Journal of Infection 89 (2024) 106301

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Infectious Disease Practice

Occurrence and predictors of laboratory abnormalities during outpatient parenteral antimicrobial therapy – A multicenter cohort study to inform laboratory test monitoring

Hester H. Stoorvogel [a,b,c,*], Maartje van Egmond [a,c], Heiman F.L. Wertheim [c,d], Jeroen A. Schouten [b,c,e], Marlies E.J.L. Hulscher [b,c], Lars Peeters [a,c], Yvonne Kiers [f], Sofie Koenders [g], Tom Sprong [g], Suzan P. van Mens [h], Mirjam Tromp [a,c], Olivier Richel [a,c], Reinier Akkermans [b], Jaap ten Oever [a,c]

[a] Radboud University Medical Center, Department of Internal Medicine, Nijmegen, the Netherlands
[b] Radboud University Medical Center, IQ Health Science Department, Nijmegen, the Netherlands
[c] Radboud University Medical Center, Radboudumc Community for Infectious Diseases (RCI), Nijmegen, the Netherlands
[d] Radboud University Medical Center, Department of Medical Microbiology, Nijmegen, the Netherlands
[e] Radboud University Medical Center, Department of Intensive Care Medicine, Nijmegen, the Netherlands
[f] Rijnstate, Department of Internal Medicine, Arnhem, the Netherlands
[g] Canisius Wilhelmina Hospital, Department of Internal Medicine, Nijmegen, the Netherlands
[h] Maastricht University Medical Center+, Department of Medical Microbiology, Infectious Diseases & Infection Prevention, Maastricht, the Netherlands

ARTICLE INFO

Article history:
Accepted 24 September 2024
Available online 30 September 2024

Keywords:
Outpatient parenteral antimicrobial therapy
Laboratory abnormalities
Laboratory test monitoring
Antimicrobial stewardship
Multicenter cohort study

SUMMARY

Objectives: Evidence on the optimal frequency of laboratory testing during outpatient parenteral antimicrobial therapy (OPAT) is lacking. Therefore, we investigated how often and when laboratory abnormalities occur during OPAT and which factors are associated with these abnormalities.

Methods: We performed a multicenter cohort study in four Dutch hospitals among adult patients receiving OPAT and collected routinely obtained laboratory test results. Incidence and incidence rates were calculated for various laboratory abnormalities. Survival analysis was performed to visualize the time to the first occurrence of laboratory abnormalities and Poisson regression analysis to compare the number of abnormalities in the first and second 30 OPAT days among patients receiving OPAT for ≥60 days. Predictors were identified using a multivariable Cox proportional hazard regression model.

Results: 45.1% of 1152 included patients developed laboratory abnormalities, but only 2% led to OPAT discontinuation. Hepatotoxicity was most common (33.9 events/1000 OPAT days), with a time-dependent decrease in the occurrence of the first hepatotoxic event, while hypokalemia was rare (1.7 events/1000 OPAT days). In the subgroup of patients receiving ≥60 days of OPAT, nephrotoxicity was more common in days 31–60. We observed partly toxicity-specific associations between antibiotic type, concomitant medication, baseline laboratory values, patient characteristics, and the occurrence of laboratory abnormalities.

Conclusions: While laboratory abnormalities are frequently observed during OPAT, they rarely lead to discontinuation of OPAT. Specific patient, treatment and laboratory characteristics were associated with the occurrence of laboratory abnormalities. Based on our results, we recommend a more personalized laboratory monitoring policy with less blood sampling.

Introduction

Outpatient parenteral antimicrobial therapy (OPAT) is cost-effective and enables person-centered care.[1,2] Despite these benefits and its overall safety,[2,3] a considerable proportion of patients experience adverse events during treatment.[3–6] Some of these

* Correspondence to: Radboud University Medical Center, Postbus 9101, Route 462, 6500 HB Nijmegen, the Netherlands.
E-mail address: Hester.Stoorvogel@radboudumc.nl (H.H. Stoorvogel).

https://doi.org/10.1016/j.jinf.2024.106301

complications are due to antibiotic toxicity that can be detected by laboratory tests.

The British and American guidelines for OPAT recommend weekly blood tests, but acknowledge a lack of evidence regarding the frequency of laboratory test monitoring.[7,8] Daily practice often falls short of guideline-recommended high-frequency laboratory testing, with logistical challenges likely playing a role.[9,10] Moreover, the risk of laboratory abnormalities is probably not the same for every patient and likely depends on the type of antibiotic and comorbidities, among other factors.[4,6,11–14] Two recent studies also described a time-dependent OPAT complication rate, with most complications, including laboratory abnormalities, occurring in the first two weeks of OPAT.[3,4]

Altogether, it is plausible that personalized and less frequent laboratory test monitoring than currently recommended is safe and appropriate.[15] To date, studies monitoring the frequency of laboratory tests have been limited to single center studies and included different types of adverse events without focusing specifically on laboratory abnormalities alone.[3–6,16] Therefore, the aim of this large multicenter study was to investigate how often and when laboratory abnormalities occur during OPAT and to identify patient and treatment factors that are associated with these abnormalities.

Methods

Study design and patients

We performed a multicenter cohort study in four Dutch acute care hospitals (two university hospitals and two teaching hospitals). Potential patients who initiated OPAT before November 1st, 2022, were identified from existing OPAT registries of the OPAT teams or hospital pharmacies and screened for eligibility (see S1 for a detailed description of the Dutch OPAT setting and the participant identification; the start of registry varied from 2015 to 2020).

The inclusion criteria were: 1) ≥18 years at start of OPAT, 2) intravenous (IV) treatment with: benzylpenicillin, amoxicillin, flucloxacillin, piperacillin/tazobactam, cefazolin, cefuroxime, ceftriaxone, ceftazidime, ertapenem, imipenem/cilastatin, meropenem, teicoplanin or vancomycin, as these agents are most commonly used for OPAT in Dutch hospitals (e.g. daptomycin was not included because it is rarely used in the Netherlands), 3) treatment duration of ≥8 days, unless treatment was discontinued due to laboratory abnormalities, and 4) patient consent to use the medical records. For patients who received multiple episodes of OPAT, the episode with the most available laboratory test results was included.

Data collection

Data were retrospectively extracted from the electronic medical records and captured into standardized electronic case records in Castor EDC. The data collected included patient characteristics, comedication, characteristics of the OPAT episode and, if applicable, prior hospitalization, and laboratory tests and values (Table 1). This selection of tests is based on the recommendations as outlined in the IDSA guidelines.[7] We only investigated hypokalemia because, unlike hyperkalemia, it is a reported complication associated with the antibiotics studied. Two hospitals conducted laboratory tests at a fixed frequency: one hospital performed tests twice a week, with the frequency reduced to once a week if possible. The other hospital conducted tests on a weekly basis. In the two remaining hospitals, the frequency of laboratory monitoring was not standardized.

Definitions

The start date of the OPAT episode was either the day of discharge for hospitalized patients or the day of the first IV antibiotics administration for outpatients. The end date was the first day without IV antibiotics, or in case of readmission, the date of readmission. The baseline for each laboratory value was the most recent value in the three months prior to initiation of OPAT, if available.

Laboratory abnormalities were determined by toxicity category (Table 1) and defined as ≥1 abnormal laboratory test result in the corresponding category from a single blood draw.

Outcomes and statistical analyses

Our outcome measures were 1) the incidence of laboratory abnormalities, 2) the occurrence of laboratory abnormalities over time and 3) predictors of the occurrence of laboratory abnormalities. We used 60-day follow-up for all analyses.

Incidence of laboratory abnormalities during OPAT

The incidence of laboratory abnormalities during OPAT was summarized as the proportion of patients with laboratory abnormalities and the incidence rate (number of events/1000 OPAT days). Additionally, we assessed the proportion of OPAT episodes that were discontinued or where the antibiotic was changed due to laboratory abnormalities as a measure of severe toxicity. Patients who were readmitted and had their antibiotic stopped or changed due to toxicity were included in this outcome measure.

Occurrence of laboratory abnormalities over time during OPAT

We calculated the time to the first laboratory abnormality and visualized it using survival plots.

To test whether most laboratory abnormalities occur early in a long OPAT episode, we used Poisson regression to compare the number of laboratory abnormalities in the first 30 days of OPAT with days 31–60, including only patients with ≥60 days of OPAT and laboratory tests in both periods. To adjust for the frequency of laboratory tests, the number of laboratory tests in each period was included as an offset variable.

Predictors of occurrence of laboratory abnormalities during OPAT

We used a multivariable Cox proportional hazard regression analysis to determine predictors of laboratory abnormalities. Variables considered included demographics, infection type, treatment characteristics, baseline laboratory values, and baseline medication with expected specific toxicity. Additionally, a variable representing the laboratory monitoring policy (standardized or not; each value included two hospitals) was also included. We hypothesized two opposite effects: a lower incidence in hospitals without a standardized monitoring policy due to fewer laboratory tests being performed, or conversely, a higher incidence in these hospitals due to the selection of more vulnerable patients with a higher risk of toxicity.

Variables were selected for the multivariable analyses based on univariable analyses with a Wald test (p-value ≤ 0.2). After backward selection, statistically significant variables remained in the final model. Moreover, we included IV antibiotic type as a fixed variable in the multivariable analysis because we expected toxicity to vary by antibiotic class. This was also the reason to consider flucloxacillin separately in the nephrotoxicity analysis.

To provide insight into any selection bias caused by the inconsistent performance of laboratory tests, we compared the clinical and treatment characteristics of the patients with and without laboratory test monitoring during OPAT in addition to including the laboratory monitoring policy variable in the multivariable analysis.

A p-value of < 0.05 was considered statistically significant, based on two-sided testing. All statistical analyses were performed in IBM SPSS Statistics 29 (IBM, Armonk, NY, USA).

Table 1
Definitions of laboratory abnormalities.

Type of laboratory abnormality	Definition	Source
Hematological toxicity		
Hemoglobin	Decrease of ≥10% compared to previous value	Pilot study, see S2
Leukocytes	Leukocyte count ≤2.0 × 10^9 /L	DAIDS grade 2[24]
Neutrophils	Neutrophil count ≤0.8 × 10^9 /L	DAIDS grade 2[24]
Eosinophils	Eosinophil count ≥0.5 × 10^9 /L	[14]
Thrombocytes	Thrombocyte count ≤100 × 10^9 /L	DAIDS grade 2[24]
Hypokalemia		
Potassium	Potassium < 3.0 mmol/L	DAIDS grade 2[24]
Nephrotoxicity		
Creatinine	Creatinine ≥1.3 x patient's baseline	DAIDS grade 2[24]
Hepatotoxicity		
Bilirubin	Bilirubin total ≥1.6 x ULN (=27.2) or patient's baseline[a]	DAIDS grade 2[24]
Alkaline phosphatase	AP ≥2.5 x ULN (= 250) or patient's baseline[a]	DAIDS grade 2[24]
GGT	GGT ≥2.5 x ULN (= 75) or patient's baseline[a]	DAIDS grade 2[24]
AST	AST ≥2.5 x ULN (= 75) or patient's baseline[a]	DAIDS grade 2[24]
ALT	ALT ≥2.5 x ULN (= 87.5) or patient's baseline[a]	DAIDS grade 2[24]

Abbreviations – ALT: alanine aminotransferase, AP: alkaline phosphatase, AST: aspartate aminotransferase, DAIDS: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, GGT: gamma-glutamyl transferase, ULN: upper limit of normal.
[a] If patient's baseline value was ≥1.25x ULN, ULN, patient's baseline value was used. This is not included in the DAIDS, but could prevent overestimation of laboratory abnormalities.

Ethical considerations

According to Dutch legislation and confirmed by the medical-ethical evaluation boards of all participating hospitals, this study was exempted from the Human Subjects Act.

Three hospitals did not require active patient consent for this study. Patients who previously did not consent further use of their medical data were excluded. In the fourth hospital, patients were retrospectively approached for participation and given the opportunity to opt-out.

Results

Study population

In the OPAT registries, 2752 OPAT patients were identified. 1672 patients met our inclusion criteria of which 1152 patients had at least one laboratory test performed during OPAT (69%), as shown in S3 and S4. Compared to patients in whom no monitoring was performed, included patients were more often male, slightly older, had more comorbidities, received OPAT more frequently following hospital admission and for a longer duration due to differences in underlying infections (S5).

The characteristics of the 1152 patients included are shown in Table 2 and S6.1–2. One third of the patients were female and the median age was 66 years (56–74). Penicillins were the most commonly prescribed IV antibiotics (48%), followed by cephalosporins (28%). The individual IV and oral antibiotics are shown in S7.

Incidence of laboratory abnormalities during OPAT

Almost half of the patients (45%) developed one or more laboratory abnormalities within the first 60 days of OPAT, with hepatotoxicity being the most common (29%) (Table 3). Hypokalemia was least frequent, affecting 2.1% of the patients. The incidence rate of all laboratory abnormalities was 43.7 laboratory abnormalities/1000 OPAT days in the first 60 OPAT days and 58.3/1000 OPAT days when considering the entire follow-up period (Table 3 & S8). Differences in the outcomes of the four hospitals are presented in S6.3. Laboratory abnormalities were the reason to discontinue OPAT in only 27 patients (2%), with nephrotoxicity being the most common reason (Table 3 & S9.1). Patients who discontinued OPAT due to laboratory abnormalities were more likely to have primary bacteremia or intravascular infection, a history of antibiotic drug hypersensitivity, certain comedications, glycopeptide treatment, and concurrent oral antibiotics compared to the other patients (S9.2).

Occurrence of laboratory abnormalities over time during OPAT

The median time to the first laboratory abnormality was 7 days (4–14), with hypokalemia and hepatotoxicity occurring earliest (Table 3). The survival curves of the different types of laboratory abnormalities are shown in Fig. 1a-d. The hazard rate for hepatotoxicity was highest for approximately the first 10 days and then stabilized, while the hazard rate for the other forms of toxicity was similar over time.

In patients receiving OPAT ≥60 days, nephrotoxicity occurred significantly more frequently in the second 30 days (Table 4). Exploratory analysis revealed that this was mainly due to flucloxacillin (S10). For the other toxicity types, the incidence rate of the various toxicity types was similar in both periods. The ratio of the number of laboratory abnormalities to the number of laboratory tests was not constant, indicating that individual patients did not experience a consistent number of events in the first 30 and 31–60 days (S10). The 129 patients receiving OPAT ≥60 days are described in S11.

Predictors of occurrence of laboratory abnormalities during OPAT

The factors independently associated with the occurrence of laboratory abnormalities are presented in Table 5 and the complete univariable analyses and multivariable analyses in S12.1–3. There were too few events of hypokalemia to perform a reliable multivariable analysis to identify predictors of hypokalemia, although potassium measurements were conducted in 979 patients (85.0%). The demographic and clinical characteristics of patients with hypokalemia are summarized in S13. Standardized laboratory monitoring was associated with all types of toxicity. Patients treated with glycopeptides were more likely to experience hematological toxicity, as were patients with more comorbidities and those with a medical specialty as the initial care provider. Flucloxacillin, glycopeptides, and diuretics were associated with nephrotoxicity, whereas patients with a NSAID prescription at baseline were less likely to experience nephrotoxicity (in-depth analysis shown in S14). Baseline creatinine concentration showed a negative correlation with nephrotoxicity. Finally, females were at lower risk of experiencing hepatotoxicity. Baseline liver parameters concentrations correlated positively with the occurrence of hepatotoxicity.

Table 2
Demographics and clinical characteristics of the 1152 patients included.

	Patients with laboratory tests during OPAT (n = 1152)
Demographics	
Age, median (1st quartile – 3rd quartile)	66.0 (56.0–74.0)
Female, n (%)	384 (33.3%)
Infection and comorbidity	
Primary infection site, n (%)	
Bone and joint infection, incl. prosthetic joint infections	298 (25.9%)
Genitourinary infection	164 (14.2%)
Endocarditis	140 (12.2%)
Primary bacteremia	129 (11.2%)
Skin and soft tissue infection	112 (9.7%)
Intravascular, vascular prosthesis infection and CRBSI	130 (11.3%)
Other[a]	179 (15.5%)
History of antibiotic drug hypersensitivity, n (%)	249 (21.6%)
Charlson Comorbidity Index, median (1st quartile – 3rd quartile)	3.0 (2.0–5.0)
Baseline medication, n (%)	
Proton pump inhibitors	569 (49.4%)
Paracetamol	416 (36.1%)
Beta blocker	380 (33.0%)
ACE inhibitor and/or ARB	302 (26.2%)
Diuretics	224 (19.4%)
Anti-aldosterone diuretics	35 (3.0%)
Other diuretics	211 (18.3%)
NSAID	146 (12.7%)
Treatment characteristics	
Hospitalization before OPAT, n (%)	1060 (92.0%)
Treated in hospital with standardized laboratory monitoring policy, n (%)	581 (50.4%)
Frequency of laboratory test monitoring, tests per 1000 OPAT days, median (1st quartile – 3rd quartile)	100.0 (61.2–200.0)
Specialty treating physician, n (%)	
Medicine	642 (55.7%)
Surgery	510 (44.3%)
Type of IV antibiotics, n (%)	
Penicillins	552 (47.9%)
Flucloxacillin	268 (23.3%)
Cephalosporins	327 (28.4%)
Glycopeptides	161 (14.0%)
Carbapenems	112 (9.7%)
Treatment duration of IV antibiotics, days, median (1st quartile – 3rd quartile)	24.0 (12.0–38.0)
Additional oral antibiotics, n (%)	
Rifampicin-containing regimen	128 (11.1%)
Other oral antibiotic(s) than rifampicin	150 (13.0%)

Abbreviations – ACE inhibitor: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CRBSI: catheter-related bloodstream infections, IV: intravenous, NSAID: non-steroidal anti-inflammatory drug, OPAT: outpatient parenteral antimicrobial therapy.

[a] Including intra-abdominal infection (n = 75), Lyme disease (n = 64), central nervous system infection (n = 64), respiratory tract infection (n = 54), head and neck infection (n = 30), mediastinitis (n = 15) and Whipple's disease (n = 13).

Discussion

In this large multicenter study, almost half of the patients (45.1%) developed laboratory abnormalities during OPAT, yet these abnormalities rarely (2.3%) led to discontinuation, indicating they were generally not regarded as severe enough to stop treatment. Hypokalemia was rare, while hepatotoxicity was most common, with a time-dependent decrease in the first hepatotoxic event. Other toxicity types showed stable incidence over time. Only for nephrotoxicity, the number of adverse events increased over time, with individual patients experiencing more adverse events in days 31–60 compared to days 0–30. We observed partially toxicity-specific associations between antibiotic type, concomitant medication, baseline laboratory values, patient characteristics, and the occurrence of laboratory abnormalities.

Table 3
Incidence of laboratory abnormalities during the first 60 days of OPAT and time to first laboratory abnormality.

	Patients with laboratory tests during OPAT (N = 1152)
Incidence of laboratory abnormalities, n (%)	520 (45.1%)
hematological toxicity	170 (14.8%)
hypokalemia	24 (2.1%)
nephrotoxicity	131 (11.4%)
hepatotoxicity	335 (29.1%)
Laboratory abnormalities / 1000 OPAT days, mean (SD)	43.7 (96.5)
hematological toxicity / 1000 OPAT days	9.9 (31.4)
hypokalemia / 1000 OPAT days	1.7 (14.4)
nephrotoxicity / 1000 OPAT days	8.3 (34.1)
hepatotoxicity / 1000 OPAT days	33.9 (72.4)
Time to first laboratory abnormality, days, median (1st quartile – 3rd quartile)	7.0 (4.0–14.0)
hematological toxicity	10.0 (5.0–20.0)
hypokalemia	6.5 (5.0–13.8)
nephrotoxicity	12.0 (7.0–20.0)
hepatotoxicity	6.0 (3.0–11.0)
Reasons for discontinuation OPAT, n (%)[a]	
Treatment completed as planned	940 (81.6%)
Readmission	166 (14.4%)
Clinical or microbiological failure	74 (6.4%)
Adverse events	49 (4.3%)
Laboratory abnormalities	27 (2.3%)
Death[b]	5 (0.4%)
Other[c]	106 (9.2%)

Abbreviations – OPAT: outpatient parenteral antimicrobial therapy, SD: standard deviation

[a] More than one reason possible.

[b] Not attributable to OPAT.

[c] Including, among others, patient's preference, catheter failure, transfer of coordination of OPAT care to other hospital.

Our unique focus on laboratory abnormalities during OPAT, rather than adverse events in general, makes comparisons with other studies difficult. Most comparable studies had a broader definition of adverse events, often including catheter-related adverse events or other drug-related adverse events such as nausea, in addition to laboratory abnormalities.[3–5,15,16] Additionally, some studies solely focused on severe adverse events by reporting only clinically significant ones or those reported by the patient or physician. This may explain why our study showed higher rates of laboratory abnormalities compared to rates of adverse drug events reported in these studies.[4,5,16]

The findings in other studies that most adverse events occurred in the first two weeks of OPAT[3,4] were confirmed only for the first hepatotoxic event where we observed a time-dependent effect. In the subgroup of patients receiving OPAT for at least 60 days, nephrotoxicity was more common in days 31–60 compared to the first 30 days. The difference between our results and those of previous studies could be explained by varying definitions of adverse events employed. The other studies used a stricter definition of toxicity and examined a broader range of adverse events beyond just laboratory abnormalities. Additionally, those studies and ours differ in their methods and the selection criteria for patients included in the analysis of the timing of adverse events.

Toxicity-associated factors in this study were medical versus surgical care, comorbidities, baseline laboratory values, male gender, type of antibiotic, and certain co-medication. We assume that the specialty of the treating physician may serve as a proxy for the type of infection and possibly certain comorbidities. Our study indeed confirms the relationship between the degree of comorbidity and laboratory abnormalities.[12] Unexpectedly, better baseline kidney function was associated with increased nephrotoxicity during

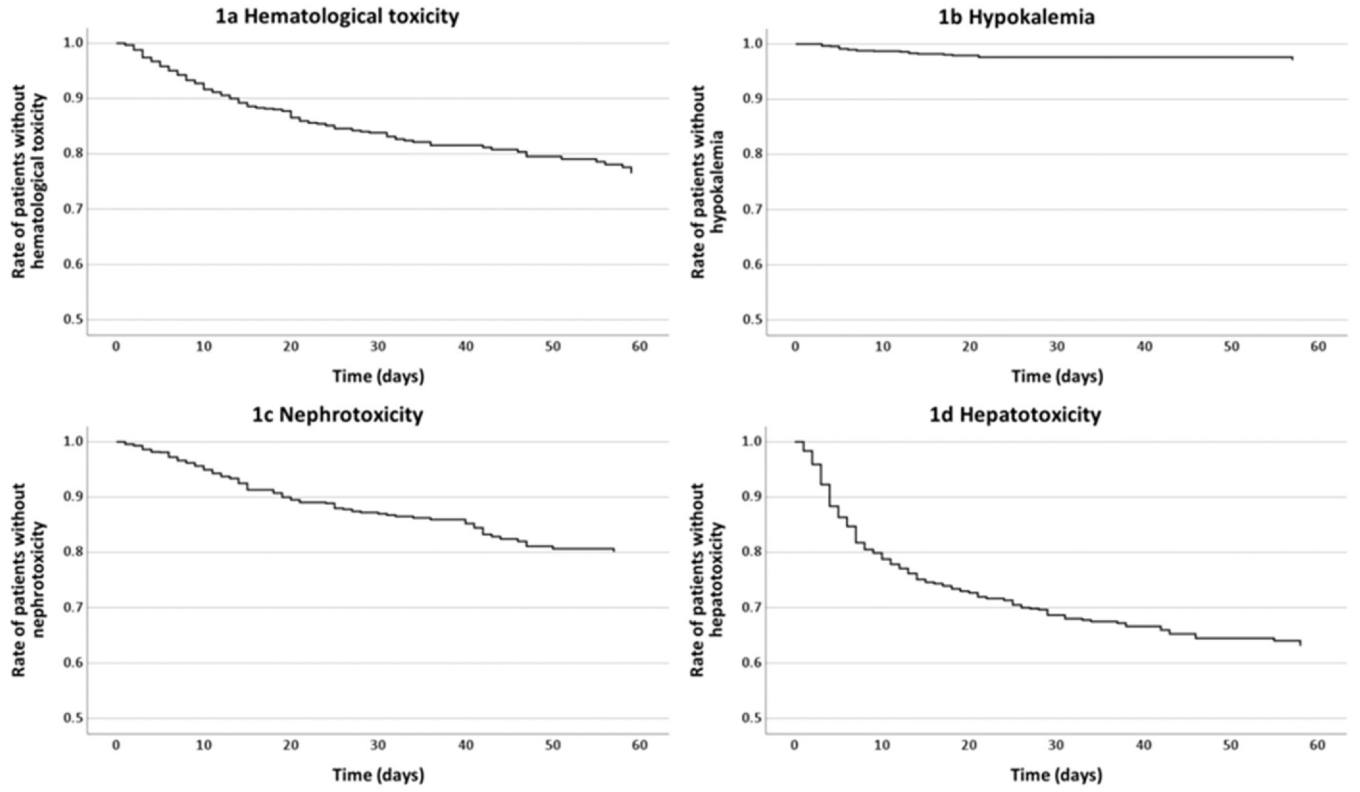

Fig. 1. a-d. Survival plots for the different types of toxicity in the first 60 OPAT days.

follow-up. Our hypothesis is that due to the prevalence of renal dysfunction among hospitalized patients, which often resolves after discharge,[17] toxicity resulting from new causes may be less noticeable. Additionally, the use of a definition that incorporates percentage increases over baseline may overestimate nephrotoxicity.[17] The effect of gender on adverse events is disputed, with both protective and non-protective effects of female gender being described.[4,18] Patients treated with glycopeptides were at particular risk of hematological and nephrotoxicity, neither of which is unexpected.[4,6,19,20] Patients treated with flucloxacillin were also more at risk for nephrotoxicity. Tubulointerstitial nephritis may be the underlying mechanism,[21] but this was not further assessed in our patients. In addition to the type of IV antibiotic prescribed, baseline use of diuretics was positively associated, while NSAIDs were negatively associated with nephrotoxicity. The negative association between NSAID prescription and nephrotoxicity was unexpected. It is questionable whether there was true NSAID exposure during follow-up, as these were primarily discharge medications for pain management. Since NSAIDs were mainly prescribed to patients with fewer comorbidities and better renal function, the observed effect was likely due to residual confounding by indication.

Patients receiving OPAT need follow-up, most intensively shortly after starting OPAT.[3,4,9,12] This is partly due to other adverse events besides laboratory abnormalities, which occur more frequently than those identified by a physician.[4] These latter events are primarily detected through laboratory testing. Since our results indicate that discontinuation of OPAT is not often warranted, despite the frequent occurrence of laboratory abnormalities, a less intensive laboratory monitoring policy during OPAT is justified. This is also suggested in studies by Sunagawa et al. and implicitly by Browning et al., who found a low incidence rate of major adverse events, including laboratory abnormalities.[3,15] While a study by Huck et al. found an association between a lack of availability of laboratory results and readmissions during OPAT,[9] their definition of laboratory result availability was at least one recommended test. Therefore, their conclusion is consistent with our recommendation to maintain follow-up during OPAT, but to reduce the frequency of laboratory monitoring.

Although overall laboratory monitoring frequency can be reduced, a long duration of OPAT alone doesn't justify a reduction, as our study found no decrease in laboratory abnormalities in patients receiving at least 60 days of OPAT. Our findings do suggest that it

Table 4
Poisson regression model comparing the number of laboratory abnormalities in days 31–60 compared with those in day 0–30 in 129 patients receiving > 60 OPAT days.

	Absolute events P1, *n*	Estimated marginal means[a] P1, mean (SE)	Absolute events P2, *n*	Estimated marginal means[a] P2, mean (SE)	Incidence rate ratio (95% CI)[b]	*p*-value
All laboratory abnormalities	155	0.109 (0.009)	147	0.129 (0.011)	1.175 (0.931–1.484)	0.175
hematological toxicity	47	0.131 (0.019)	37	0.110 (0.020)	0.840 (0.536–1.317)	0.448
hypokalemia	3	0.010 (0.006)	2	0.009 (0.006)	0.828 (0.138–4.953)	0.836
nephrotoxicity	40	0.105 (0.017)	50	0.163 (0.024)	1.548 (1.006–2.382)	**0.047**
hepatotoxicity	65	0.182 (0.024)	58	0.220 (0.029)	1.212 (0.840–1.750)	0.304

Abbreviations – CI: confidence interval, P1: period 1 (0-30 days), P2: period 2 (31-60 days), SE: standard error.
Bold value indicates significant *p*-value.
[a] Average number of laboratory abnormalities per laboratory test during the period.
[b] Period 1 is the reference category.

Table 5
Final multivariable Cox proportional hazards model: Factors independently associated with the occurrence of laboratory abnormalities.

	Hematological toxicity	*Nephrotoxicity*	*Hepatotoxicity*
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Demographics			
Female			0.727 (0.546–0.969)$^{+}$
Infection and comorbidity			
Charlson Comorbidity Index	1.075 (1.013–1.141)$^{+}$	1.098 (1.019–1.182)$^{+}$	
Baseline medication[a]			
Diuretics		1.792 (1.208–2.658)$^{++}$	
NSAID		0.490 (0.246–0.975)$^{+}$	
Treatment characteristics			
Treated in hospital with standardized laboratory monitoring policy	1.448 (1.055–1.988)$^{+}$	1.531 (1.061–2.208)$^{+}$	2.448 (1.884–3.182)$^{+++}$
Medical specialty, compared to surgical	1.513 (1.081–2.119)$^{+}$		
Type of IV antibiotics			
Cephalosporins (ref)	1	1	
Penicillins	1.089 (0.750–1.581)	1.781 (1.020–3.113)$^{+}$	
Flucloxacillin[b]		2.982 (1.743–5.102)$^{+++}$	
Glycopeptides	1.987 (1.248–3.163)$^{++}$	2.385 (1.313–4.332)$^{++}$	
Carbapenems	1.066 (0.583–1.949)	1.358 (0.596–3.095)	
Baseline laboratory values[c]			
Creatinine		0.995 (0.991–1.000)$^{+}$	
Bilirubin			1.012 (1.000–1.024)$^{+}$
GGT			1.002 (1.002–1.003)$^{+++}$
ALT			1.004 (1.002–1.006)$^{+++}$

^{+}p-value = < 0.05,
^{++}p-value = < 0.01,
^{+++}p-value = < 0.001.
Abbreviations – ALT: alanine aminotransferase, CI: confidence interval, GGT: gamma-glutamyl transferase, IV: intravenous, NSAID: non-steroidal anti-inflammatory drug, OPAT: outpatient parenteral antimicrobial therapy, ref: reference category.
[a] For each type of toxicity, baseline medication expected to have an effect was included in the multivariable analysis, respectively ACE inhibitor and/or ARB, diuretics and NSAID for nephrotoxicity and paracetamol for hepatotoxicity.
[b] Flucloxacillin was considered separately from the other penicillins for nephrotoxicity.
[c] Only the value(s) that determined the type of toxicity were included in the multivariable analysis (e.g. only creatinine for nephrotoxicity).

may be possible to significantly reduce the frequency of monitoring for hepatotoxicity if it has not occurred after approximately 10 days.

We also argue that a more individualized frequency of laboratory monitoring with a reduced number of blood sampling does not expose the patient to unnecessary risks, while it will be less invasive for the patient and it saves costs and resources. Because of the observed low incidence of hypokalemia, potassium monitoring would rarely be indicated. Patients who are administered flucloxacillin, especially those also receiving potassium-losing diuretics, should be considered for this monitoring until it is confirmed that this side effect has not occurred.[22] In addition, monitoring for hyperkalemia may be necessary in some patients, for example when co-trimoxazole is prescribed as an oral antibiotic alongside OPAT.[23] Additionally, patients with few comorbidities may require less frequent monitoring, as well as those who are not receiving glycopeptides and flucloxacillin. However, the latter two agents would require regular renal function monitoring as they were associated with the occurrence of nephrotoxicity, with glycopeptides also needing closer monitoring of blood counts and drug concentrations. Monitoring patients with a history of antibiotic drug hypersensitivity for toxicity seems particularly important, as they were overrepresented in the group who discontinued OPAT due to laboratory abnormalities. This is also supported by the previous observation during OPAT that eosinophilia is associated with a subsequent hypersensitivity reaction.[11]

Our study has several strengths. First, our study had a large patient cohort compared to other studies investigating adverse events during OPAT.[4,5,12] Second, these patients were treated in both university and non-university hospitals, two of which had a highly standardized laboratory monitoring policy, resulting in a complete overview of laboratory results during their OPAT episodes. Third, our study focused specifically on laboratory abnormalities during OPAT, unlike almost all other studies that included a variety of adverse events, including e.g. catheter-related complications.[3,4] Therefore, our results are suitable to provide guidance on the need for and optimal frequency of laboratory monitoring.

Our study also has several limitations. First, the hospitals had different laboratory monitoring policies. Structured monitoring was associated with more toxicity, despite the fact that individuals undergoing testing in other hospitals were more vulnerable than those who did not. Therefore, the true incidence is likely somewhat higher. However, since hospitals with standardized monitoring did not discontinue OPAT significantly more often, severe laboratory abnormalities do not seem to be missed frequently. Second, we did not collect data on antibiotic treatment prior to OPAT initiation, which means that we may have missed an early time-dependent effect of antibiotics on the incidence of laboratory abnormalities. Also, the dosages of therapy during OPAT were not known, nor were changes in dosage. Third, when considering the effect of other medications, we assumed that baseline medications were continued during follow-up. However, it is likely that patients were not continuously exposed to the medication, due to noncompliance or discontinuation during OPAT.

In conclusion, laboratory abnormalities during OPAT are common but rarely a reason to discontinue OPAT. For the occurrence of the first hepatotoxic event, we observed a time-dependent decline, with the vast majority of hepatotoxic events occurring in the first two weeks. In the subgroup of patients receiving long courses of OPAT, nephrotoxicity was more common in days 31–60 compared to the first 30 days, which appeared to be related to flucloxacillin. Additionally, laboratory abnormalities were associated with specific patient, treatment, and laboratory characteristics. These factors can guide the necessity and frequency of laboratory monitoring in individual patients. Overall, our findings support a more personalized laboratory monitoring policy with less blood draws.

Funding

This work was supported by a grant from the Gelderland Care Network for Antimicrobial resistance and Infection prevention (Gelders Antimicrobiële resistentie en Infectiepreventie Netwerk; GAIN) [331619], and a grant from the Academic Alliance Fund (Academisch Alliantie Fonds; AAF) [PI-00416]. HHS, HFLW, JAS, MEJLH and JtO received an unrestricted research grant from Pfizer [62050035].

Author contributions

HHS, ME, HFLW, JAS, MEJLH, LP and JtO conceptualized the study. HHS, ME, LP, YK, SK, TS, SPvM, MT and JtO contributed to data acquisition. HHS, RA, OR and JtO decided on and performed the data analysis. HHS and JtO wrote the first draft of the manuscript. All authors critically reviewed the manuscript.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106301.

References

1. Berrevoets MAH, Oerlemans AJM, Tromp M, et al. *Quality of outpatient parenteral antimicrobial therapy (OPAT) care from the patient's perspective: a qualitative study. BMJ Open* 2018;**8**:e024564.
2. Mitchell ED, Czoski Murray C, Meads D, Minton J, Wright J, Twiddy M. *Clinical and cost-effectiveness, safety and acceptability of community intravenous antibiotic service models: CIVAS systematic review. BMJ Open* 2017;**7**:e013560.
3. Browning S, Loewenthal MR, Freelander I, Dobson PM, Schneider K, Davis JS. *Safety of prolonged outpatient courses of intravenous antibiotics: a prospective cohort study. Clin Microbiol Infect* 2022;**28**(6):832–7.
4. Keller SC, Williams D, Gavgani M, et al. *Rates of and risk factors for adverse drug events in outpatient parenteral antimicrobial therapy. Clin Infect Dis* 2017;**66**(1):11–9.
5. Underwood J, Marks M, Collins S, Logan S, Pollara G. *Intravenous catheter-related adverse events exceed drug-related adverse events in outpatient parenteral antimicrobial therapy. J Antimicrob Chemother* 2019;**74**(3):787–90.
6. Ng N, Bailey P, Pryor R, et al. *Experiences in outpatient parenteral antimicrobial therapy (OPAT): barriers and challenges from the front lines. Antimicrob Steward Healthc Epidemiol* 2021;**1**(1):e42.
7. Norris AH, Shrestha NK, Allison GM, et al. *2018 Infectious Diseases Society of America Clinical Practice Guideline for the Management of Outpatient Parenteral Antimicrobial Therapy. Clin Infect Dis* 2019;**68**(1):1–4.
8. 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 Antimicrob Resist* 2019;**1**(2):dlz026.
9. Huck D, Ginsberg JP, Gordon SM, Nowacki AS, Rehm SJ, Shrestha NK. *Association of laboratory test result availability and rehospitalizations in an outpatient parenteral antimicrobial therapy programme. J Antimicrob Chemother* 2014;**69**(1):228–33.
10. Townsend J, Keller S, Tibuakuu M, et al. *Outpatient parenteral therapy for complicated Staphylococcus aureus infections: a snapshot of processes and outcomes in the real world. Open Forum Infect Dis* 2018;**5**(11):ofy274.
11. Blumenthal KG, Youngster I, Rabideau DJ, et al. *Peripheral blood eosinophilia and hypersensitivity reactions among patients receiving outpatient parenteral antibiotics. J Allergy Clin Immunol* 2015;**136**(5):1288–94.
12. Frisby J, Ali N, Niemotka S, Abate G. *Usefulness of routine laboratory tests for follow up of patients receiving outpatient parenteral antimicrobial therapy run by infectious diseases fellows. Antibiotics* 2023;**12**(2):330.
13. Lee B, Tam I, Weigel 4th B, et al. *Comparative outcomes of β-lactam antibiotics in outpatient parenteral antibiotic therapy: treatment success, readmissions and antibiotic switches. J Antimicrob Chemother* 2015;**70**(8):2389–96.
14. Youngster I, Shenoy ES, Hooper DC, Nelson SB. *Comparative evaluation of the tolerability of cefazolin and nafcillin for treatment of methicillin-susceptible Staphylococcus aureus infections in the outpatient setting. Clin Infect Dis* 2014;**59**(3):369–75.
15. Sunagawa SW, Arduser S, Miller MM, et al. *Serious adverse events and laboratory monitoring regimens for outpatient parenteral antimicrobial therapy with cefazolin and ceftriaxone. Open Forum Infect Dis* 2023;**10**(12):ofad606.
16. Billmeyer KN, Ross JK, Hirsch EB, Evans MD, Kline SE, Galdys AL. *Predictors of adverse safety events and unscheduled care among an outpatient parenteral antimicrobial therapy (OPAT) patient cohort. Ther Adv Infect Dis* 2023;**10**:20499361231179668.
17. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. *Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol* 2014;**9**(1):12–20.
18. Kaul CM, Haller M, Yang J, et al. *Assessment of risk factors associated with outpatient parenteral antimicrobial therapy (OPAT) complications: a retrospective cohort study. Antimicrob Steward Healthc Epidemiol* 2022;**2**(1):e183.
19. Felder KK, Marshall LM, Vaz LE, Barnes PD. *Outpatient parenteral antimicrobial therapy for adult orthopedic and neurosurgical infections. South Med J* 2016;**109**(1):53–60.
20. Bruniera FR, Ferreira FM, Saviolli LR, et al. *The use of vancomycin with its therapeutic and adverse effects: a review. Eur Rev Med Pharmacol Sci* 2015;**19**(4):694–700.
21. Bakker SJ, Luik AJ, Leunissen KM. *Flucloxacillin-induced acute interstitial nephritis. Nephrol Dial Transpl* 1995;**10**(4):579.
22. van der Heijden Cdcc, Duizer ML, Fleuren Hwha, et al. *Intravenous flucloxacillin treatment is associated with a high incidence of hypokalaemia. Br J Clin Pharmacol* 2019;**85**(12):2886–90.
23. Fralick M, Macdonald EM, Gomes T, et al. *Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study. BMJ* 2014;**349**:g6196.
24. U.S. Department of Health and Human Services National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1; 2017. Available from: ⟨https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf⟩.