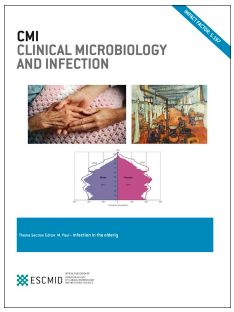

Article:
Durojaiye, O., Kritsotakis, E. orcid.org/0000-0002-9526-3852, Johnston, P. et al. (3 more authors) (2019) Developing a risk prediction model for 30-Day unplanned hospitalisation in patients receiving outpatient parenteral antimicrobial therapy. Clinical Microbiology and Infection, 25 (7). 905.e1-905.e7. ISSN 1198-743X

https://doi.org/10.1016/j.cmi.2018.11.009

Accepted Manuscript



Developing a Risk Prediction Model for 30-Day Unplanned Hospitalisation in Patients Receiving Outpatient Parenteral Antimicrobial Therapy

Oyewole C. Durojaiye, MPH, MSc, DLSHTM, MRCP(UK) (Infect Dis), FRCPath, FRCP(Glasg), Consultant Physiciana, Evangelos I. Kritsotakis, BSc, MSc, PhD, FHEA, Assistant Professor of Epidemiology & Medical Statistics, Peter Johnston, BA (Hons), MBChB (Hons), PGDip, DTM&H, MRCP(UK), Specialty Registrar, Thomas Kenny, BSc (Hons), MBBS (Hons), DTM&H, Specialty Registrar, Fotinie Ntziora, MD, MSc, PhD, DTM&HFHEA, Specialty Physician, Katharine Cartwright, FRCPath, MRCP(UK), Consultant Physician

PII: S1198-743X(18)30736-5

DOI: https://doi.org/10.1016/j.cmi.2018.11.009

Reference: CMI 1481

To appear in: *Clinical Microbiology and Infection*

Received Date: 22 August 2018

Revised Date: 4 November 2018

Accepted Date: 11 November 2018

Please cite this article as: Durojaiye OC, Kritsotakis EI, Johnston P, Kenny T, Ntziora F, Cartwright K, Developing a Risk Prediction Model for 30-Day Unplanned Hospitalisation in Patients Receiving Outpatient Parenteral Antimicrobial Therapy, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2018.11.009.

TITLE PAGE

Intended category:

Original article

Article Title:

Developing a Risk Prediction Model for 30-Day Unplanned Hospitalisation in Patients Receiving Outpatient Parenteral Antimicrobial Therapy

Author Names and Affiliations:

- Oyewole C. Durojaiye (Corresponding Author)

  MPH, MSc, DLSHTM, MRCP(UK) (Infect Dis), FRCPath, FRCP(Glasg)

  Consultant Physician, Department of Infection and Tropical Medicine, Royal Hallamshire Hospital, Sheffield S10 2JF, UK.

  Tel: +44 (0)7728739704. Fax: + 44 (0)114 22 68875. Email: chris.durojaiye@sth.nhs.uk

- Evangelos I. Kritsotakis

  BSc, MSc, PhD, FHEA

  Assistant Professor of Epidemiology & Medical Statistics, School of Health and Related Research (ScHARR), The University of Sheffield, Sheffield, S1 4DA, UK.

  Tel: +44 (0) 114 22 26301 Email: e.kritsotakis@sheffield.ac.uk

- Peter Johnston

  BA (Hons), MBChB (Hons), PGDip, DTM&H, MRCP(UK)

  Specialty Registrar, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, S10 2JF, UK.

  Email: peterjohnston@doctors.org.uk

- Thomas Kenny

  BSc (Hons), MBBS (Hons), DTM&H

  Specialty Registrar, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, S10 2JF, UK. Email: thomaskenny@btinternet.com

- Fotinie Ntziora

  MD, MSc, PhD, DTM&H, FHEA

  Specialty Physician, Department of Infection and Tropical Medicine, Royal Hallamshire Hospital, Sheffield S10 2JF, UK. Email: fotinientziora@gmail.com

  Present address: Consultant Physician, First Department of Propaedeutic and Internal Medicine, Laiko General Hospital, University of Athens Medical School, 11527 Athens, Greece

- Katharine Cartwright

  FRCPath, MRCP(UK)

  Consultant Physician, Department of Infection and Tropical Medicine, Royal Hallamshire Hospital, Sheffield S10 2JF, UK. Email: katharine.cartwright@sth.nhs.uk

Keywords:

OPAT; readmission; hospitalisation; risk factors; predictive model

Running Title:

Prediction Model of Unplanned Hospitalisation in OPAT

ABSTRACT

Objectives: Outpatient parenteral antimicrobial therapy (OPAT) is increasingly used to treat a wide range of infections. However, there is risk of hospital readmissions. The study aim was to develop a prediction model for the risk of 30-day unplanned hospitalisation in patients receiving OPAT.

Methods: Using a retrospective cohort design, we retrieved data on 1073 patients who received OPAT over two years (01/2015 - 01/2017) at a large teaching hospital in Sheffield, UK. We developed a multivariable logistic regression model for 30-day unplanned hospitalisation and assessed its discrimination and calibration abilities, and internally validated using bootstrap resampling.

Results: The 30-day unplanned hospitalisation rate was 11% (123/1073). The main indication for hospitalisation was worsening or non-response of infection (42%; 52/123). The final regression model consisted of age (adjusted odds ratio [aOR], 1.18 per decade; 95% confidence interval [CI], 1.04-1.34), Charlson comorbidity score (aOR, 1.11 per unit increase; 95%CI, 1.00-1.23), prior hospitalisations in past 12 months (aOR, 1.30 per admission; 95%CI, 1.17-1.45), concurrent intravenous antimicrobial therapy (aOR, 1.89; 95%CI, 1.03-3.47), and endovascular infection (aOR, 3.51; 95%CI, 1.49-8.28). Mode of OPAT treatment was retained in the model as a confounder. The model had adequate concordance (c-statistic 0.72; 95%CI 0.67-0.77) and calibration (Hosmer-Lemeshow P=0.546; calibration slope 0.99; 95%CI 0.78-1.21) and low degree of optimism (bootstrap optimism corrected c-statistic, 0.70).

Conclusions: We identified a set of six important predictors of unplanned hospitalisation based on readily available data. The prediction model may help improve OPAT outcomes through better identification of high-risk patients and provision of tailored care.

TEXT

Introduction

Intravenous (IV) antimicrobials are increasingly administered in outpatient settings to treat a wide range of infections in patients who require parenteral therapy, but are otherwise well enough not to need hospitalisation. Outpatient parenteral antimicrobial therapy (OPAT) has been shown to be safe, clinically efficacious and cost-effective with high levels of patient satisfaction and acceptability.[1-8] Despite its benefits, OPAT is potentially associated with increased clinical risk due to reduced monitoring and supervision. Even with careful patient selection and multidisciplinary team (MDT) driven therapeutic plans, the nature of the infections treated and durations of treatment mean readmission for some patients is inevitable. Thirty-day readmission rates have been used in the UK and internationally as a marker of health care quality.[9] Predicting and preventing unplanned hospitalisation could improve patient outcomes and reduce healthcare costs. Few studies have assessed risk factors for unplanned hospitalisation in OPAT.[10-12] To the best of our knowledge, no risk prediction models for hospitalisation have been developed for patients receiving OPAT within the UK National Health Service.

This study aimed to identify factors that might be associated with increased risk of hospital readmission in an OPAT service based in a large tertiary referral teaching hospital in Sheffield, UK and to develop a predictive model for 30-day unplanned hospitalisation. The development of an accurate prediction rule may help identify high-risk patients, and provide personalised care and support.

Methods

Patient Population and Setting

We performed a retrospective analysis of all patients who received OPAT between January 2015 and January 2017 at Sheffield Teaching Hospitals (STH), South Yorkshire, England. The Sheffield OPAT service, established in January 2006, is one of the largest in the UK. The OPAT service, patient selection criteria, and a prospectively maintained database have been previously described.[13] Patient selection, antimicrobial regimens and mode of OPAT delivery were the responsibility of the OPAT physicians.

Data Collection

The OPAT database, hospital electronic clinical and laboratory databases were reviewed. Data extracted included patient demographics, comorbidities, hospitalisation at STH in the previous 12 months, treatment indication, microbiology culture data, antimicrobial regimen, mode of OPAT delivery, type of IV access, length of OPAT stay, OPAT outcome, prior OPAT stay, hospital readmission, reason and length of hospitalisation. Age (years) was determined at the time of commencing OPAT. Weighted Charlson comorbidity score was calculated for each patient and was determined at the time OPAT commenced.[14] Drug-resistant organisms were defined as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, multi-drug-resistant tuberculosis, extended-spectrum beta-lactamases producing bacteria and multidrug-resistant Candida.

The primary outcome was 30-day unplanned hospitalisation, defined as unplanned inpatient admission to an acute care hospital for any reason within 30 days of discharge from the OPAT service.

Sample Size

To ensure a reliable prediction model, we adhered to the accepted rule of having at least 10 events per regression coefficient estimated.[15] We planned for 15 predictor degrees of freedom. Using an anticipated hospitalisation rate of 10% with approximately 750 OPAT episodes per year, we chose to review two years' worth of OPAT records to ensure adequate sample size for formulating the model.

Statistical Analysis

Because some patients had more than one episode of OPAT treatment during the study period, we performed individual level analysis by taking a simple random sample of one OPAT episode per patient. Univariate analysis was performed to describe differences between patients with 30-day unplanned hospitalisation and those without, and to confirm expected predictive relations from previous studies. Crude associations were quantified using odds ratios (OR) with 95% confidence intervals (95%CI) calculated by binary logistic regression.

A multivariable logistic regression model was developed to predict the risk of unplanned hospitalisation within 30 days of discharge from OPAT. We initially considered 13 predictor variables based on review of the literature, clinical relevance and data availability at time of OPAT initiation. These included patient sex, age, number of prior hospitalisations in the past 12 months, Charlson comorbidity score, mode of antimicrobial delivery, drug-resistant organisms, concurrent intravenous antimicrobial therapy, four antimicrobial classes (penicillin, cephalosporin, carbapenem and glycopeptide), indication for OPAT and type of vascular access (peripheral vs. central).[10-12,16-23] None of the candidate predictor variables had missing values in our database. To minimize the risk of overfitting, no exploratory search beyond the pre-specified set of predictors was carried out.

To limit collinearity and ensure a parsimonious prognostic model, we examined Spearman's correlations and variance inflation factors among the 13 initial predictors. Of the four antimicrobial

155 classes examined, we retained only the cephalosporin in the analysis because it had strong negative
156 correlations with other classes and is the most commonly prescribed antimicrobial class in OPAT [1,5,12]
157 (limiting candidate predictors to 10 variables). We assessed nonlinear effects of continuous variables
158 using restricted cubic splines. A linear relationship with the log odds of 30-day unplanned
159 hospitalisation was found to be a good approximation for age, Charlson score and the number of
160 prior hospitalisations.
161
162 Following the fit of the logistic regression model with the pre-selected set of 10 predictors, those
163 that did not retain statistical significance (at the alpha level of 0.05) were tested for confounding and
164 predictive contributions by dropping them one at a time starting from the least significant.
165 Predictors that caused substantial confounding (change in model coefficient by at least 10%) or
166 improved prediction (non-zero difference in c-statistic of nested models) were retained in the
167 model. We also considered changes in the Bayesian Information Criterion (BIC) during this process.
168 To provide a graphical depiction of all variables in the final risk-prediction model and enable an
169 approximate computation of output probabilities, we constructed a Kattan-style nomogram in which
170 the length of the line corresponding to a given predictor is indicative of its importance. Points were
171 assigned to each predictor variable and total points corresponded to an absolute predicted risk for
172 30-day unplanned hospitalisation.
173
174 The validity of the final model was assessed by estimating its concordance and calibration ability.
175 Model calibration (agreement between observed outcomes and predictions) was assessed by the
176 Hosmer–Lemeshow goodness-of-fit test and by evaluating how much the slope of the calibration
177 line (plotting the predicted probabilities against the observed probabilities) deviates from the ideal
178 of 1.0. Discrimination ability (the extent to which the model distinguishes patients with unplanned
179 hospitalisation from those without) was assessed using the concordance statistic (c-statistic).

Internal validation was carried out by calculating the c-statistic with correction for 'optimism' overfitting using 200 bootstrap samples.

Data were processed and analysed using STATA/IC v.13.1 (StataCorp, College Station, TX). The nomolog program was used to produce the nomogram.[24]

Ethical approval for this study was not deemed necessary as the data were routinely collected and analysed for clinical governance, service development and service evaluation activities. The study complies with the transparent reporting of studies developing multivariable prediction models for individual prognosis (TRIPOD) statement.[25]

Results

Cohort characteristics

Over the two-year study period, we recorded 1324 episodes of OPAT in 1073 individual patients. To develop the risk prediction model, a random sample of one episode per patient was selected. **Table 1** shows the demographic and clinical characteristics of the cohort. The mean age of the patients was 56 (range 16-95) years and 57% (611/1073) were male. Skin and soft tissue infection (SSTI) was the most common indication for OPAT (616/1073; 57%) and use of cephalosporins (577/790; 73%). Most patients received intravenous therapy by attending the infusion centre daily (767/1073; 71%). The median duration of OPAT was seven days (IQR 4-19; range <1 to 261).

Hospitalisation within 30 days of discharge from the OPAT service was recorded in 14% (145/1073) patients. The majority of these hospitalisations were unplanned (123/1073; 11%; 95%CI 9.6% - 13.4%). 78 of the 123 patients (63%) with unplanned hospitalisation were admitted during OPAT treatment. Half of these patients (38/78; 49%) were admitted within the first week of treatment.

More than a third of the patients (17/45; 38%) that required hospitalisation after completion of OPAT were admitted two weeks after OPAT therapy. Reasons for the unplanned hospitalisation are shown in **Table 2**. The leading indication for hospitalisation was progression or non-response of infection (52/123; 42%). The median length of hospitalisation was five days (IQR 2-10; range <1 to 114 days).

Univariate (unadjusted) analysis

Patients with unplanned hospitalisation were older (mean 61 vs. 56 years), had higher Charlson comorbidity score (median 2 vs. 1) and more prior hospital admissions in the past 12 months (median 1 vs. 0) compared to patients without 30-day unplanned hospitalisation (**Table 1**). Unplanned hospitalisation was also more likely to have occurred in patients who had received OPAT by a community nurse as opposed to an infusion centre, patients with central vascular access devices as opposed to peripheral access, and patients treated for endovascular, urogenital or bone and joint infections as opposed to SSTI. Regarding antimicrobial class, unplanned hospitalisation was positively associated with receipt of penicillin, carbapenem and glycopeptide, but negatively associated with use of cephalosporin. Patients who had an unplanned hospitalisation were also more likely to have been treated simultaneously with multiple parenteral antimicrobial agents.

Multivariable Model

Results of logistic regression analysis are shown in **Table 3** for the full set of the 10 pre-selected predictors (model 1) and for the model that retained only predictors with important predictive contribution or confounding effects (model 2). Age, prior non-OPAT hospitalisation in the past 12 months, endovascular infection and receipt of concurrent intravenous antimicrobial therapy were independently and significantly associated with increased risk of 30-day unplanned hospitalisation. Receipt of intravenous cephalosporin therapy was significantly associated with decreased risk of 30-day unplanned hospitalisation. Charlson comorbidity score and mode of OPAT delivery had high p-

values. However, both variables were retained in the model because the former made an important predictive contribution and the latter was an important confounder. By contrast, patient sex, type of vascular access device or multidrug resistant organism had no predictive contribution in the risk of hospitalisation. Because antimicrobial treatment may reflect local practices that may limit generalisability of the prediction model to different OPAT settings, we examined the possibility of removing cephalosporin variable from the model. Model discrimination and calibration were affected only slightly, but the BIC improved slightly supporting the removal of cephalosporin from the final model (**Table 3**).

Independent predictors of the risk of 30-day unplanned hospitalisation in the final model (model 3) were age (adjusted odds ratio [aOR], 1.18 per decade; 95% confidence interval [CI], 1.04 - 1.34), Charlson comorbidity score (aOR, 1.11 per unit increase; 95%CI, 1.00 - 1231), prior non-OPAT hospitalisation in the past 12 months (aOR, 1.30 per prior admission; 95%CI, 1.17 - 1.45), receipt of concurrent intravenous antimicrobial therapy (aOR, 1.89; 95%CI, 1.03 - 3.47), and treatment for endovascular infection (aOR, 3.51; 95% CI, 1.49 – 8.28), urogenital infection (aOR, 2.62; 95%CI, 1.27 – 5.43) and bone and joint infection (aOR, 2.09; 95% CI, 1.06 – 4.12) as opposed to SSTI. Mode of OPAT delivery was retained in the final model as an important confounder. **Figure 1** provides a nomogram of the model's predicted risks for 30-day unplanned hospitalisation.

The final model's discrimination ability was adequate (c-statistic 0.72; 95%CI 0.67 – 0.77) and internal validation indicated a low degree of overfitting (bootstrap optimism corrected c-statistic, 0.70). Model predicted probabilities ranged between 1.8% and 83.4%. The Hosmer-Lemeshow test (P=0.546) and the calibration slope (0.99; 95%CI 0.78 – 1.21) indicated a good agreement between predicted and observed probabilities. In addition, the calibration plot did not indicate a pattern of either over- or underestimation (**Figure 2**).

Discussion

Our study highlights the fact that patients treated with OPAT are at risk of unplanned hospital readmission. The rate of unplanned hospitalisation (11%; 123/1073) in our cohort is comparable to other OPAT studies.[18,21] Worsening or non-response of infection was the main indication for unplanned hospitalisation. These patients were readmitted for further management including change in antimicrobial therapy and source control. We found these factors, which are readily available at time of commencing OPAT, to be important predictors of unplanned hospitalisation: age, prior non-OPAT hospitalisations in past 12 months, Charlson comorbidity index score, concurrent receipt of more than one intravenous antimicrobial agent and indication for OPAT.

Patient age, underlying comorbid conditions and prior hospital admissions have been recognised as important patient-related risk factors for hospital readmission in OPAT patients in previous research.[12,16-18,20,23] We estimated a relative increase in the odds of 30-day hospitalisation of about 18% per decade increase in age and of about 30% per prior admission of patients attending our OPAT service, which are close to those reported in a comparable study in Tufts Medical Center in Boston.[12] Patients with prior hospital admissions were more likely to be hospitalised because they usually have more medical comorbidities and were likely to be readmitted due to other conditions. Using the composite Charlson comorbidity index, we additionally identified an important risk increase associated with patient multimorbidity (an increase in the odds of 30-day hospitalisation by 11% per unit increase in Charlson score).

The increased risk of hospitalisation in patients who were treated simultaneously with multiple parenteral antimicrobial agents (i.e. concurrent antimicrobial therapy) in our cohort may reflect a higher severity of infection, adverse drug reactions or drug interactions. Similar to other OPAT services,[1,5,7,10,12,17,19,23] cephalosporins were the most frequently prescribed parenteral antimicrobial agent in our cohort (70%; 790/1136). Patients who received IV cephalosporin were less likely to be

hospitalised. We mostly use IV ceftriaxone to treat patients with uncomplicated SSTI. These patients are generally well and are at lower risk of hospitalisation. In Glasgow, UK, ceftriaxone therapy was found to be associated with reduced duration of OPAT in patients with SSTIs.[10] Nevertheless, we decided to exclude cephalosporin treatment from our risk prediction model because it might reflect our specific OPAT setting and might be a less influential clinical factor in other settings. Future studies should consider examining a potential association between cephalosporin use in OPAT and readmission.

Similar to Kouma *et al*,[20] we also found a strong association of endovascular infection with unplanned hospitalisation. Endocarditis accounted for more than two thirds of endovascular infections treated in our cohort. These patients were properly selected for OPAT in line with national guidelines. Larraza *et al* additionally reported respiratory and post intra-abdominal surgery infections as risk factors for readmission in their cohort.[18] However, the indication for OPAT (infection treated) was not identified as a risk factor for readmission in other comparable studies.[12,16,17,19]

Unlike other OPAT studies,[12,16,17,19] we did not identify aminoglycoside use, presence of drug-resistant organisms and length of treatment as predictors of unplanned hospitalisation. In our cohort, aminoglycosides were administered only in eight patients. We seldom use aminoglycosides in our OPAT service due to the toxicity of these agents and challenges in therapeutic drug monitoring in an outpatient setting. Although OPAT administered at home by community nurses appeared to be associated with an increased risk of hospitalisation in univariate analysis, the association diminished after adjusting for other predictors. Nevertheless, we retained mode of OPAT treatment in our risk prediction model as an important confounder.

Some limitations of this study should be acknowledged. This was a single-centre study. Although our epidemiological data are consistent with those reported in different settings in the UK and the USA,[10-12,16,17] our risk prediction model needs to be externally validated to assess its generalisability to patients treated in other settings. Our analysis was retrospective, but the data were originally collected prospectively, which reduces the risk of measurement bias or poor accuracy of data records. However, we cannot be certain that we have not missed some patients who were readmitted to other hospitals. The potential for undocumented hospital readmissions might result in an underestimate of the actual risk of 30-day hospitalisation. Nevertheless, most patients' interactions with healthcare systems are documented in their clinical records, and they were usually reviewed four to six weeks after completion of OPAT. Despite extensively analysing factors previously reported to be associated with hospitalisation, we cannot be certain that we have not missed other important predictors or that unrecorded confounders may have influenced our findings. We did not explore factors (such as therapeutic drug levels, frequency of monitoring or follow-up visits) that are not readily available pre-OPAT but are plausible readmission risk factors; our aim was to develop a risk prediction model based on data available on presentation to the OPAT service. Our risk prediction model produces excellent agreement (calibration) between observed and predicted probabilities of 30-day hospitalisation, and the bootstrap internal validation suggests only a small degree of bias from overfitting the model to our data. However, our model should be prospectively validated in an independent diverse patient population before use in actual patient care. We intend to continue the project and are currently planning for quasi-external validation of the model in future patients in our centre and external validation in patients from other UK centres.

This study adds to existing literature by showing that patients receiving OPAT are at risk of unplanned hospitalisations, some of which may be preventable. Averting unnecessary hospitalisation depends on understanding which patients are likely to be readmitted. The predictive model for 30-day unplanned hospitalisation developed in this study is based on six easily obtainable

335 variables and has adequate prediction metrics. This model has the potential to identify high-risk
336 patients upon presentation to the OPAT service at a large tertiary referral teaching hospital, thereby
337 informing evidence-based interventions, and personalised care and support to prevent hospital
338 readmissions. Further research is required to assess how this model may perform in different
339 settings, and to elucidate how it may be incorporated into clinical practice to improve the care of
340 patients receiving OPAT.

Transparency Declaration

Conflict of Interest

None of the authors has potential conflict of interest

Funding

No funding was received for the production of this report. This study was carried out as part of our routine work.

Acknowledgements

The authors wish to thank all the clinical and administrative staff working in the Sheffield OPAT service.

REFERENCES

1. Barr DA, Semple L, Seaton RA. Outpatient parenteral antimicrobial therapy (OPAT) in a teaching hospital-based practice: a retrospective cohort study describing experience and evolution over 10 years. Int J Antimicrob Agents 2012; 39: 407–13.

2. González-Ramallo VJ, Mirón-Rubio M, Mujal A, Estrada O, Forne C, Aragon B *et al*. Costs of outpatient parenteral antimicrobial therapy (OPAT) administered by Hospital at Home units in Spain. Int J Antimicrob Agents 2017; 50: 114-8.

3. Wai AO, Frighetto L, Marra CA, Chan E, Jewesson PJ. Cost analysis of an adult outpatient parenteral antibiotic therapy (OPAT) programme. A Canadian teaching hospital and Ministry of Health perspective. Pharmacoeconomics 2000; 18: 451– 7.

4. Williams DN, Baker CA, Kind AC, Sannes MR. The history and evolution of outpatient parenteral antibiotic therapy (OPAT). Int J Antimicrob Agents 2015; 46: 307-12.

5. Chambers S, Gallagher K, Metcalf S, Pithie A. Home intravenous antimicrobial service—twelve months experience in Christchurch. N Z Med J 2002; 115: 216-8.

6. Fisher DA, Kurup A, Lye D, Tambyah PA, Sulaiman Z, Poon EY *et al*. Outpatient parenteral antibiotic therapy in Singapore. Int J Antimicrob Agents 2006; 28: 545–50.

7. Matthews PC, Conlon CP, Berendt AR, Kayley J, Jefferies L, Atkins BL *et al*. Outpatient parenteral antimicrobial therapy (OPAT): is it safe for selected patients to self-administer at

home? A retrospective analysis of a large cohort over 13 years. J Antimicrob Chemother 2007; 60: 356–62.

8. Paladino JA, Poretz D. Outpatient parenteral antimicrobial therapy today. Clin Infect Dis 2010; 51: S198–208.

9. Rumball-Smith J, Hider P. The validity of readmission rate as a marker of the quality of hospital care, and a recommendation for its definition. N Z Med J 2009; 122: 63-70.

10. Seaton RA, Sharp E, Bezlyak V, Weir CJ. Factors associated with outcome and duration of therapy in outpatient parenteral antimicrobial therapy (OPAT) patients with skin and soft-tissue infections. Int J Antimicrob Agents 2011; 38: 243-8.

11. Duncan CJA, Barr DA, Ho A, Sharpe E, Semple L, Seaton RA *et al*. Risk factors for failure of outpatient parenteral antimicrobial therapy (OPAT) in infective endocarditis. J Antimicrob Chemother 2013; 68: 1650-4.

12. Allison GM, Muldoon EG, Kent DM, Paulus JK, Ruthazer R, Ren A *et al*. Prediction model for 30-day hospital readmissions among patients discharged receiving outpatient parenteral antimicrobial therapy. Clin Infect Dis 2014; 58: 812-9.

13. Durojaiye OC, Bell H, Andrews D, Ntziora F, Cartwright K. Clinical efficacy, cost analysis and patient acceptability of outpatient parenteral antibiotic therapy (OPAT): a decade of Sheffield (UK) OPAT service. Int J Antimicrob Agents 2018; 51: 26-32.

14. D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. Methods Inf Med 1993; 32: 382 -7.

15. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007; 165: 710-8.

16. Means L, Bleasdale S, Sikka M, Gross AE. Predictors of hospital readmission in patients receiving outpatient parenteral antimicrobial therapy. Pharmacotherapy 2016; 36: 934-9.

17. Schmidt M, Hearn B, Gabriel M, Spencer MD, McCurdy L. Predictors of unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy across a large integrated healthcare network. Open Forum Infect Dis 2017; 4: ofx086.

18. Larraza AV, Sopena N, Pedro-Botet ML, Bonet M, Felipe ED, Manjon H *et al*. Unplanned 30-day hospital readmission of patients receiving outpatient parenteral antimicrobial therapy. Poster presented at: 27th ECCMID; 2017 Apr 22-25; Vienna, Austria.

19. Huang V, Lerner P, Ruhe J, Fedorenko M. Risk factors for readmission in patients with outpatient parenteral antimicrobial therapy. Open Forum Infect Dis 2017; 4: S334.

20. Kouma M, Cutrell J, Duquaine S. Predictors of early unplanned readmission in a veteran population receiving outpatient parenteral antimicrobial therapy (OPAT). Open Forum Infect Dis 2015; 2: 1462.

21. Bengoetxea I, Onaindia MJ, Apezetxea A, Gomez M, Goyeneche M, Fernandez M *et al*. Predictive Clinical Rule for Readmissions in OPAT. Improving in Security. Open Forum Infect Dis 2017; 4: S335.

22. Keller SC, Williams D, Gavgani M, Hirsch D, Adamovich J, Hohl D *et al*. Rates of and Risk Factors for Adverse Drug Events in Outpatient Parenteral Antimicrobial Therapy. Clin Infect Dis 2018: 66: 11-9.

23. Jacobs DM, Leung WY, Essi D, Park W, Shaver A, Claus J *et al*. Incidence and risk factors for healthcare utilisation among patients discharged on outpatient parenteral antimicrobial therapy. Epidemiol Infect. 2018; 146: 782-7.

24. Zlotnik A, Abraira V. A general-purpose nomogram generator for predictive logistic regression models. Stata Journal 2015; 15: 537-46.

25. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015; 162: 55-63.

FIGURE CAPTIONS

Figure 1. Prediction rule nomogram for the risk of 30-day unplanned hospitalisation following outpatient parenteral antimicrobial therapy.

Abbreviations: BJI, bone and joint infection; CN, community nurse; EI, endovascular infection; IC, infusion centre; IV, intravenous; OT, other indication; RD, respiratory disease; SC, self/carer administration; SSTI, skin and soft tissue infection; UGI, urogenital infection.

Figure 2. Calibration plot for the final model of the risk of 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy.

TABLES

Table 1. Demographic and Clinical Characteristics of Patients Receiving Outpatient Parenteral Antimicrobial Therapy

Characteristic	With 30-day unplanned hospitalisation (n = 123)	Without 30-day unplanned hospitalisation (n = 950)	Odds ratio (95%CI) [1]
Male sex	67 (54.5)	544 (57.3)	0.89 (0.61 - 1.30)
Age in years, mean (SD)	60.8 (17.1)	55.5 (17.5)	1.02 (1.01 - 1.03)
Comorbidities, n (%)			
Chronic pulmonary disease	34 (27.6)	163 (17.2)	1.84 (1.20 - 2.83)
Diabetes with complications	21 (17.1)	88 (9.3)	1.42 (1.10 - 1.84)
Peripheral vascular disease	19 (15.4)	68 (7.2)	2.37 (1.37 - 4.10)
Diabetes without complications	9 (7.3)	98 (10.3)	0.69 (0.34 - 1.40)
Tumour without metastasis	16 (13.0)	74 (7.8)	1.33 (1.00 - 1.77)
Moderate or severe renal disease	20 (16.3)	62 (6.5)	1.67 (1.27 - 2.19)

Connective tissue disease	12 (9.8)	59 (6.2)	1.63 (0.85 - 3.13)
Myocardial infarction	19 (15.4)	60 (6.3)	2.71 (1.56 - 4.72)
Cerebrovascular disease	7 (5.7)	42 (4.4)	1.30 (0.57 - 2.97)
Congestive heart failure	12 (9.8)	41 (4.3)	2.40 (1.22 - 4.70)
Peptic ulcer disease	7 (5.7)	33 (3.5)	1.68 (0.72 - 3.88)
Moderate or severe liver disease	8 (6.5)	17 (1.8)	1.56 (1.17 - 2.08)
Metastatic solid tumour	1 (0.8)	20 (2.1)	0.85 (0.61 - 1.19)
Lymphoma	1 (0.8)	7 (0.7)	1.05 (0.37 - 3.01)
Leukaemia	1 (0.8)	10 (1.1)	0.88 (0.31 - 2.46)
Hemiplegia	0 (0.0)	6 (0.6)	-
Dementia	1 (0.8)	5 (0.5)	1.55 (0.18 - 13.37)
AIDS	0 (0.0)	2 (0.2)	-
Mild liver disease	0 (0.0)	0 (0.0)	-
Charlson comorbidity score, median (IQR)	2 (0 - 3)	1 (0 - 2)	1.23 (1.13 - 1.34)
Indication for OPAT, n (%)			
Skin and soft tissue infection	48 (39.0)	568 (59.8)	1.00 (Ref.)
Bone and joint infection	22 (17.9)	115 (12.1)	2.26 (1.31 - 3.90)
Urogenital infection	13 (10.6)	57 (6.0)	2.70 (1.38 - 5.28)

Respiratory disease	6 (4.9)	39 (4.1)	1.82 (0.73 - 4.52)
Endovascular infection	11 (8.9)	34 (3.6)	3.83 (1.82 - 8.03)
Other indication	23 (18.7)	137 (14.4)	1.99 (1.17 - 3.38)
Multidrug resistant organism, n (%)	15 (12.2)	71 (7.5)	1.72 (0.95 - 3.11)
Mode of antimicrobial delivery, n (%)			
Infusion centre	75 (61.0)	692 (72.8)	1.00 (Ref.)
Self/carer administration	15 (12.2)	90 (9.5)	1.54 (0.85 – 2.79)
Community nurse	33 (26.8)	168 (17.7)	1.81 (1.16 – 2.82)
Type of Vascular Access, n (%)			
Central line	54 (43.9)	261 (27.5)	2.07 (1.41 - 3.03)
Peripheral access	69 (56.0)	689 (72.5)	1.00 (Ref.)
Antimicrobial agent, n (%)[2,3]			
Penicillin	19 (15.4)	74 (7.8)	2.16 (1.26 - 3.72)
Cephalosporin	66 (53.7)	724 (76.2)	0.36 (0.25 - 0.53)
Carbapenem	22 (17.9)	82 (8.6)	2.31 (1.38 - 3.85)
Glycopeptide	21 (17.1)	77 (8.1)	2.33 (1.38 - 3.94)
Other	8 (6.5)	43 (4.5)	1.47 (0.67 - 3.20)
Concurrent intravenous antimicrobial therapy, n (%)	21 (17.1)	60 (6.3)	3.05 (1.78 - 5.23)

Oral antibiotic included, n (%)	8 (6.5)	114 (12.0)	0.51 (0.24 - 1.07)
Duration of OPAT in days, median (IQR)	9 (4 - 20)	7 (4 - 19)	1.00 (0.98 - 1.01)
Number of prior hospitalisations, median (IQR)[4]	1 (0 - 3)	0 (0 - 1)	1.38 (1.26 - 1.52)
Prior OPAT stay in past 12 months, n (%)	23 (18.7)	150 (15.8)	1.23 (0.75 – 1.99)
Initiation of OPAT as inpatient, n (%)	87 (70.7)	615 (64.7)	1.32 (0.87 - 1.98)

AIDS, acquired immunodeficiency syndrome; CI, confidence interval; OPAT, outpatient parenteral antimicrobial therapy; SD, standard deviation; IQR, interquartile range.

[1] Odds ratios for numerical variables refer to unit increases.

[2] The reference category for each antimicrobial agent is receipt of any other antibiotic (e.g. receipt of penicillin vs no penicillin).

[3] Some patients received more than one parenteral antimicrobial agent. Thus, the total number of antimicrobial agents is greater than the total number of patients.

[4] In the 12 months preceding the current OPAT episode.

Table 2. Reasons for 30-Day Unplanned Hospitalisation (n = 123)

Reason for hospitalisation	n (%) of patient episodes
Worsening of existing infection/no improvement	52 (42.3)
Non-OPAT related	50 (40.7)
New infection	8 (6.5)
Adverse drug reaction	7 (5.7)
Intravenous line-related complications	3 (2.4)
Clostridium difficile-associated diarrhoea	2 (1.6)
Unknown	1 (0.8)

OPAT, outpatient parenteral antimicrobial therapy.

15 **Table 3.** Multivariable Logistic Regression Models for the Risk of 30-Day Unplanned Hospitalisation in Patients Receiving Outpatient Parenteral

16 Antimicrobial Therapy (n = 1073)

	Model 1[1]			Model 2[2]			Model 3 (final)[3]		
Predictors	**aOR**	**95% CI**	**P value**	**aOR**	**95% CI**	**P value**	**aOR**	**95% CI**	**P value**
Male sex	0.77	0.51 – 1.17	0.217	-	-	-	-	-	-
Age, per 10 years	1.19	1.04 – 1.35	0.010	1.18	1.03 - 1.34	0.012	1.18	1.04 - 1.34	0.012
Prior hospitalisations	1.29	1.16 - 1.44	<0.001	1.28	1.15 - 1.43	<0.001	1.30	1.17 - 1.45	<0.001
Charlson comorbidity score	1.10	0.99 – 1.22	0.065	1.09	0.99 - 1.21	0.082	1.11	1.00 – 1.23	0.045
Mode of delivery									
Infusion center	1.00	-	-	1.00	-	-	1.00	-	-
Self/carer administration	0.76	0.36 - 1.62	0.484	0.75	0.37 - 1.53	0.426	0.79	0.39 – 1.62	0.525
Community nurse	0.60	0.33 - 1.10	0.098	0.60	0.33 - 1.07	0.083	0.62	0.35 – 1.11	0.108
Multidrug resistant organism	0.71	0.35 – 1.44	0.342	-	-	-	-	-	-
Concurrent IV antimicrobial therapy	2.15	1.15 – 4.01	0.017	2.01	1.09 - 3.70	0.026	1.89	1.03 – 3.47	0.041
Receipt of intravenous cephalosporin	0.49	0.28 – 0.84	0.010	0.55	0.33 - 0.91	0.020	-	-	-
Indication for OPAT									
Skin and soft tissue infection	1.00	-	-	1.00	-	-	1.00	-	-
Bone and joint infection	1.65	0.75 – 3.62	0.212	1.46	0.69 - 3.07	0.318	2.09	1.06 – 4.12	0.032

Urogenital infection	1.84	0.79 – 4.30	0.160	1.74	0.77 - 3.91	0.180	2.62	1.27 – 5.43	0.009
Respiratory disease	1.28	0.46 – 3.56	0.642	1.22	0.45 - 3.35	0.695	1.55	0.58 – 4.14	0.382
Endovascular infection	3.19	1.22 – 8.31	0.018	2.74	1.13 - 6.65	0.026	3.51	1.49 – 8.28	0.004
Other indication	1.96	0.97 – 3.95	0.061	1.78	0.93 - 3.42	0.084	2.17	1.16 – 4.06	0.015
Central line access	0.85	0.45 – 1.61	0.610	-	-	-	-	-	-
Model performance statistics									
Calibration slope	1.01	0.77 – 1.25	-	0.96	0.68 - 1.25	-	0.99	0.78 – 1.21	-
HL goodness of fit, x^2 (df)	7.83 (8)	-	0.450	11.79 (8)	-	0.161	6.91 (8)	-	0.546
C-statistic	0.74	0.69 - 0.79	-	0.73	0.69 - 0.78	-	0.72	0.67 – 0.77	-
C-statistic, BOC	0.70	-	-	0.71	-	-	0.70	-	-
BIC	793.1	-	-	774.9	-	-	773.3	-	-

aOR, adjusted odds ratio; BOC, bootstrap optimism corrected; BIC, Bayesian information criterion; CI, confidence interval; df, degrees of freedom; HL, Hosmer-Lemeshow; IV, intravenous; OPAT, outpatient parenteral antimicrobial therapy.

[1] The initial model (model 1) contains the full set of candidate predictors.

[2] Model 2 retains only predictors with substantial predictive contribution and/or important confounders.

[3] The final model (model 3) excludes the cephalosporin variable (based on the lowest BIC).