerous similar reports including several case series from Australia [1–13]. From these reports a well-defined clinical picture of flucloxacillin-associated liver disease was described, which consisted of prolonged painless

jaundice with elevation of cholestatic liver enzymes diagnosed within 2–6 weeks after prescription, and as much as 3 weeks after the drug was stopped. Although most patients eventually recovered within several months, a chronic vanishing bile duct syndrome was reported in some patients [5, 9, 10, 14], and fatal cases were also described [5, 7]. In the early 1990s two population-based epidemiological studies were performed with data from the UK General Practice Research Database (GPRD), which estimated the risk of cholestatic liver disease within 45 days after first-time use of flucloxacillin at about 7 in 100 000 patients [15, 16].

By 1994 the Australian Adverse Drug Reactions Advisory Committee had received 310 reports of liver disease in association with the use of flucloxacillin, including 17 cases with a fatal outcome [17]. After 1994 the Australian Department of Human Services and Health restricted the use of flucloxacillin to severe infections, all advertising by the manufacturer was stopped, and cephalexin and erythromycin were recommended and advertised as alternative treatments [18]. Subsequently prescription dispensings in Australia decreased by about 30% between June 1994 and December 1995 [18]. In the UK only a warning was published by the Medicines Controls Agency (MCA) in the Current Problems in Pharmacovigilance bulletin in 1992 [19], and flucloxacillin is still recommended as first-line treatment for soft-tissue infections caused by *S. aureus* [20].

The primary objective of the current study was to update the frequency estimation of cholestatic liver disease associated with the use of flucloxacillin within the population of the GPRD from 1992 to 2002. Given that in Australia a major change in the usage pattern of flucloxacillin occurred, the second objective of this study was to investigate the prescribing practices of flucloxacillin in the UK following the MCA warning letter and publications in medical journals regarding the risk of flucloxacillin-induced cholestatic liver disease.

Methods

Data resource

The General Practice Research Database (GPRD) is a population-based patient database that comprehensively records medical diagnoses, hospital referrals, prescriptions and demographic details from UK general practices. The GPRD has been described in detail and has been used extensively for pharmacoepidemiological studies. The data have been validated for completeness and quality by the Boston Collaborative Drug Surveillance Program and others [21]. Data collection for the GPRD has also been described in detail in the previous report on cholestatic liver disease associated with flucloxacillin [16]. All the information we received was identified by an anonymous patient number only.

Study population

From the GPRD we derived a study population of all subjects with a first-time prescription of flucloxacillin or oxytetracycline, recorded after 31 October 1992 (end date of previous study [15]) to the end of data collection in 2002.

Case definition

To detect cases of cholestatic liver disease of uncertain origin, we used similar criteria as in the previous studies [15, 16]. All subjects with a coded diagnosis related to cholestatic liver disease recorded within 1–45 days after a prescription for flucloxacillin were identified from the study population. The restriction to cholestatic forms of liver disease and to the interval of 1–45 days after prescription were chosen because of the characteristic clinical picture of flucloxacillin-associated liver disease described in clinical reports of liver disease associated with flucloxacillin [1–13]. For comparison we identified all subjects with a coded diagnosis related to cholestatic liver disease 1–45 days after a prescription for oxytetracycline, a drug that has not been associated with cholestatic liver disease. In addition we also looked for cases of cholestatic liver disease with an onset between 46 and 90 days after prescription of flucloxacillin in the cohort of flucloxacillin users. The comparison with the risk of cholestatic liver disease in oxytetracycline users and during the period of 46–90 days in flucloxacillin users was chosen in order to control for potential selection bias that may be related to the prescription of antibiotic treatment or other unknown factors. The computer-recorded information on all those subjects was then individually reviewed by two of the authors (SR and HJ). For those cases where computer-recorded data were consistent with the diagnosis of idiopathic cholestatic liver disease, detailed clinical records were requested from the corresponding practices, including relevant consultant letters, laboratory test results and hospitalization summaries. Subsequently cases were classified as characteristic of drug-induced cholestatic liver disease when they showed the typical clinical and laboratory features of drug-induced cholestatic liver disease, i.e. painless jaundice with predominant elevation of alkaline phosphatase and bilirubin concentrations, and when no other causes of cholestasis were identifiable. In cases where we did not receive requested patient records because patients had transferred out of the practice, we based our assessment on the available computer-recorded information, which often included laboratory

liver function tests. We excluded all subjects where a causal relationship was unlikely, i.e. if the history and/or laboratory findings were not suggestive of cholestatic liver disease, if a cause of liver disease other than the drug under study was likely, or if the onset of liver disease had occurred before exposure to the drug under study.

Prescribing practices over time

The number of first-time flucloxacillin users and the number of all subjects in the GPRD was recorded for each year between 1991 and 2000, and the frequency of first-time flucloxacillin users per 1000 subjects in the GPRD was calculated.

Data analysis

We calculated the 45 day risks of cholestatic liver disease and their 95% confidence intervals for the time periods of 1–45 days and 46–90 days after the first recorded exposure to flucloxacillin, and 1–45 days after the first recorded exposure to oxytetracycline. For the categorical covariates of male or female sex, and age below 60 years or higher, risk ratios and their 95% confidence intervals were calculated. All calculations were done with STATA statistical software, version 8.2 for MacOS X (STATA corporation, College Station, Texas, USA).

Results

We identified 283 097 patients with a first-time prescription for flucloxacillin and 131 189 patients with a first-time prescription for oxytetracycline from 1 November 1992 until end of data collection in 2002. Age and sex distributions of these two populations are shown in Table 1. After initial review of the computerized patient records, clinical records were requested for 36 subjects, of which 23 were received. After reviewing all available additional clinical information we identified 30 cases considered to be idiopathic cholestatic liver disease. Of these cases, 24 occurred in the 1–45 days after starting flucloxacillin, five occurred in the 46–90 days thereafter, and one occurred in the 1–45 days after starting oxytetracycline. The diagnostic GPRD codes and individual features of all included cases are presented in Tables 2 and 3, respectively. Six out of the 24 cases occurring 1–45 days after flucloxacillin were hospitalized. In all but two cases flucloxacillin was prescribed for soft tissue infections. The median total dose and duration of treatment in the identified cases of flucloxacillin-induced cholestatic liver disease 1–45 days after exposure were 8 g (range 5–56 g) and 7 days (range 5–28 days), respectively, and the median latency time between start of flucloxacillin treatment and diagnosis of liver disease was 25.5 days (range 14–44 days). The concomitant use of a potentially hepatotoxic drug was observed in 4 out of the 24 cases that occurred 1–45 days post flucloxacillin, and in one out of the five cases that occurred 46–90 days after flucloxacillin. In one case augmentin, in

Table 1a
Distribution of flucloxacillin users by age and sex

Age (years)	Male	Female	Total row	%
<20	30599	28973	59572	21.0
20–39	38213	46603	84816	30.0
40–59	32966	36466	69432	24.5
60–79	22696	27267	49963	17.6
>79	5814	13500	19314	6.8
Total column	130288	152809	283097	
%	46.0	54.0		

Table 1b
Distribution of oxytetracycline users by age and sex

Age (years)	Male	Female	Total row	%
<20	10414	7546	17960	13.7
20–39	19780	23279	43059	32.8
40–59	16449	21170	37619	28.7
60–79	12281	14696	26977	20.6
>79	2015	3559	5574	4.2
Total column	60939	70250	131189	
%	46.5	53.5		

Table 2
GPRD diagnostic codes of included cases

GPRD code	Diagnosis
Oxmis codes	
7852	Jaundice
576 A	Obstructive jaundice
7852 JC	Cholestatic jaundice
Read codes	
J66y600	Obstructive jaundice nos
1675.11	Jaundice – symptom
J633.00	Hepatitis unspecified
R024.00	Jaundice (not of newborn)
R024111	Jaundice

Table 3
Individual features of all included cases

	Age (years)	Sex	Latency time (days)	Treatment duration (days)	Total dose (g)	Indication	Concomitant medication and comments
a) Cases 1–45 days after first exposure to flucloxacillin							
Cases where detailed clinical records were available							
1	69	F	41	10	10	Phlebitis	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
2	61	F	24	7	7	Eczema	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
3	58	F	33	7	7	Sebaceous cyst	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
4	69	M	25	7	28	Unknown	Diagnostic work-up identified no other cause of liver disease.
5	61	M	42	14	28	Skin infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
6	35	F	25	7	14	Vaginal infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
7	87	F	26	7	7	Cellulitis	Missed diagnosis caused extensive invasive and noninvasive work-up.
8	68	F	33	14	14	Postop. wound infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
9	69	M	14	7	14	'Rash'	Augmentin 2 days after flucloxacillin
10	47	F	29	7	7	Cellulitis/ abscess	Erythromycin 7 days after flucloxacillin.
11	78	M	18	14	28	Cellulitis/ abscess	Diagnostic work-up identified no other cause of liver disease.
12	42	F	22	5	5	Rosacea	Diagnostic work-up identified no other cause of liver disease.
13	76	F	19	14	56	Postop. wound infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
14	62	F	32	28	28	Phlebitis	History includes explicit expert diagnosis of drug-induced liver disease. Erythromycin 12 days before flucloxacillin

three cases erythromycin, and in one case trimethoprim-sulfamethoxazole were prescribed in close temporal relationship to flucloxacillin (Table 3), and they can therefore not be ruled out as alternative causes for cholestasis in these patients.

The estimated 45-day risk per 100 000 first-time users 1–45 days after flucloxacliin (8.48, 95% CI 5.43, 12.61) was substantially higher than the risk 46–90 days after flucloxacillin (1.77, 95% CI 0.57, 4.12) and 1–45 days after oxytetracycline (0.76, 95% CI 0.02, 4.25) (Table 4).

Only 25% of all first-time flucloxacillin users were age 60 years or more, whereas 67% of patients with cholestatic liver disease after flucloxacillin exposure were within this age group. Subjects with an age of 60 years or above were 6.1 times more likely to develop cholestatic liver disease after flucloxacillin exposure than those with an age below 60 years (95% CI 2.9, 13.0). Sixteen out of the 24 cases were female (67%) compared with 54% in the study population (relative risk 1.7, 95% CI 0.7, 3.9).

The number of first-time flucloxacillin users between 1991 and 2000 remained stable at about 23 first-time users per 1000 subjects in the GPRD per year (Figure 1), and also the average number of prescriptions per user per year remained stable with a mean value of 1.23 (range of mean values for each year from 1991 to 2000 1.20–1.27).

Discussion

In the absence of a validated specific diagnostic test, the establishment of the causal relationship of an adverse event and a drug is a diagnosis of exclusion that is particularly difficult if the manifestation occurs after stopping the treatment and the recovery is prolonged, as is typical for flucloxacillin-induced cholestasis [5, 7, 10,

Table 3
Continued

	Age (years)	Sex	Latency time (days)	Treatment duration (days)	Total dose (g)	Indication	Concomitant medication and comments
Cases where only computer-recorded data were available							
15	43	F	30	7	14	Postop. wound infection	
16	83	F	21	5	5	Toe infection	
17	61	F	24	7	14	Leg abscess	
18	46	M	17	12	12	Finger wound infection	
19	15	M	21	4	8	Hand wound infection	
20	16	F	16	7	7	Chest infection	Trimethoprim/sulfamethoxazole 8 days before flucloxacillin
21	73	M	34	7	14	Pneumonia	
22	68	F	37	7	7	Phlebitis	
23	88	F	44	7	7	Cellulitis	
24	85	M	36	6	6	Skin infection	
b) Cases 46–90 days after first exposure to flucloxacillin							
Cases where detailed clinical records were available							
1	81	F	82	7	7	Cellulitis	Three prescriptions within 6 weeks. Latency time, dose and treatment duration refer only to first prescription. History includes explicit expert diagnosis of drug-induced liver disease.
Cases where only computer-recorded data were available.							
2	84	F	49	5	10	Cellulitis/ abscess	
3	88	F	75	6	6	Abscess	
4	49	F	63	5	5	"lump superficial	Erythromycin 15 days after flucloxacillin.
5	54	F	58	27	27	Phlebitis	First flucloxacillin for 7 days, then flucloxacillin plus ampicillin for 20 days. Latency time refers to first prescription.
c) Case 1–45 days after oxtetracycline							
Detailed clinical records were available							
1	47	M	26	5	5	Cough	Computer-recorded data and detailed patient records were available.

Table 4
45 day risk estimates for cholestatic liver disease after first exposure to flucloxacillin or oxytetracycline

	1–45 days post flucloxacillin	46–90 days post flucloxacillin	1–45 days post oxytetracycline
Study population	283 097	283 097	131 189
Cases	24	5	1
45 day risk with 95% CI per 100 000 users	8.48 (5.43, 12.61)	1.77 (0.57, 4.12)	0.76 (0.02, 4.25)

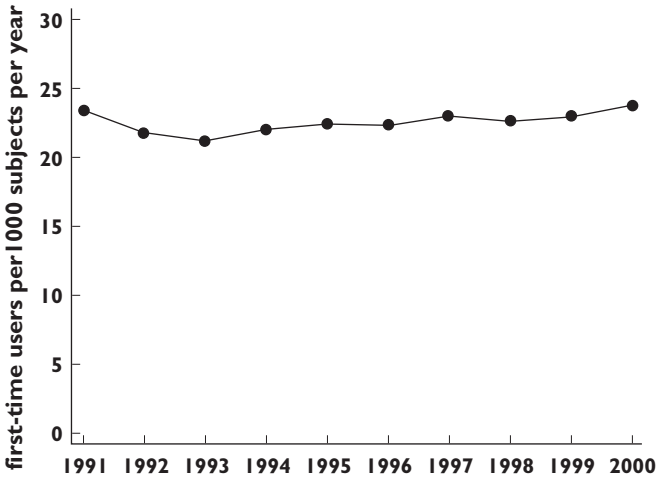

Figure 1
Flucloxacillin use in the UK from 1991 to 2000. Number of first-time flucloxacillin users per 1000 subjects in the GPRD between 1991 and 2000

16]. This may explain the long time-lag between the first marketing of flucloxacillin in the 1970s and the first reports of its idiosyncratic hepatotoxicity in the mid 1980s.

After a large number of individual case reports of flucloxacillin-associated cholestatic liver disease appeared between 1982 and 1993, the association was confirmed by two formal epidemiological studies, which provided a frequency estimation of flucloxacillin-associated cholestatic liver disease of about 7 per 100 000 first-time users [15, 16]. The current follow-up study yielded a similar risk estimate of 8.5 per 100 000 users.

This study relates only to cases of cholestatic liver disease, whereas other forms of liver disease that may be drug-induced were not studied. As in the previous studies oxytetracycline was chosen as a comparison drug because it is a frequently prescribed antibiotic and it has rarely been reported to cause cholestatic hepatitis [15, 16]. Additionally we also determined the risk of developing cholestatic liver disease of unknown origin 46–90 days after exposure to flucloxacillin, i.e. at a time when we assumed that exposure to flucloxacillin was much less likely to be the cause of liver disease. However, a latency time of more than 45 days may be possible in rare cases, and our study does not exclude the possibility that cholestatic liver disease was caused by flucloxacillin in one or more of the five patients where the diagnosis was made between 46 and 90 days after exposure.

Age over 55 years, female sex and a treatment duration longer than 14 days have previously been proposed as risk factors for flucloxacillin-induced liver disease [13, 22]. The current study estimated a six-fold higher risk of cholestatic liver disease after flucloxacillin in patients aged 60 years and older compared with younger patients. By contrast, female sex was not clearly identified as a risk factor, and only one case of cholestasis occurring 1–45 days after flucloxacillin use, and two cases occurring 46–90 days thereafter had a treatment duration of more than 14 days.

We did not detect any material changes in the frequency of first-time prescriptions of flucloxacillin in this UK population-based study between 1991 and 2000. Following the large number of publications in the early 1990s concerning the risk of flucloxacillin-induced liver injury, the UK regulatory authority only published a single warning concerning this issue in 1992 [19]. By comparison the use of flucloxacillin decreased by about 30% after 1994 in Australia, and this was presumably the result of a range of initiatives and interventions that were implemented concurrently and repeatedly over several years, including a governmental restriction of the indication for flucloxacillin use to severe infections, changing the product information, stopping of advertising and recommending cephalexin and erythromycin as alternative treatments [4, 18]. The risk of drug-induced cholestatic liver disease for these alternative drugs has been estimated to be lower, i.e. about 3.6 and 2.0 per 100000 users for erythromycin and cephalexin, respectively [23, 24]. Dicloxacillin is another halogenated isoxazolyl penicillin that is used as oral treatment for *S. aureus* infections in the United States, and that was introduced onto the Australian market in 1997 to provide another alternative to flucloxacillin [25]. It has been reported to have a similar efficacy in soft tissue infections to flucloxacillin [26, 27], but is not marketed in the UK. In previous publications it was stated that there are fewer spontaneous reports of liver disease related to dicloxacillin as compared with flucloxacillin, and that the risk may be lower [4, 22, 25]. The question of the comparative hepatotoxic risk of flucloxacillin and dicloxacillin is highly relevant to public health. However, in the current absence of formal population-based epidemiological studies investigating the risk of liver disease associated with dicloxacillin, differences in the reporting frequency of adverse reactions for flucloxacillin and dicloxacillin cannot be ruled out as the reason for the higher number of reports of liver disease after flucloxacillin use.

We noted that in the previous epidemiological study covering the period from 1985 to 1991, flucloxacillin was diagnosed by the treating physician as the cause of liver disease in only two out of 10 cases, and in one of those two only after flucloxacillin rechallenge with sub-

sequent recurrence of jaundice [16]. By contrast, in the current study that included cases from 1992 to 2002 we identified such an explicit flucloxacillin attribution in eight out of the 14 cases that occurred 1–45 days after flucloxacillin where we received detailed patient records. This finding may well reflect an increased awareness of flucloxacillin's potential hepatotoxicity amongst physicians in the UK, who nevertheless continue to use flucloxacillin as a first-line treatment for soft-tissue infections caused by *S. aureus* [20]. Though one case of cholestatic liver disease per 12 000 first-time users may be considered to be a relatively rare event, it must be taken into account, that the risk is apparently higher in older patients, that flucloxacillin-induced liver disease is a potentially irreversible and lethal disease [5, 7, 17], and that the cases identified in this study only represent a small proportion of the absolute number of cases that occur each year in the UK, where flucloxacillin is a frequently used drug with about two million prescriptions per year [19].

The presented study was entirely investigator-originated and not funded by a third party. Dr Russmann is supported by a Merck Sharp & Dohme International Fellowship in Clinical Pharmacology. We are indebted to the general practitioners who contribute information to the GPRD for their continuing effort and cooperation.

References

1 Australian Adverse Drug Reactions Advisory Committee (ADRAC). Flucloxacillin hepatitis. Australian Adverse Drug Reactions Bulletin 1990; 9: 2.

2 Bengtsson F, Floren CH, Hagerstrand I, Soderstrom C, Aberg T. Flucloxacillin-induced cholestatic liver damage. Scand J Infect Dis 1985; 17: 125–8.

3 Deboever G. Cholestatic jaundice due to derivatives of oxacillin. Am J Gastroenterol 1987; 82: 483.

4 Devereaux BM, Crawford DH, Purcell P, Powell LW, Roeser HP. Flucloxacillin associated cholestatic hepatitis. An Australian and Swedish epidemic? Eur J Clin Pharmacol 1995; 49: 81–5.

5 Eckstein RP, Dowsett JF, Lunzer MR. Flucloxacillin induced liver disease. histopathological findings at biopsy and autopsy. Pathology 1993; 25: 223–8.

6 Gotell P, Loof L. [Effects of floxacillin on the liver. 3 cases of floxacillin-induced cholestatic liver disease]. Lakartidningen 1987; 84: 954–5.

7 Koek GH, Stricker BH, Blok AP, Schalm SW, Desmet VJ. Flucloxacillin-associated hepatic injury. Liver 1994; 14: 225–9.

8 Lobatto S, Dijkmans BA, Mattie H, Van Hooff JP. Flucloxacillin-associated liver damage. Neth J Med 1982; 25: 47–8.

9 Miros M, Kerlin P, Walker N, Harris O. Flucloxacillin induced delayed cholestatic hepatitis. Aust N Z J Med 1990; 20: 251–3.

10 Turner IB, Eckstein RP, Riley JW, Lunzer MR. Prolonged hepatic cholestasis after flucloxacillin therapy. Med J Aust 1989; 151: 701–5.

11 Tauris P, Jorgensen NF, Petersen CM, Albertsen K. Prolonged severe cholestasis induced by oxacillin derivatives. A report on two cases. Acta Med Scand 1985; 217: 567–9.

12 Victorino RM, Maria VA, Correia AP, de Moura C. Floxacillin-induced cholestatic hepatitis with evidence of lymphocyte sensitization. Arch Intern Med 1987; 147: 987–9.

13 Fairley CK, McNeil JJ, Desmond P, et al. Risk factors for development of flucloxacillin associated jaundice. Br Med J 1993; 306: 233–5.

14 Davies MH, Harrison RF, Elias E, Hubscher SG. Antibiotic-associated acute vanishing bile duct syndrome: a pattern associated with severe, prolonged, intrahepatic cholestasis. J Hepatol 1994; 20: 112–6.

15 Jick H, Derby LE, Dean AD, Henry DA. Flucloxacillin and cholestatic hepatitis. Med J Aust 1994; 160: 525.

16 Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. Med J Aust 1993; 158: 596–600.

17 Australian Adverse Drug Reactions Advisory Committee (ADRAC). Fatal hepatic reactions to flucloxacillin. Australian Adverse Drug Reactions Bulletin 1994; 13: 10–1.

18 Roughead EE, Gilbert AL, Primrose JG. Improving drug use: a case study of events which led to changes in use of flucloxacillin in Australia. Soc Sci Med 1999; 48: 845–53.

19 UK Medicines Control Agency (MCA). Flucloxacillin-induced cholestatic jaundice. Current Problems Pharmacovigilance 1992; 35: 2.

20 PRODIGY Guidance. http://www.prodigy.nhs.uk. Access date May 11, 2004.

21 Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy 2003; 23: 686–9.

22 Olsson R, Wiholm BE, Sand C, Zettergren L, Hultcrantz R, Myrhed M. Liver damage from flucloxacillin, cloxacillin and dicloxacillin. J Hepatol 1992; 15: 154–61.

23 Derby LE, Jick H. Henry DA, Dean AD. Erythromycin-associated cholestatic hepatitis. Med J Aust 1993; 158: 600–2.

24 Jick H, Derby LE. A large population-based follow-up study of trimethoprim-sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. Pharmacotherapy 1995; 15: 428–32.

25 Australian Adverse Drug Reactions Advisory Committee (ADRAC). A comparison of dicloxacillin with flucloxacillin. Australian Adverse Drug Reactions Bulletin 1999; 18: 7.

26 Roder BL, Frimodt-Moller N, Espersen F, Rasmussen SN. Dicloxacillin and flucloxacillin. pharmacokinetics, protein binding and serum bactericidal titers in healthy subjects after oral administration. Infection 1995; 23: 107–12.

27 Rodriguez-Solares A, Perez-Gutierrez F, Prosperi J, Milgram E, Martin A. A comparative study of the efficacy, safety and tolerance of azithromycin, dicloxacillin and flucloxacillin in the treatment of children with acute skin and skin-structure infections. J Antimicrob Chemother 1993; 31(Suppl E): 103–9.