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Frequency of drug-induced liver injury in children receiving anti-staphylococcal penicillins

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Introduction: Anti-staphylococcal penicillins (ASPs) are among the most commonly prescribed antibiotics in children and are associated with a risk of drug-induced liver injury (DILI). Despite the frequent use of ASPs in children, there is no consensus on whether liver function tests (LFTs) should be routinely monitored during treatment.

Objectives: To review the literature on the frequency of ASP-related DILI in children to determine the incidence, risk factors and outcomes of hepatotoxicity.

Methods: PubMed, MEDLINE and Embase were searched in January 2022 for original studies of children who received cloxacillin, dicloxacillin, flucloxacillin, methicillin, nafcillin or oxacillin that included ≥ 10 children aged up to 18 years, and presented data on the incidence of DILI in children exposed to ASPs.

Results: Overall, two studies of oral flucloxacillin, two of intravenous (IV) methicillin, three of IV nafcillin and four of IV oxacillin were included. The mean onset of DILI ranged between 7.0 and 19.0 days following commencement of antibiotic treatment and all episodes resolved between 14.2 and 16.0 days after drug discontinuation, with no specific treatment required. This review found that the incidence of DILI in children was 1 in 50 000 for oral flucloxacillin and ranged from 1 in 3 to 13 for IV oxacillin, methicillin and nafcillin.

Conclusions: This review found that routine LFT monitoring is not required in children receiving low dose oral flucloxacillin in a primary care setting, although pharmacovigilance is critical. For IV preparations, the existing data support routine LFT monitoring in those receiving treatment for at least 7 days.

Introduction

Anti-staphylococcal penicillins (ASPs) are among the most commonly prescribed antibiotics in children with 600 000 flucloxacillin prescriptions given to children in general practices each year in the UK.¹ In Australia, flucloxacillin accounts for 7% of all antibiotic prescriptions to children aged 0 to 19 years.² ASPs are associated with a risk of drug-induced liver injury (DILI), typically manifesting as cholestatic hepatitis with an incidence of 0.007%, 2% and 13.3% for flucloxacillin, nafcillin and oxacillin in adults, respectively.^{3–6}

DILI is associated with high health economic costs; in Thailand, DILI costs the economy USD\$534 million per year and accounts for 5.4% of healthcare costs.⁷ The mechanism by which ASPs cause DILI is unclear but has been shown to be associated

with immune-mediated hypersensitivity and chemically mediated metabolic processes. Also, genetic predisposition with a major histocompatibility complex region genotype of HLA-B*57:01 is associated with an 80-fold increased risk of DILI.^{8–10} Identified risk factors for flucloxacillin-related DILI from adult cohorts include age greater than 55 years, female sex and prolonged treatment for more than 2 weeks.^{11,12} Therefore, treatment guidelines for flucloxacillin in adults recommend close monitoring for symptoms of hepatitis and jaundice.¹³

Despite the frequent use of ASPs in children, there is a paucity of data on the frequency and risk factors for DILI in this age group. Although studies have stated that the risk of hepatotoxicity is lower in children than adults, this risk has not been quantified.⁸ As a result, in children, there are no guidelines recommending routine monitoring of liver function tests (LFTs) even during a

prolonged ASP course.¹⁴ Therefore, this study aims to review the published literature on the frequency of ASP-related DILI in children to determine the incidence, risk factors and outcomes of hepatotoxicity.

Materials and methods

Search strategy

PubMed, MEDLINE (from 1946) and Embase (from 1974) were searched on 10 January 2022, the latter two databases using the OVID interface. The search strategy was developed by K.T. and A.G. with the assistance of an expert medical librarian. Subject headings and keywords included 'flucloxacillin/ae', 'cloxacillin/ae', 'dicloxacillin/ae', 'methicillin/ae', 'nafcillin/ae', 'penicillins/ae', 'liver disease', 'cholestasis', 'liver or hepatitis or cholestasis or cholestatic', 'newborn', 'neonate*', 'infant*', 'toddler', 'child', 'preschooler', 'adolescent*' and 'paediatric' (Figure 1).

The search was carried out by a single investigator (K.T.) to identify articles that met the inclusion and exclusion criteria and checked by two researchers (K.T. and A.G.). Studies were included if they reported original data in children who received cloxacillin, dicloxacillin, flucloxacillin, methicillin, nafcillin or oxacillin; included 10 or more children aged up to 18 years at the time of presentation; and presented data on the incidence of DILI in children exposed to ASPs. Studies were excluded if the total number of children who received ASPs was not reported (as the incidence of DILI could not be determined), the study did not report paediatric specific data or this data was not available after contacting the corresponding author. Case studies, conference papers, editorials and letters were also excluded. This review used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.^{15,16} Strength of clinical data was graded using the Oxford Centre for Evidence-Based Medicine.¹⁷

Data extraction and synthesis

Data including population demographics, pattern and severity of liver injury, and outcome of DILI were extracted from the included articles. Where available, specific values for liver enzymes including ALT, alkaline phosphatase (ALP) and GGT were collected. Pattern of liver injury was classified as hepatocellular, cholestatic or a mixed pattern according to criteria in LiverTox: Clinical and Research Information on Drug-Induced Liver Injury by the National Institute of Diabetes and Digestive and Kidney Diseases.^{18–21} The Common Toxicity Criteria for Adverse Events grading system (Table 1) was applied to assess severity of DILI, with the values expressed as multiples of the upper limit of the normal range (ULN), where the default ULN for ALT was 40 U/L and for ALP was 115 U/L.²²

Roussel Uclaf Causality Assessment Method (RUCAM) assessment

The RUCAM was used to determine the likelihood of ASP-related DILI (Table 2) and provide a causality grading, where a score of 0 excludes causality, 1–2 is 'unlikely' to cause DILI, 3–5 is 'possible', 6–8 is 'probable' and >9 is 'highly probable'.²³

Results

The search retrieved 246 articles in MEDLINE, 640 in Embase and 35 in PubMed. After duplicates were removed, 816 manuscripts remained. After title and abstract screening, 86 full text articles were identified for review. The authors of 10 articles were contacted to query whether data were available to fulfil the inclusion criteria for the search.^{5,24–32} Responses were received from five

authors and all five papers were subsequently excluded.^{5,29–32} An additional article was identified through hand searching the references of relevant articles and overall, eight studies were included (see Figure 2).

Table 3 summarizes the eight included studies, of which five were retrospective cohort studies and three were prospective cohort studies. Two studies of oral flucloxacillin were from the UK, two of intravenous (IV) methicillin from Costa Rica, three of IV nafcillin and four of IV oxacillin from the USA. Indications for treatment with an ASP included bone and joint infections, abscess, pyomyositis and other miscellaneous conditions. Only five studies reported the antibiotic doses received. No studies of cloxacillin- or dicloxacillin-related DILI in children were identified.

Overall, in the seven studies where ASP-related DILI occurred, the mean age of presentation ranged between 8.9 and 15.5 years. The mean onset of DILI ranged between 7.0 and 19.0 days following commencement of antibiotic treatment and all episodes resolved between 14.2 and 16.0 days after drug discontinuation, with no specific treatment required. Of the three studies that reported the outcomes of DILI (follow up until LFTs returned to baseline), none of the 12 children with DILI had chronic liver disease.

Flucloxacillin

Two retrospective cohort studies including 97 457 children receiving oral flucloxacillin in the primary healthcare setting identified two children who developed DILI. The incidence of DILI was low (1 in 50 000), however, both studies only reported cases of cholestatic DILI.

One of these studies included 37 885 children who were identified through the UK General Practice Research Database (data from 1985 to 1991) (Derby³³) and reported no episodes of cholestatic DILI in those children receiving oral flucloxacillin. Similarly, another large study (Russman³⁴) that used the same database (data from 1992 to 2002) of 59 572 children who received their first flucloxacillin prescription in general practice found two patients (0.003%) developed cholestatic DILI. Of the two patients with DILI, one was aged 15 years and received a cumulative dose of 7 g and the other was 16 years and received 8 g, both developing DILI on day 21 and day 16, respectively. Notably, the latter patient also received trimethoprim-sulfamethoxazole 8 days before flucloxacillin. The long-term outcomes for these children were not reported. Using the RUCAM criteria, both reported episodes of DILI were 'possibly' related to flucloxacillin. In both studies, only those patients who presented with jaundice had LFT testing, and therefore the true incidence of ASP-related LFT abnormalities may have been higher.

Oxacillin

Four cohort studies included a total of 84 children who received IV oxacillin, of whom 19 developed DILI, with an incidence of DILI ranging from 12.5% to 29.4% across the studies. Three were retrospective and reported on outpatient parenteral antibiotic therapy (OPAT) where LFTs were performed weekly, while one was prospective and reported on inpatient IV administration. Three studies^{35–37} excluded patients with underlying liver disease, and only one study reported the indication for oxacillin therapy.

1. cloxacillin/ae, to or flucloxacillin/ae, to or exp penicillin derivative/ae, to
2. (Flucloxacillin or Floxacillin or Fluorochloroxacillin or Cloxacillin or flopen or floxapen or flucil or heracillin or stafoxil or staphylex or penicillin*).tw,kw,dq.
3. 1 or 2
4. (newborn* or new-born* or baby or babies or neonat* or neo-nat* or infan* or toddler* or pre-schooler* or preschooler* or kinder or kinders or kindergarten* or kinder-aged or boy or boys or girl or girls or child or children or childhood or pediatric* or paediatric* or school-age* or schoolage* or schoolchild* or schoolgirl* or schoolboy* or adolescen* or youth or youths or teen or teens or teenage*).tw,kw,dq,hw.
5. exp liver disease/
6. Cholestasis/
7. exp Liver/
8. (Liver or hepatitis or cholestasis or cholestatic).tw,kw,dq.
9. 5 or 6 or 7 or 8
10. 3 and 4 and 9
11. limit 10 to english
12. limit 11 to (books or conference abstract or conference paper or "conference review" or editorial or letter)
13. case report/
14. 11 not (12 or 13)

Figure 1. Embase search strategy.

A retrospective audit (Maraqa³⁶) of 222 children aged 0 to 19 years receiving OPAT found that 9/41 (21.9%) developed oxacillin-related DILI while no children (0/58) receiving nafcillin developed DILI. Included patients received a mean oxacillin dose of 176 mg/kg/day (range 130–200) and the mean timing of onset of DILI was 18 days (range 6–43). DILI occurred at a mean age of 8.9 years (range 0.8–16) and in all cases, resolved by a mean of 14 days (range 7–25) after treatment discontinuation. Patterns of liver injury included hepatocellular in five children (4 with Grade 4, 1 with Grade 3), cholestatic in one child (Grade 1) and a mixed pattern in one child (Grade 4). Two children had isolated elevation of liver enzymes, where one had a Grade 3 ALT rise and another had a Grade 1 ALP rise. Although a greater proportion of children who developed DILI were male (7/9, 77.8%) compared to those who did not (16/32, 50%), this difference was not significant. This study was the only one that reported clinical symptoms associated with DILI, which included: nausea, vomiting, fatigue, abdominal pain (four patients) and rash (two patients). Three children were asymptomatic.

A similar incidence of hepatotoxicity was found in two small retrospective studies of children receiving OPAT oxacillin. Fernandes³⁵ found that 4/18 (22.2%) children had a median ALT of 176 U/L (range 82–624) and Faden³⁸ reported that of 17 children aged up to 20 years, five (29.4%) developed DILI. For both studies, specific details on those patients that developed DILI were not provided.

A single-centre prospective study (Nahata³⁷) compared children who received IV methicillin, nafcillin or oxacillin in an inpatient setting and found an incidence of DILI of 0% (0/28), 3.1% (1/32) and 12.5% (1/8), respectively. High IV doses were used with mean doses of 106 mg/kg/day (SD±31.2) for methicillin, 118 mg/kg/day (SD±33.9) for nafcillin and 153 mg/kg/day (SD±24.6) for oxacillin. Of the two children that developed DILI, one received 100 mg/kg/day of nafcillin for juvenile arthritis and developed a raised ALT level of 98 U/L (Grade 1) 3 days after treatment commencement. The other child received oxacillin at a dose of 175 mg/kg/day for osteomyelitis and developed a raised ALT level of 409 U/L (Grade 3) 7 days after treatment commencement.

that resolved 16 days after treatment discontinuation. This patient was concomitantly receiving acetaminophen.

All identified episodes of DILI related to oxacillin were classified as ‘possibly’ ($n=2$) or ‘probably’ ($n=2$) associated with oxacillin using the RUCAM criteria as none of the patients were rechallenged.

Methicillin

Two prospective studies of IV methicillin found an overall incidence of DILI of 14/103 (13.6%).^{37,39} In both studies, children had LFTs performed weekly.

In addition to the prospective study by Nahata³⁷ previously mentioned, a randomized controlled trial (Kitzing³⁹) of 149 children aged 0 to 13 years compared the frequency of DILI in children with soft tissue, and bone and joint infections who received either IV methicillin 200 mg/kg/day or IV nafcillin 150 mg/kg/day. The incidence of DILI was comparable between the methicillin group (14/75, 18.7%) and the nafcillin group (12/74, 16.2%) ($\chi^2=0.155$, $P=0.69$). For the 14 children with methicillin-related DILI, the mean elevation of AST, ALT and ALP was less than 2.5x the ULN (Grade 1). Similarly, the 12 cases of nafcillin-related DILI had Grade 1 elevations AST and ALT with values less than 100 U/L. The timing and symptoms of DILI as well as the presence of underlying liver disease or significant comorbidities were not reported, the latter may have contributed to the higher frequency of DILI in this study.

Reported episodes of DILI in these studies were ‘possibly’ ($n=1$) or ‘probably’ ($n=1$) related to methicillin according to the RUCAM criteria, as information regarding the time of onset of DILI following methicillin administration and time to recovery following methicillin discontinuation was not reported.

Table 1. Common terminology criteria for adverse events

Feature	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	Normal	>1.0–3.0	>3.0–5.0	>5.0–20	>20
ALP	Normal	>1.0–2.5	>2.5–5.0	>5.0–20	>20

Abbreviations: ALP, Alkaline phosphatase

Table 2. Roussel Uclaf Causality Assessment Method (RUCAM)

	Derby <i>et al.</i>	Faden <i>et al.</i>	Feldman <i>et al.</i>	Fernandes <i>et al.</i>	Kitzing <i>et al.</i>	Maraqá <i>et al.</i>	Nahata <i>et al.</i>	Russman <i>et al.</i>
Time of onset	0	0	0	0	0	2	2	2
Course	0	0	0	0	0	2	2	0
Risk factors	0	0	0	0	0	0	0	0
Concomitant drugs	0	0	0	0	0	–2	0	–1
Exclusion of other causes of liver injury	0	2	2	2	2	2	2	2
Previous information on hepatotoxicity of the drug	0	2	2	2	2	2	2	2
Response to re-administration	0	0	0	0	0	0	0	0
Total	0	4	4	4	4	6	8	5

Nafcillin

In addition to the randomized controlled trial (Kitzing³⁹), retrospective audit (Maraga³⁶) and prospective study (Nahata³⁷) of nafcillin already discussed, IV nafcillin was also studied in another single-centre prospective study. Feldman⁴⁰ evaluated 46 inpatients aged 1 month to 14 years who received 100–200 mg/kg/day of IV nafcillin and identified three (6.5%) children who developed DILI. These three children had an elevated AST less than twice the ULN (53, 59 and 79 U/L), however, the other liver enzymes were not reported nor were further details provided. In all four studies of nafcillin, LFTs were performed weekly in asymptomatic patients, and the incidence of DILI ranged between 0% and 16.2%.

Reported episodes of DILI were classified as ‘possibly’ ($n=2$) or ‘probably’ ($n=2$) associated with nafcillin using the RUCAM criteria as there was limited information on the time course of DILI following nafcillin administration and discontinuation.

Discussion

To our knowledge, this is the first review of ASP-related DILI in children. This review found that for oral flucloxacillin, the incidence of cholestatic DILI in children is 1 in 50 000. However, for IV oxacillin, methicillin and nafcillin, the incidence ranges between 1 in 3 and 13 children. These findings are comparable to studies in adults that found the incidence of DILI was 1 in 7 to 8 for IV oxacillin,^{41,42} and 1 in 19 for IV nafcillin (Table 4).⁴³ These results challenge the long-standing belief that the incidence of ASP-related DILI in children is lower than in adults.⁴⁴ The premise for this theory was that children tend to have fewer comorbidities and receive fewer concomitant medications thereby reducing the risk of drug interactions and adverse reactions.⁴⁴ However, most children receiving prolonged treatment with an IV ASP have an invasive infection and often are receiving other medications.

Current treatment guidelines in adults do not recommend routine LFT monitoring in patients unless the ASP treatment course is longer than 2 weeks, with the responsibility on the prescriber to be alert and monitor for signs of liver injury.^{13,32,45} Paediatric guidelines and formularies recommend LFT monitoring in neonates who receive high-dose flucloxacillin, and children who receive prolonged high-dose treatment with ASPs.^{46–49} The findings of our review suggest that routine LFT monitoring should be considered in children receiving IV therapy for at least 7 days

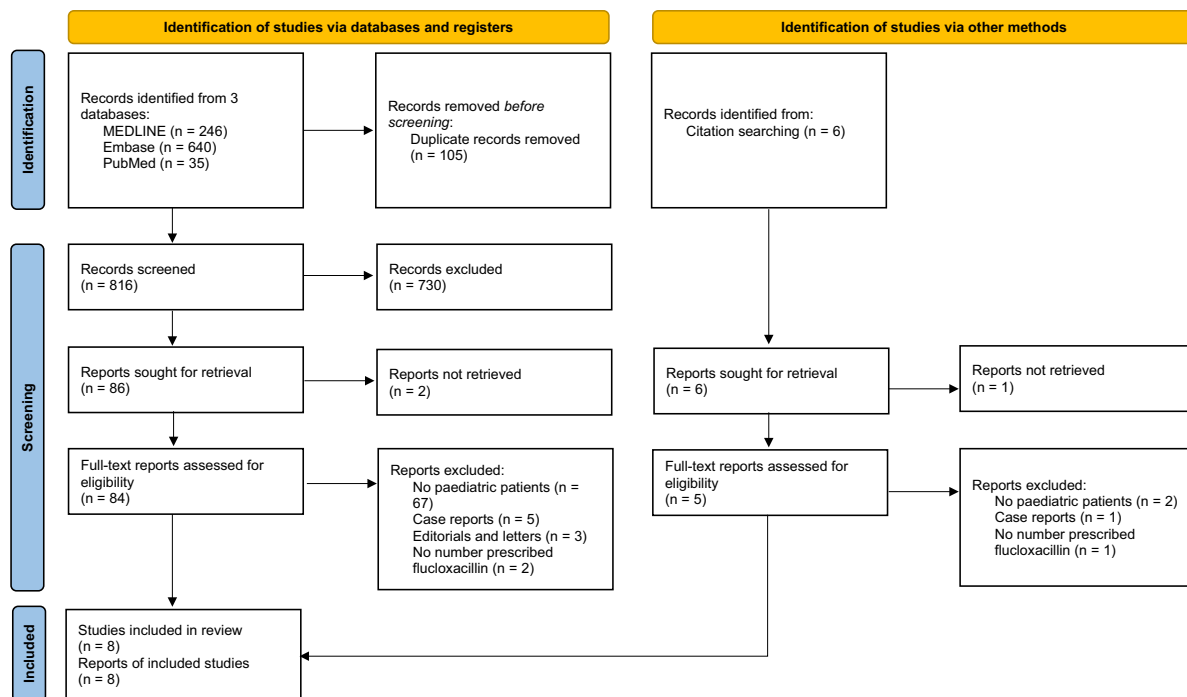


Figure 2. PRISMA flow diagram of the study selection process.^{15,16}

with the number needed to investigate ranging from 3 to 13 to identify one child with deranged LFTs.^{36,50,51} For oral treatment, awareness and monitoring for symptoms of hepatotoxicity is appropriate based on current evidence.³²

This review did not identify any children who experienced serious or long-term liver injury related to ASP antibiotics, although data are limited.³⁶ These findings contrast to a study of 4687 reports of DILI in Swedish adults, where flucloxacillin was the third most common drug associated with fatality from DILI (three fatal episodes of DILI per 100 reports of liver injury).²⁵ Fatality was strongly associated with increasing age, and early onset of DILI occurring at 11 days, suggesting a hypersensitivity mechanism.²⁵ Previous studies in adults have found that increasing age, female gender and a high daily dose of more than 1.5 g/day are independent risk factors for flucloxacillin-related DILI.^{5,11,12,52} Also, prolonged treatment with flucloxacillin for a duration longer than 2 weeks increased the odds of DILI more than 7-fold (OR 7.13, 95% CI 2.90–17.58).¹² However, these risk factors were not identified in any of the included studies in this review, largely due to the small sample sizes of the paediatric studies.

The mechanism of DILI remains unclear. Studies have proposed that flucloxacillin, nafcillin and oxacillin cause liver injury via an idiosyncratic hypersensitivity reaction.^{41,53–56} Genome-wide association studies have shown genetic susceptibility for flucloxacillin-related DILI in individuals with a major histocompatibility complex region genotype HLA-B*57:01.^{9,10} Also, some reports suggest a chemically mediated reaction to toxic metabolites from high doses of nafcillin and oxacillin; this has been reported for doses exceeding 12 g/day of oxacillin.^{42,56–58} However, other studies failed to replicate this dose-response relationship.⁵⁰

Although this review found a higher incidence of DILI with IV methicillin, nafcillin and oxacillin compared to oral flucloxacillin, this is most likely due to the drug formulation studied rather than the drug itself. IV route of administration is associated with an increased risk of DILI (OR 1.40, 95% CI 0.40–4.94),^{5,12} and patients receiving IV therapy are likely to receive higher drug doses, have other concomitant medications and are more likely to be systemically unwell compared to the studies of oral formulations in primary care.⁴⁴ Further, studies that have directly compared the frequency of DILI with methicillin, nafcillin and oxacillin found a similar incidence of hepatotoxicity.^{6,39} Further studies are needed on the incidence of DILI with different ASPs, however, it is likely the incidence of DILI would be similar for these drugs.

The limitations of this review include the limited number of studies with most being retrospective. Also, most of the studies lacked dosing and clinical outcome data, and none used a formal causality assessment tool to determine whether DILI was related to the ASP. Studies of flucloxacillin only reported cholestatic DILI and patients were identified only if they presented with painless jaundice, likely resulting in an underestimate of the true incidence of DILI. Finally, as studies of IV flucloxacillin and oral methicillin, nafcillin and oxacillin were not identified, the generalizability of these results to different formulations is unclear.

Conclusion

This review found that the incidence of DILI in children was 1 in 50 000 for oral flucloxacillin and ranged from 1 in 3 to 13 for IV oxacillin, methicillin and nafcillin. These data indicate that routine LFT monitoring is not required in children receiving low

Table 3. Summary of studies of anti-staphylococcal penicillin-related DILI in children

Citation	Study group	Study type	Outcome	Key results	Evidence level ^a
Flucloxacillin Russman <i>et al.</i> (2005) ³⁴ UK	59 572 children aged 0–19 y who received a first prescription of oral flucloxacillin in general practice Exclusion criteria: history and/or laboratory findings not suggestive of cholestatic liver disease; other cause likely; onset of DILI prior to drug exposure	Retrospective cohort study	Frequency of DILI	2/59 572 (0.003%) had flucloxacillin-related cholestatic DILI. For the 2 cases with DILI: <ul style="list-style-type: none"> • 1/2 male • Mean age 15.5 y (range 15–16) • Time of onset after flucloxacillin 19 d (range 17–21) • Treatment duration 5.5 d (range 4–7) • Total cumulative dose 7.5 g/course (range 7–8) 	Level 3
Derby <i>et al.</i> (1993) ³³ UK	37 885 children aged 0–19 y who received oral flucloxacillin across 600 general practices Exclusion criteria: other cause of liver disease; onset of liver disease prior to flucloxacillin	Retrospective cohort study	Frequency of DILI	0/37 885 had flucloxacillin-related cholestatic DILI occurring 1–90 days after prescription	Level 3
Methicillin Nahata <i>et al.</i> (1982) ³⁷ USA	68 children aged 0–18 y with various infections ^b including: <ul style="list-style-type: none"> • 28 who received IV methicillin, mean dose 106.0 ± 31.2 mg/kg/d • 32 who received IV nafcillin, mean dose 118.0 ± 33.9 mg/kg/d • 8 who received IV oxacillin, mean dose 153.0 ± 24.6 mg/kg/d Exclusion criteria: inadequate data; other cause likely	Single-centre prospective cohort study	Frequency of DILI	Methicillin 0/28 Nafcillin 1/32 (3.1%): The child with DILI received nafcillin 100 mg/kg/d and developed DILI 3 d after commencement Oxacillin 1/8 (12.5%): The child with DILI received oxacillin 175 mg/kg/d for osteomyelitis and developed DILI 7 d after commencement Nafcillin (n=1): †AST 179 U/L, †ALT 98 U/L (Grade 1) ^{c,d} Oxacillin (n=1): ALT 409 U/L (Grade 3) ^{c,d}	
Kitzing <i>et al.</i> (1981) ³⁹ Costa Rica	149 children aged 0–13 y with bone and joint infections randomized (1:1 ratio) to IV methicillin 200 mg/kg/d vs IV nafcillin 150 mg/kg/d including: <ul style="list-style-type: none"> • 75 who received IV methicillin. Duration 10 d (range 3–19) or 21 d (range 21–39) • 74 who received IV nafcillin. Duration 9 d (range 3–19) or 21 d (range 20–23) 	Randomized controlled trial	Pattern/severity of liver injury Treatment Frequency of DILI Pattern/severity of liver injury	Treatment discontinuation. Time to resolution was 16 d for oxacillin Methicillin 14/75 (18.7%) Nafcillin 12/74 (16.2%) Methicillin: <ul style="list-style-type: none"> • 14/75 (18.7%) †AST ±ALT <100 U/L (Grade 1)^{c,d} • 2/75 (2.7%) †ALP <100 U/L (Grade 1)^{c,d} Nafcillin: <ul style="list-style-type: none"> • 12/74 (16.2%) †AST ±ALT <100 U/L (Grade 1)^{c,d} • 1/74 (1.4%) †ALP <100 U/L (Grade 1)^{c,d} 	Level 2

Nafcillin	Maraqa <i>et al.</i> (2002) ³⁶ USA	222 children aged 0–19 y with bone and joint infections, abscess, empyema and other conditions ^e who received OPAT: • 58 treated with nafcillin • 41 treated with oxacillin. Mean dose 176 mg/kg/d (range 130–200) Exclusion criteria: underlying predisposition to hepatotoxicity; other cause of liver disease	Single-centre retrospective cohort study	Frequency of DILI	Nafcillin 0/58 Oxacillin 9/41 (21.9%) Of the 9 cases of DILI with oxacillin: 7/9 (77%) male; mean age 8.9 y (range 0.8–16); time of onset after commencement 17.7 d (range 6–43) Oxacillin (n = 9): • 5/9 hepatocellular: 4 Grade 4, 1 Grade 3 ^{c,f} • 1/9 cholestatic: 1 Grade 1 ^{c,f} • 1/9 mixed: 1 Grade 4 ^{c,f} • 2/9 isolated elevation of liver enzymes: 1 Grade 3 ALT, 1 Grade 1 ALP ^{c,d}	Level 3
Oxacillin	Feldman <i>et al.</i> (1978) ⁴⁰ USA	46 children aged 1–163 m who received IV nafcillin 100–200 mg/kg/d for suspected or proven staphylococcal infections Exclusion criteria: allergy to penicillin; history of liver disease or coagulopathy	Single-centre prospective cohort study	Frequency of DILI	Treatment discontinuation; mean time to resolution was 14.2 d (range 7–25) 3/46 (6.5%) had nafcillin-related DILI For the 3 cases of DILI, all had ↑AST with levels of 53, 59 and 79 U/L ^d	Level 2
Oxacillin	Fernandes <i>et al.</i> (2018) ³⁵ USA	540 children aged 0–21 y who received 707 OPAT courses, of which 18 were for IV oxacillin Median duration 30 d (IQR 22.5–43)	Single-centre retrospective cohort study	Frequency of DILI	4/18 (22.2%) had oxacillin-related DILI Time of onset after commencement 13.5 d (range 8–25) Median elevated ALT levels (range) 176 U/L (82–624) (Grade 2) ^{c,f}	Level 3
Oxacillin	Faden <i>et al.</i> (2009) ³⁸ USA	45 children aged 0–20 y who received 82 OPAT courses for osteomyelitis, abscesses, wound infections and septic arthritis, of which 17 were for IV oxacillin Mean duration 3.4 d (total 57)	Single-centre retrospective cohort study	Frequency of DILI	5/17 (29.4%) had oxacillin-related DILI	Level 3

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; d, days; DILI, drug-induced liver injury; IQR, interquartile range; IV, intravenous; LFT, liver function test; m, months; OPAT, outpatient parenteral anti-microbial therapy; U/L, units per litre; USA, United States of America; y, years
^aThe Oxford Centre for Evidence-Based Medicine was used to grade the level of evidence; it is a 5-point scale system where level 1a corresponds to the highest quality and level 5 corresponds to the lowest quality.¹⁷

^bVarious infections including cellulitis, osteomyelitis, submandibular adenitis and wound infections.

^cSeverity using Common Toxicity Criteria for Adverse Events grading system on data extracted from published paper.²²

^dOther liver enzymes not reported.

^eOther conditions include osteomyelitis, septic arthritis, abscess, empyema and miscellaneous infections.

^fPattern classified using criteria in LiverTox: Clinical and Research Information on Drug-Induced Liver Injury by the National Institute of Diabetes and Digestive and Kidney Diseases on data extracted from published paper.^{18–21}

Table 4. Key recommendations for LFT monitoring in children who receive ASPs

Condition	Key conclusions	Key supporting results	Evidence level ^a
Oral	Low dose, oral flucloxacillin is associated with a low incidence of DILI. Routine LFT monitoring not recommended in these children.	Incidence of DILI in children receiving low dose oral flucloxacillin was low (1 in 50 000) ^{33,34} Time of onset after prescription 19 d	Level 3
IV	IV ASPs and prolonged treatment is associated with an increased incidence of DILI. Routine LFT monitoring is recommended.	Incidence of DILI in children receiving IV ASPs is higher <ul style="list-style-type: none"> • 1 in 4 (range 1 in 3 to 1 in 8) for IV oxacillin^{35–38} • 1 in 7 (range 0 to 1 in 5) for IV methicillin^{37,39} • 1 in 13 (range 0 to 1 in 6) for IV nafcillin^{36,37,39,40} Time of onset after prescription 9.2 d (range 3–19)	Level 3 Level 2 Level 2

Abbreviations: ASP, anti-staphylococcal penicillins; d, days; DILI, drug-induced liver injury; IV, intravenous; LFT, liver function test

^aThe Oxford Centre for Evidence-Based Medicine was used to grade the level of evidence; it is a 5-point scale system where level 1a corresponds to the highest quality and level 5 corresponds to the lowest quality.¹⁷

dose oral flucloxacillin in a primary care setting (CEBM level 3 evidence), although pharmacovigilance and monitoring for symptoms of hepatotoxicity is critical. For IV preparations, the existing data support routine LFT monitoring particularly in those receiving treatment for at least 7 days. Notably, no child developed serious or long-term complications of DILI and all episodes of DILI resolved with treatment discontinuation.

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Transparency declarations

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References

- 1 Saxena S, Ismael Z, Murray ML, *et al.* Oral penicillin prescribing for children in the UK: a comparison with BNF for Children age-band recommendations. *Br J Gen Pract* 2014; **64**: e217–222. <https://doi.org/10.3399/bjgp14X676285>
- 2 Osowicki J, Gwee A, Noronha J, *et al.* Australia-wide point prevalence survey of the use and appropriateness of antimicrobial prescribing for children in hospital. *Med J Aust.* 2014; **201**: 657–62. <https://doi.org/10.5694/mja13.00154>
- 3 Levy C, Lindor KD. Drug-induced cholestasis. *Clin Liver Dis* 2003; **7**: 311–30. [https://doi.org/10.1016/S1089-3261\(03\)00032-1](https://doi.org/10.1016/S1089-3261(03)00032-1)
- 4 Pas AT, Quinn EL. Cholestatic hepatitis following the administration of sodium oxacillin. *JAMA* 1965; **191**: 674–5. <https://doi.org/10.1001/jama.1965.03080080064024>

5 de Abajo FJ, Montero D, Madurga M, *et al.* Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br J Clin Pharmacol* 2004; **58**: 71–80. <https://doi.org/10.1111/j.1365-2125.2004.02133.x>

6 Viehman JA, Oleksiuk LM, Sheridan KR, *et al.* Adverse events lead to drug discontinuation more commonly among patients who receive nafcillin than among those who receive oxacillin. *Antimicrob Agents Chemother* 2016; **60**: 3090–5. <https://doi.org/10.1128/AAC.03122-15>

7 Sobhonslidsuk A, Poovorawan K, Soonthornworasiri N, *et al.* The incidence, presentation, outcomes, risk of mortality and economic data of drug-induced liver injury from a national database in Thailand: a population-base study. *BMC Gastroenterol* 2016; **16**: 135.

8 Serranti D, Montagnani C, Indolfi G, *et al.* Antibiotic induced liver injury: what about children? *J Chemother* 2013; **25**: 255–72. <https://doi.org/10.1179/1973947813Y.0000000090>

9 Daly AK, Donaldson PT, Bhatnagar P, *et al.* HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet* 2009; **41**: 816–9.

10 Teixeira M, Macedo S, Batista T, *et al.* Flucloxacillin-induced hepatotoxicity - association with HLA-B*5701. *Rev Assoc Med Bras* 2020; **66**: 12–7. <https://doi.org/10.1590/1806-9282.66.1.12>

11 Olsson R, Wiholm BE, Sand C, *et al.* Liver damage from flucloxacillin, cloxacillin and dicloxacillin. *J Hepatol* 1992; **15**: 154–61. [https://doi.org/10.1016/0168-8278\(92\)90029-0](https://doi.org/10.1016/0168-8278(92)90029-0)

12 Christopher KF, John JM, Paul D, *et al.* Risk factors for development of flucloxacillin associated jaundice. *BMJ-BRIT MED J* 1993; **306**: 233–5. <https://doi.org/10.1136/bmj.306.6872.233>

13 Wu YL, Scott EM, Po AL, *et al.* Ability of azlocillin and tobramycin in combination to delay or prevent resistance development in *Pseudomonas aeruginosa*. *J Antimicrob. Chemother* 1999; **44**: 389–92. <https://doi.org/10.1093/jac/44.3.389>

14 The Royal Children's Hospital. Flucloxacillin. 2021. https://www.rch.org.au/piper/neonatal_medication_guidelines/Flucloxacillin/.

15 Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015; **4**: 1.

16 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol* 2021; **134**: 178–89.

17 Oxford Centre for Evidence-Based Medicine. The Oxford Levels of Evidence 2. 2011. <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebml-levels-of-evidence>

- 18** National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. 2012. Acute Hepatitis. <https://www.ncbi.nlm.nih.gov/books/NBK548606/>
- 19** National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* 2012. Cholestatic Hepatitis. <https://www.ncbi.nlm.nih.gov/books/NBK548914/>
- 20** National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* 2012. Mixed Hepatitis. <https://www.ncbi.nlm.nih.gov/books/NBK547938/>
- 21** National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* 2012. Enzyme Elevations Without Jaundice. <https://www.ncbi.nlm.nih.gov/books/NBK548558/>
- 22** National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* 2012. Severity Grading in Drug Induced Liver Injury. <https://www.ncbi.nlm.nih.gov/books/NBK548241/>
- 23** Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; **46**: 1323-30. [https://doi.org/10.1016/0895-4356\(93\)90101-6](https://doi.org/10.1016/0895-4356(93)90101-6)
- 24** Barbosa dos Santos D, Luna Coelho HL. Adverse drug reactions in hospitalized children in Fortaleza, Brazil. *Pharmacoepidemiol Drug Saf.* 2006; **15**: 635-40.
- 25** Bjornsson E, Jerlstad P, Bergqvist A, et al. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. *Scand J Gastroenterol.* 2005; **40**: 1095-101. <https://doi.org/10.1080/00365520510023846>
- 26** Bjornsson ES, Bergmann OM, Bjornsson HK, et al. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology.* 2013; **144**: 1419-25. <https://doi.org/10.1053/j.gastro.2013.02.006>
- 27** Dipaola F, Molleston JP, Gu J, et al. Antimicrobials and antiepileptics are the leading causes of idiosyncratic drug-induced liver injury in American children. *J Pediatr Gastroenterol. Nutr.* 2019; **69**: 152-9. <https://doi.org/10.1097/MPG.0000000000002383>
- 28** Hunt CM, Yuen NA, Stirnadel-Farrant HA, et al. Age-related differences in reporting of drug-associated liver injury: data-mining of WHO safety report database. *Regul Toxicol Pharmacol.* 2014; **70**: 519-26. <https://doi.org/10.1016/j.yrtph.2014.09.007>
- 29** Blix HS, Viktil KK, Moger TA, et al. Risk of drug-related problems for various antibiotics in hospital: assessment by use of a novel method. *Pharmacoepidemiol Drug Saf.* 2008; **17**: 834-41. <https://doi.org/10.1002/pds.1595>
- 30** Bretherick AD, Craig DGN, Masterton G, et al. Acute liver failure in Scotland between 1992 and 2009; incidence, aetiology and outcome. *QJM.* 2011; **104**: 945-56. <https://doi.org/10.1093/qjmed/hcr098>
- 31** Smith IDM, Simpson KJ, Garden OJ, et al. Non-paracetamol drug-induced fulminant hepatic failure among adults in Scotland. *Eur J Gastroenterol Hepatol.* 2005; **17**: 161-7. <https://doi.org/10.1097/00042737-200502000-00006>
- 32** Devereaux BM, Crawford DHG, Purcell P, et al. Flucloxacillin associated cholestatic hepatitis. An Australian and Swedish epidemic? *Eur J Clin Pharmacol.* 1995; **49**: 81-5.
- 33** Derby LE, Jick H, Henry DA, et al. Cholestatic hepatitis associated with flucloxacillin. *Med J Aust.* 1993; **158**: 596-600. <https://doi.org/10.5694/j.1326-5377.1993.tb137624.x>
- 34** Russmann S, Kaye JA, Jick SS, et al. 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. *Br J Clin Pharmacol.* 2005; **60**: 76-82. <https://doi.org/10.1111/j.1365-2125.2005.02370.x>
- 35** Fernandes P, Milliren C, Mahoney-West HM, et al. Safety of outpatient parenteral antimicrobial therapy in children. *Pediatr Infect Dis J.* 2018; **37**: 157-63. <https://doi.org/10.1097/INF.0000000000001716>
- 36** Maraqa NF, Gomez MM, Rathore MH, et al. Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. *Clin Infect Dis.* 2002; **34**: 50-4. <https://doi.org/10.1086/338047>
- 37** Nahata MC, DeBolt SL, Powell DA. Adverse effects of methicillin, nafcillin and oxacillin in pediatric patients. *Dev Pharmacol Ther.* 1982; **4**: 117-23. <https://doi.org/10.1159/000457400>
- 38** Faden D, Faden HS. The high rate of adverse drug events in children receiving prolonged outpatient parenteral antibiotic therapy for osteomyelitis. *Pediatr Infect Dis J.* 2009; **28**: 539-41. <https://doi.org/10.1097/INF.0b013e318193ef38>
- 39** Kitzing W, Nelson JD, Mohs E. Comparative toxicities of methicillin and nafcillin. *Am J Dis Child.* 1981; **135**(1): 52-5.
- 40** Feldman WE, Nelson JD, Stanberry LR. Clinical and pharmacokinetic evaluation of nafcillin in infants and children. *J Pediatr.* 1978; **93**: 1029-33. [https://doi.org/10.1016/S0022-3476\(78\)81251-7](https://doi.org/10.1016/S0022-3476(78)81251-7)
- 41** Onorato IM, Axelrod JL. Hepatitis from intravenous high-dose oxacillin therapy: findings in an adult inpatient population. *Ann Intern Med.* 1978; **89**: 497-500. <https://doi.org/10.7326/0003-4819-89-4-497>
- 42** Pollock AA, Berger SA, Simberkoff MS, et al. Hepatitis associated with high-dose oxacillin therapy. *Arch Intern Med.* 1978; **138**: 915-7. <https://doi.org/10.1001/archinte.1978.03630310015010>
- 43** Burrelli C, Broadbent E, Margulis A, et al. Comparison of outcomes and adverse effects following treatment with nafcillin or cefazolin for methicillin-susceptible *Staphylococcus aureus* bacteraemia. Twenty-Eighth European Congress of Clinical Microbiology and Infectious Diseases, Madrid, Spain. 2018. Abstract P2021.
- 44** Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J Urol.* 2004; **172**: 448-53. <https://doi.org/10.1097/01.ju.0000130653.74548.d6>
- 45** United Kingdom: Electronic Medicines Compendium 2021. Flucloxacillin 1 g Powder for Solution for Injection or Infusion. <https://www.medicines.org.uk/emc/product/2239/smpc#gref>
- 46** Queensland Clinical Guidelines. Flucloxacillin. 2021. https://www.health.qld.gov.au/__data/assets/pdf_file/0030/856470/nmq-flucloxacillin.pdf
- 47** ANMF Consensus Group. Flucloxacillin. 2020. <https://www.anmfonline.org/wp-content/uploads/2021/06/flucloxacillin-16112020-5.1.pdf>
- 48** UpToDate. Nafcillin: Pediatric Drug Information. 2022. <https://www.uptodate.com/contents/nafcillin-pediatric-drug-information>
- 49** Methicillin. *Nurse's Drug Handbook.* 9th edn. Jones & Bartlett Learning, 2019; 733-4.
- 50** Al-Homaidhi H, Abdel-Haq NM, El-Baba M, et al. Severe hepatitis associated with oxacillin therapy. *South Med J.* 2002; **95**: 650-2. <https://doi.org/10.1097/00007611-200295060-00015>
- 51** Chapman ALN, Patel S, Horner C, et al. Updated good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults and children in the UK. *JAC-AMR.* 2019; **1**: 1-18.
- 52** Wing K, Bhaskaran K, Pealing L, et al. Quantification of the risk of liver injury associated with flucloxacillin: a UK population-based cohort study. *J Antimicrob Chemother.* 2017; **72**: 2636-46. <https://doi.org/10.1093/jac/dkx183>
- 53** National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*

2012. Penicillins (2nd Generation). <https://www.ncbi.nlm.nih.gov/books/NBK548033/>

54 Dismukes WE. Oxacillin-induced hepatic dysfunction. *JAMA*. 1973; **226**: 861-3. <https://doi.org/10.1001/jama.1973.03230080011003>

55 Bruckstein AH, Attia AA. Oxacillin hepatitis. Two patients with liver biopsy, and review of the literature. *Am J Med*. 1978; **64**: 519-22. [https://doi.org/10.1016/0002-9343\(78\)90246-2](https://doi.org/10.1016/0002-9343(78)90246-2)

56 Presti ME, Janney CG, Neuschwander-Tetri BA. Nafcillin-associated hepatotoxicity. Report of a case and review of the

literature. *Dig Dis Sci*. 1996; **41**: 180-4. <https://doi.org/10.1007/BF02208602>

57 National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* 2012. Oxacillin. <https://www.ncbi.nlm.nih.gov/books/NBK548078/>

58 Olans RN, Weiner LB. Reversible oxacillin hepatotoxicity. *J Pediatr*. 1976; **89**: 835-8. [https://doi.org/10.1016/S0022-3476\(76\)80820-7](https://doi.org/10.1016/S0022-3476(76)80820-7)