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Article Title:

Risk of venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT): a systematic review and meta-analysis

Running Title: Systematic review of risk of VTE in OPAT

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ABSTRACT

The risk of venous thromboembolism (VTE) in outpatient parenteral antimicrobial therapy (OPAT) is not fully understood and the optimal strategy for thromboprophylaxis remains unclear. This systematic review investigated the incidence of VTE in OPAT settings (PROSPERO CRD42022381523). MEDLINE, CINAHL, EMCARE, EMBASE, Cochrane Library and grey literature were searched from earliest records to 18 January 2023. Eligible were primary studies reporting non-catheter-related or catheter-related thromboembolic (CRT) events in adults who received parenteral antibiotics in home or outpatient settings. In all, 43 studies involving 23,432 patient-episodes were reviewed. Four studies reported non-catheter related VTE while 39 included CRT. Based on generalised linear mixed-effects models, pooled risk estimates of non-catheter-related VTE and CRT were 0.2% (95% confidence interval [CI], 0.0 – 0.7%) and 1.1% (95% CI, 0.8 – 1.5%; prediction interval [PI], 0.2 – 5.4%), respectively. Heterogeneity was largely attributed to risk of bias by meta-regression ($R^2 = 21\%$). Excluding high-risk studies, CRT risk was 0.8% (95% CI, 0.5 - 1.2%; PI, 0.1 - 4.5%). From 25 studies, pooled CRT rate per 1,000 catheter-days was 0.37 (95% CI, 0.25 – 0.55; PI, 0.08 – 1.64). Our findings do not support universal thromboprophylaxis nor routine use of inpatient VTE risk assessment model in the OPAT setting. However, high index of suspicion should be maintained, especially for patients with known risk factors for VTE. An optimised protocol of OPAT-specific VTE risk assessment should be sought.

KEYWORDS:

Complications; deep vein thrombosis; outpatient parenteral antimicrobial therapy; risk assessment; systematic review; thromboembolism; vascular access device

62 **1. Introduction**

63 Outpatient parenteral antimicrobial therapy (OPAT) programmes are widely used to administer
64 intravenous (IV) antibiotics via vascular access device to facilitate early hospital discharge and admission
65 avoidance of patients with infection. The effectiveness and safety of OPAT have been well documented [1-
66 3]. Despite its benefits, patients receiving OPAT remain at risk of adverse events, including antibiotic-related
67 and vascular access-related complications, which could result in unplanned hospital readmissions [4,5].
68 Venous thromboembolism (VTE) is a common complication of intravascular access devices, and is
69 associated with interruption of antimicrobial therapy, unplanned readmission, increased healthcare costs,
70 post-thrombotic syndrome, and pulmonary embolism (PE) [6,7]. The potential risk of VTE in OPAT is further
71 increased by the presence of infection and restricted mobility [8]. VTE prophylaxis is an established
72 standard of care for hospitalised patients after individualised risk assessment [9]. Appropriate
73 thromboprophylaxis in at-risk hospitalised patients has been shown to reduce risk of VTE and related
74 mortality [10]. However, the risk of VTE in OPAT is not fully understood and the optimal strategy for
75 thromboprophylaxis for OPAT patients has not been established [11].

76
77 To guide strategy for optimal thromboprophylaxis in OPAT, this systematic review aims to examine the
78 incidence of VTE in adult patients with infection treated with IV antimicrobials in home and outpatient
79 settings.

80
81

82 **2. Material and methods**

83 The protocol for this systematic review was registered with the International Prospective Register of
84 Systematic Reviews – PROSPERO (CRD42022381523) and complies with the Preferred Reporting Items for
85 Systematic Reviews and Meta-Analyses (PRISMA) checklist ([Supplementary Table A.1](#)) [12].

86

87 *2.1. Search strategy and Information sources*

88 The search strategy and source of evidence were developed after an initial review of existing literature. In
89 this systematic review, a three-step search strategy was utilised. An initial limited search of MEDLINE
90 (PubMed) and CINAHL was undertaken followed by an analysis of the text words contained in the titles and
91 abstracts, and of the index terms used to describe the articles. A second search using all identified keywords
92 and index terms was then conducted across CINAHL, EMBASE (Ovid), Ovid Emcare, MEDLINE (PubMed) and
93 the Cochrane Library. The reference lists of all identified articles were then searched for additional sources.

94 Supplementary searches of clinical trial registries, Web of Science Conference Proceedings, Google/Google
95 Scholar and the websites of the British Infection Association, European Society of Clinical Microbiology and
96 Infectious Diseases, and Infectious Diseases Society of America were conducted to identify relevant
97 unpublished work and grey literature. The search terms were generated based on the two main key terms
98 (i.e., VTE and OPAT) and their corresponding alternative terms. The full search strategy is available in the
99 [Supplementary Table A.2](#). The search was not restricted by date of publication but was limited to studies
100 published in English. The last electronic search was undertaken on 18 January 2023.

101
102 *2.2. Eligibility criteria*
103 Eligibility criteria were based on the PICO framework (population, intervention, comparator, and outcome)
104 [13]. Studies were eligible if they reported catheter-related thromboembolism (CRT) and/or non-catheter-
105 related VTE (outcome) in adult patients (>16 years old) with infection (population) who received parenteral
106 antibiotics in home or outpatient settings (intervention). Studies of any research design were considered
107 (with the exception of commentaries, editorials, reviews and guidelines). Studies which did not allow for
108 calculation of incidence rate of VTE were excluded ([Supplementary Table A.3](#)).

109
110 Due to limited studies on non-catheter-related VTE in OPAT, we considered conference abstracts as
111 recommended by Scherer et al [14]. Scherer et al suggested that conference abstracts should be considered
112 in systematic reviews if available evidence is sparse or conflicting. Attempts were made to contact the
113 authors of the abstracts to obtain further information on study methods and results. Conference abstracts
114 meeting our eligibility criteria were included in this systematic review if there were no full-length
115 publications or no response from the author.

116
117 *2.3. Study selection and data extraction*
118 All publications identified by the searches were imported into EndNote reference management software.
119 After removing duplicate records, all identified articles were screened independently against the eligibility
120 criteria by two reviewers (OCD and JC). Disagreements were resolved by consensus or with a third reviewer
121 (EIK). Data were extracted independently from retrieved studies by all reviewers (OCD, JC, EIK) using a
122 standardised and piloted data extraction spreadsheet. Extracted data included citation details (first author,
123 year and type of publication), location, study purpose, design, sample size, number of CRT and non-
124 catheter-related thromboembolic events, duration of follow-up and main findings. Any discrepancies in
125 data extraction were discussed and resolved.

126
127 *2.4. Quality assessment*
128 Mixed Methods Appraisal Tool (MMAT) version 2018 was used to assess the methodological quality of the
129 included studies [15]. Quality appraisal was independently performed by two reviewers (OCD and JC). Any
130 disagreement was resolved by discussion between the authors, and no studies were excluded based on the
131 results of the evaluation. The developers of MMAT discourage the calculation of an overall numerical score,
132 and exclusion of studies with low methodological quality [16]. Based on MMAT results, we assessed
133 separately the risks of selection bias and information bias and produced a classification of overall risk as
134 low, moderate or high as shown in [Supplementary Table A.4](#). We used the latter to examine heterogeneity
135 related to risk of bias in meta-regression and subgroup analyses.

136
137 *2.5. Meta-analysis*
138 The primary study outcome was incidence of CRT and non-catheter-related VTE. We estimated population-
139 averaged incidence proportions pooled over the studies using a random intercept logistic regression model
140 with maximum likelihood estimation [17]. The model assumed a Binomial distribution for the observed
141 number of VTE cases in each study and a normal distribution for the random effects following the logit
142 transformation. This approach correctly incorporates studies reporting zero cases and maintains confidence
143 limits of pooled proportions within the zero to one range. The resulting confidence interval (CI) estimates
144 the expected (average) VTE risk of all possible studies.

145
146 Higgin-Thompson's I^2 statistic was used as a summary index of the amount of variability of VTE incidence
147 across studies that cannot be attributed to sampling error. Because I^2 is usually high and may not be
148 discriminative for prevalence or incidence data [18], we additionally reported between-study variance (τ^2)
149 with respective 95% prediction interval (PI). The PI describes the range of VTE risks that can be expected in
150 new studies [19]. We constructed a forest plot to illustrate the distribution of VTE incidence across the
151 studies along with 95% CIs calculated by Wilson's score method. To examine potential sources of variation
152 in VTE incidence among the studies, we conducted multivariable meta-regression analysis with the
153 Binomial-Normal mixed-effects model. Adjusted odds ratios (aORs) with respective 95% CI summarised the
154 strength and direction of associations between study-level covariates and VTE incidence. For each
155 covariate, a covariate-specific R^2 was calculated as the portion of between-study variance that was reduced
156 after the inclusion of that covariate in the model (in the presence of all other variables). Moreover, for each
157 covariate level we calculated pooled estimates of VTE incidence based on univariate subgroup analysis.

158 Candidate covariates for the regression analysis were decided a priori in our study protocol [20]. The
159 following variables were examined: publication year, geographical location (WHO region), study design, and
160 risk of bias (classified as either low-to-moderate or high).

161
162 Leave-one-out sensitivity analysis was carried out to assess the robustness of pooled estimates of VTE
163 incidence against excessively influential studies. To address time-dependent confounding due to studies
164 recording VTE incidence over different risk periods, we sought studies reporting OPAT duration statistics,
165 calculated incidence density rates (expressed as number of events per 1,000 catheter-days) and estimated
166 population-averaged incidence rates based on a Poisson-Normal mixed-effects model. All analyses were
167 carried out in STATA (Version 17; Statcorp, College Station, TX, USA).

168

169

170 **3. Results**

171 *3.1. Selection results and characteristics of the studies*

172 Our initial electronic search yielded 18,436 different publications, of which 39 met the eligibility criteria. An
173 additional four articles were identified through hand-search of bibliographies and other sources. Hence, a
174 total of 43 publications (two conference abstracts [21,22], and 41 full-length articles [4,7,23-61]) were
175 included in our review (Fig. 1). [Supplementary Table A.5](#) shows the details of the reviewed studies. The
176 studies were published between 2001 and 2023; and were carried out in the United States ($n = 21$) [25, 27,
177 32-34,36,37,40,42-47,50,53-56,58,59], United Kingdom ($n = 6$) [21,22,24,28,49,60], Australia ($n = 6$)
178 [7,29,48,51,52,57], New Zealand ($n = 3$) [30,31,61], Switzerland ($n = 3$) [26,37,39], Germany ($n = 1$) [23],
179 Canada ($n = 1$) [35], Netherlands ($n = 1$) [4], and Japan ($n = 1$) [41]. We did not find any studies conducted
180 in low-income countries. The period under study ranged from 6 months [17,33,36] to 13 years [49]. Study
181 sample sizes ranged from 11 to 4160 [23,29]. Overall, the reviewed studies included 23,432 (mean 545;
182 median, 231) patient-episodes, of whom 22,292 (mean 572; median, 247) and 1140 (mean 285; median,
183 154) were enrolled in studies that explored CRT and non-catheter-related thromboembolic events
184 respectively.

185

186 *3.2. Quality appraisal*

187 An overview of the quality appraisal is provided in [Supplementary Tables A.6](#) and [A.7](#). 15 (35%) studies were
188 categorised as quantitative non-randomised studies [4,7,25,31,32,34,37,42-44,49,52-54,56], and 28 (65%)
189 as quantitative descriptive studies [21-24,26-30,33,35,36,38-41,45-51,55,57-61]. There were no qualitative

190 nor quantitative randomised controlled trials (RCTs). Using the MMAT tool, two studies [22,26] had one
191 'Yes' answer out of five criteria (weakest), while the strongest one [4] had five 'Yes' answers. Overall, six
192 (14%) studies were assessed as having low risk of bias, 22 (51%) moderate, and 15 (35%) high risk of bias
193 (Supplementary Table A.7). Inadequate information in the conference articles did not allow the rating
194 questions to be adequately answered. Key quality issues were related to nonresponse bias, accounting for
195 confounders, and appropriateness of the statistical analysis.

196

197 3.3. Incidence of VTE

198 Four studies (two full-length articles [24,52], and two conference abstracts [21,22]) examined the risk of
199 non-catheter-related VTE in OPAT. Barr et al. carried out a retrospective review over a 3-year period of 780
200 OPAT episodes who did not receive thromboprophylaxis and reported two cases of proximal lower limb
201 deep vein thrombosis (DVT) within 90 days of OPAT, giving a VTE incidence rate of 0.26% (95% CI, 0.03 –
202 0.92%) [24]. Kenyon et al. reported no VTE within 4 weeks of OPAT in their cohort of 94 patients over 40
203 years of age with cellulitis and who had no VTE prophylaxis [22]. Another study also reported zero incidence
204 of VTE among 214 patient episodes (who had no thromboprophylaxis) within 90 days of OPAT [21]. Ong et
205 al compared the outcomes of patients with cellulitis who received IV therapy in a Hospital in the Home
206 (HITH) programme with those treated in the hospital. They recorded one case of PE in the hospital group
207 but no VTE (PE/DVT) in the HITH group [52]. Pooling data from the four studies, the estimated incidence of
208 non-catheter-related VTE was 0.2% (95% CI, 0.0 – 0.7%) – Table 1. Heterogeneity statistics could not reliably
209 be estimated due to limited sample sizes, but heterogeneity should be considered low as the studies
210 consistently reported near zero events of non-catheter-related VTE.

211

212 CRT events were more commonly reported than were non-catheter-related VTE. The incidence risk of CRT
213 ranged from 0% to 7.7% among the 39 reviewed studies [4,7,23,25-51,53-61]. Some studies also reported
214 the incidence of CRT in events per OPAT/IV catheter days [7,29,34,36,42,43,55]. In these studies, the
215 incidence rate ranged between 0 and 0.9 events per 1000 OPAT/IV catheter days. Only three studies directly
216 assessed risk factors for CRT in the OPAT setting [7,25,32]. In other studies, CRTs were reported as an OPAT
217 complication. A case-control study by Ingram et al. found malposition of catheter tip and complicated
218 catheter insertion as risk factors for thrombosis [7]. Another study identified younger age, history of DVT,
219 discharge to a skilled-nursing facility and therapy with amphotericin B as risk factors for peripherally
220 inserted central catheter (PICC)-associated venous thrombosis [32]. Batayneh et al [25] did not identify a
221 risk factor for PICC-related DVT among their cohorts but observed that patients with diabetic mellitus were

222 less likely to develop DVTs. The reason for this finding is unclear and needs further clarification. All but one
223 studies differentiated between catheter-related superficial and deep vein thrombosis. Chemaly et al. [32]
224 reported that 44% of upper extremity venous thromboses in their cohort were superficial but found no
225 significant difference in mean time to diagnosis between deep and superficial thromboses.

226
227 Using the Binomial-Normal mixed-effects model, the estimated population-averaged risk of CRT was 1.1%
228 (95% CI, 0.8 – 1.5%). However, accounting for heterogeneity, the 95% PI indicated that CRT incidence in
229 future studies can be expected to range between 0.2% and 5.4%, pointing out considerable predictive
230 uncertainty (Fig. 2). As seen in Table 2, multivariable meta-regression analysis showed no significant
231 variation of CRT incidence of in relation to year of study, region, or study design. However, risk of bias was
232 a main driver of heterogeneity, explaining 21% of the between-study variance. Studies with high risk of bias
233 had significantly greater incidence of CRT than studies classified as low or moderate risk of bias (adjusted
234 odds ratio, 2.48; 95% CI, 1.20 - 5.14; p = 0.019). Excluding the high-risk studies, estimated average risk of
235 CRT was 0.8% (95% CI, 0.5 - 1.2%; 95% PI, 0.1 - 4.5%). Leave-one-out sensitivity analysis did not identify
236 excessively influential (outlier) studies (Supplementary Fig. A.1).

237
238 We retrieved data on follow-up OPAT/IV catheter-days from 25 studies, which reported 169 CRT events
239 over 431,911 catheter-days in total. Based on the Poisson-Normal mixed-effects model, the estimated
240 population-averaged incidence rate of CRT was 0.37 events (95% CI, 0.25 – 0.55; PI, 0.08 – 1.64) per 1,000
241 catheter-days. Fig. 3 presents the respective forest plot. Leave-one-out sensitivity analysis did not identify
242 outlier studies (Supplementary Fig. A.2). Meta-regression analysis of the time-adjusted incidence density
243 rates produced compatible results as those from the previous analysis of cumulative incidence proportions
244 (Supplementary Table A.8).

245
246

247 **4. Discussion**

248 The risk of VTE in hospitalised patients has been stratified into very low (< 0.5%), low (1.5%), moderate (3%)
249 and high (6%) [62]. However, VTE risk in OPAT is not entirely clear. We present a systematic review of the
250 current literature to establish the incidence of VTE in OPAT. The comprehensive analysis revealed a low
251 incidence of thromboembolic events among patients who received OPAT. The pooled estimate for non-
252 catheter-related VTE (0.2%) in our study is significantly lower than reported hospital-associated VTE

253 incidence proportions (1.0% - 1.3%) among hospitalised patients [63-65]; but comparable to the rates in
254 very low-risk hospitalised medical patients for whom thromboprophylaxis is not recommended [10,62,66].

255
256 In our review, the incidence of CRT varied among the studies, depending on the type of vascular access
257 device, indication for OPAT, antimicrobial agent administered, prior surgical intervention and underlying
258 comorbidities. IV catheters can cause endothelial injury, vein wall inflammation and haemodynamic flow
259 changes, which can lead to venous thrombosis [67]. The incidence risks of CRT we found in this review are
260 lower than the reported risks (5% - 15%) for critically ill populations and hospitalised patients [6]. The
261 relative low incidence of CRT in our review supports existing guidelines that do not recommend routine
262 prophylactic anticoagulation nor heparin flushes to prevent catheter thrombosis [68]. Nevertheless,
263 randomised controlled studies of the risks and benefits of pharmacological prophylaxis for CRT could
264 provide more convincing data. To minimise the risk of CRT in the OPAT setting, careful consideration of
265 modifiable risk factors and non-pharmacological methods such as type of vascular access device, insertion
266 techniques, location of insertion, line care and early switch to oral therapy may be more relevant [6,69].

267
268 Most cases of hospital-associated VTE are diagnosed post-hospital discharge [63,64]. In our review, the
269 highest incidence of VTE (7.7%) was observed in a small cohort of patients with osteomyelitis, most of
270 whom had surgical interventions [26]. Surgery is a major risk factor for VTE [70,71]. Extending
271 thromboprophylaxis in the outpatient period for up to 35 days post-operatively is recommended in selected
272 patients who had major orthopaedic surgery [71]. However, extended thromboprophylaxis after hospital
273 discharge in medical patients is not routinely recommended due to increased risk of adverse events and
274 uncertainty about its benefit in preventing major or fatal thromboembolic events [72]. A systematic review
275 of hospitalised medical patients found no significant effect of thromboprophylaxis on mortality but did
276 result in more bleeding events (risk ratio, 1.34; 9 events per 1000 patients treated) [73]. Thus, the low risk
277 of thromboembolic events found in our review indicates that extending thromboprophylaxis for all patients
278 receiving OPAT may cause unnecessary harm. Apart from hospitalised patients, OPAT is also administered
279 to patients with no prior hospitalisation to prevent admission.

280
281 The lower rate of non-catheter-related VTE in our review compared to hospital-associated VTE rates
282 reported in literature [63-65] also suggests that validated risk assessment tools for VTE prevention in
283 hospitalised patients may not be appropriate for patients receiving OPAT [24]. Hospitalised patients are
284 often relatively less mobile and sicker than OPAT patients. Hence, there is need for an OPAT-specific VTE

285 risk assessment protocol based a robust analysis of the risk-benefit balance. It is possible that thrombotic
286 events, especially CRT, are underdiagnosed in the OPAT settings due to lack of symptoms or signs to prompt
287 a diagnostic test [32,74]. A high index of suspicion should be maintained, especially in patients with known
288 risk factors, and appropriate diagnostic work-up should be performed. Confirmed cases should be treated
289 promptly according to existing guidelines or standards of care [75], to minimise risk of embolisation and
290 post-thrombotic syndrome without interrupting OPAT treatment.

291
292 The main strengths of this systematic review are its robust and iterative methodology approach to identify
293 all relevant literature, the large sample size, and the sensitivity analysis to assess the robustness of pooled
294 estimates of each outcome. However, there are a number of potential limitations. Since the relevant data
295 were not consistently reported in the reviewed articles, we were unable to examine potential risk factors
296 for VTE in OPAT (e.g., patient factors, history of VTE, catheter type and insertion techniques) [6,70];
297 concomitant anticoagulation in patients who had CRT; and CRT occurring after completion of OPAT.
298 Moreover, it can be presumed that in studies with shorter mean follow-up, the number of thromboembolic
299 events would be higher if the patients were followed for a longer duration; as most studies did not clearly
300 report the risk period during which they sought for thromboembolic events, our pooled estimates of VTE
301 risk are subject to confounding from this time-dependency. Nevertheless, our analysis of time-adjusted
302 incidence density rates based on about 65% of the studies provides assurance that the risk of VTE is low
303 even when considering duration of IV catheter use for OPAT. We were also unable to differentiate between
304 superficial and deep vein catheter-related thrombosis; and between the incidence of VTE in patients with
305 and those without prior hospitalisation. We included two conference abstracts due to limited publications
306 on non-catheter-related VTE in OPAT. Conference abstracts are often not peer-reviewed and reported
307 outcomes are often preliminary and/or based on limited analyses. However, inclusion of conference
308 abstracts can provide a broader overview and reduce the potential impact of publication bias [14]. Non-
309 English language articles were not assessed due to lack of language resources (i.e., professional translators),
310 and it may have resulted in some language bias. The existing OPAT-VTE literature comprises mainly
311 observational studies. The lack of high-quality RCTs comparing VTE in OPAT with hospital-associated VTE
312 limits the conclusions of this review. Finally, as it is well known, the findings of meta-analyses of
313 observational studies are limited by risk of systematic and random biases, unmeasured confounders, and
314 high heterogeneity [76]. Our meta-regression and subgroup analyses may have mitigated some of these
315 concerns.

316

317 *4.1. Implications for research*

318 Further research is needed to develop accurate VTE risk assessment tools appropriate for OPAT. Since a
319 substantial proportion of hospital-associated VTE occur after hospital discharge [63,64], future studies
320 should also differentiate between the risks of VTE in OPAT patients who had prior admission (early hospital
321 discharge) and those who did not (admission avoidance). We encourage OPAT services (especially those in
322 low-income countries) to publish their experiences to provide more prospective data on the risk of VTE.
323 Decision-analytic modelling can be conducted using existing data to compare the benefits, risks and costs
324 of thromboprophylaxis in OPAT. It would help determine the risk threshold at which prophylaxis provides
325 optimal clinical benefit. The findings from decision-analytic modelling techniques would require validation.

326

327 *4.2. Implications for practice*

328 Our findings of low risk of VTE among patients receiving OPAT do not support universal
329 thromboprophylaxis, nor anticoagulation and heparin flushes for routine prevention of CRT in this setting.
330 A validated risk assessment model for inpatients identifies one bleeding event in 52 (1.9%) low-risk medical
331 patients who had pharmacological thromboprophylaxis [66]. Thus, the risk of bleeding may outweigh the
332 benefits of thromboprophylaxis in OPAT settings. Furthermore, in agreement with Barr et al. [24], we
333 suggest that OPAT patients should not be routinely assessed for VTE risk using inpatient risk assessment
334 tools due to differences in risk profile. Risk assessment models appropriate to OPAT have been proposed
335 [22]. In the interim, as recommended by the UK OPAT guidelines [11], patients deemed at high risk of VTE
336 during hospitalisation (e.g., post-major orthopaedic surgery) should be carefully considered for extended
337 thromboprophylaxis during OPAT after an individualised risk-benefit assessment if the risk persists. OPAT
338 clinicians should maintain a high index of suspicion for prompt diagnosis and appropriate treatment of
339 VTE/catheter-related thrombosis, especially in high-risk patients.

340

341

342 **5. Conclusions**

343 This study gives insight into the risk of VTE in OPAT. Within its constraints, this review suggests that patient
344 receiving OPAT are at low risk of VTE and adds to the growing evidence that OPAT is a safe alternative to
345 inpatient care. The current findings provide a strong rationale and foundation for future studies on the
346 optimal assessment strategy for OPAT thromboprophylaxis. In the interim, a mindful individualised
347 approach that weighs the pros and cons of prophylaxis seems prudent.

348

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352

353 **Competing Interests**

354 None.

355

356 **Ethics Approval**

357 Not applicable.

358

359 **Sequencing**

360 Not applicable.

361

362 **References**

363 1. Bryant PA, Katz NT. Inpatient versus outpatient parenteral antibiotic therapy at home for acute
364 infections in children: a systematic review. *Lancet Infect Dis* 2018; 18: e45-e54.
365 [https://doi.org/10.1016/S1473-3099\(17\)30345-6](https://doi.org/10.1016/S1473-3099(17)30345-6).

366

367 2. Durojaiye OC, Bell H, Andrews D, et al. Clinical efficacy, cost analysis and patient acceptability of
368 outpatient parenteral antibiotic therapy (OPAT): a decade of Sheffield (UK) OPAT service. *Int J*
369 *Antimicrob Agents* 2018; 51: 26-32. <https://doi.org/10.1016/j.ijantimicag.2017.03.016>.

370

371 3. Mitchell ED, Czoski Murray C, Meads D, Minton J, Wright J, Twiddy M. Clinical and cost-effectiveness,
372 safety and acceptability of community intravenous antibiotic service models: CIVAS systematic
373 review. *BMJ Open* 2017; 7: e013560. <https://doi.org/10.1136/bmjopen-2016-013560>.

374

375 4. Douiyeb S, de la Court JR, Tuinte B, et al. Risk factors for readmission among patients receiving
376 outpatient parenteral antimicrobial therapy: a retrospective cohort study. *Int J Clin Pharm* 2022; 44:
377 557-563. <https://doi.org/10.1007/s11096-022-01379-7>.

378

- 379 5. Durojaiye OC, Morgan R, Chelaghma N, et al. External validity and clinical usefulness of a risk
380 prediction model for 30 day unplanned hospitalization in patients receiving outpatient parenteral
381 antimicrobial therapy. *J Antimicrob Chemother* 2021; 76: 2204-2212.
382 <https://doi.org/10.1093/jac/dkab127>.
383
- 384 6. Fallouh N, McGuirk HM, Flanders SA, Chopra V. Peripherally inserted central catheter-associated
385 deep vein thrombosis: a narrative review. *Am J Med* 2015; 128: 722-38.
386 <https://doi.org/10.1016/j.amjmed.2015.01.027>.
387
- 388 7. Ingram PR, Kilgarriff S, Grzelak M, et al, Risk factors for catheter related thrombosis during
389 outpatient parenteral antimicrobial therapy. *J Vasc Access* 2022; 23: 738-742.
390 <https://doi.org/10.1177/11297298211009361>.
391
- 392 8. Cohoon KP, Ashrani AA, Crusan DJ, Petterson TM, Bailey KR, Heit JA. Is infection an independent risk
393 factor for venous thromboembolism? A population-based, case-control study. *Am J Med* 2018; 131:
394 307-316.e2. <https://doi.org/10.1016/j.amjmed.2017.09.015>.
395
- 396 9. National Institute for Health and Care Excellence (NICE). Venous thromboembolism in over 16s:
397 reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline.
398 NICE: London, UK, 2019. Available from: <https://www.nice.org.uk/guidance/ng89>.
399
- 400 10. Skeik N, Westergard E. Recommendations for VTE prophylaxis in medically ill patients. *Ann Vasc Dis*
401 2020; 13: 38-44. <https://doi.org/10.3400/avd.ra.19-00115>.
402
- 403 11. Chapman ALN, Patel S, Horner C, et al. Updated good practice recommendations for outpatient
404 parenteral antimicrobial therapy (OPAT) in adults and children in the UK. *JAC Antimicrob Resist*
405 2019; 1: dlz026. <https://doi.org/10.1093/jacamr/dlz026>.
406
- 407 12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for
408 reporting systematic reviews. *BMJ* 2021; 372: n71. <https://doi.org/10.1136/bmj.n71>.
409

- 410 13. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic reviews of effectiveness. In:
411 Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available
412 from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-04>.
413
- 414 14. Scherer RW, Saldanha IJ. How should systematic reviewers handle conference abstracts? A view
415 from the trenches. *Syst Rev* 2019; 8: 264. <https://doi.org/10.1186/s13643-019-1188-0>.
416
- 417 15. Hong QN, Fàbregues S, Bartlett G, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018
418 for information professionals and researchers. *Educ Inf* 2018; 34: 285 - 291.
419 <https://doi.org/10.3233/EFI-180221>.
420
- 421 16. Hong QN, Pluye P, Fàbregues S, et al. Mixed Methods Appraisal Tool (MMAT), version 2018.
422 Registration of Copyright (#1148552), Canadian Intellectual Property Office, Industry Canada.
423
- 424 17. Lin L, Chu H. Meta-analysis of proportions using generalized linear mixed models. *Epidemiology*
425 2020; 31:713 – 717. <https://doi.org/10.1097/EDE.0000000000001232>.
426
- 427 18. Migliavaca CB, Stein C, Colpani V, et al. Meta-analysis of prevalence: I² statistic and how to deal with
428 heterogeneity. *Res Synth Methods* 2022; 13: 363-367. <https://doi.org/10.1002/jrsm.1547>.
429
- 430 19. IntHout J, Ioannidis JP, Rovers MM, et al. Plea for routinely presenting prediction intervals in meta-
431 analysis. *BMJ Open*. 2016; 6: e010247. <https://doi.org/10.1136/bmjopen-2015-010247>.
432
- 433 20. Durojaiye OC, Cole J, Kritsotakis E. Risk of venous thromboembolism (VTE) in outpatient parenteral
434 antimicrobial therapy (OPAT): a systematic review. PROSPERO 2022 CRD42022381523. Available
435 from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022381523.
436
- 437 21. Keeley A, Keil C, Hiles H, et al. Incidence of venous thromboembolism among patients receiving
438 outpatient parenteral antimicrobial therapy at Sheffield Teaching Hospitals Trust, UK: an
439 observational study. In: Abstract Book - 30th European Congress of Clinical Microbiology &
440 Infectious Diseases (ECCMID) 2020. Basel: ESCMID, pp. 1589. [Accessed 20 January 2023]. Available
441 from: <https://markterfolg.de/ESCMID/Abstractbook2020.pdf>
442

- 443 22. Kenyon PC, Chapman ALN. Venous thromboembolism risk assessment of patients with cellulitis
444 receiving Outpatient Parenteral Antibiotic Therapy (OPAT). *J Infect* 2011; 63: 493-494.
445 <https://doi.org/10.1016/j.jinf.2011.04.228>.
446
- 447 23. Baecker H, Gessmann J, Hanusrichter Y, et al. Outpatient parenteral antibiotic therapy (OPAT) with
448 peripherally inserted central catheter in patients with periprosthetic joint infection. *Z Orthop Unfall*
449 2019; 157: 510-514. <https://doi.org/10.1055/a-0830-4776>.
450
- 451 24. Barr DA, Irvine S, Ritchie ND, et al. Risk of venous thromboembolism in patients treated for bacterial
452 infection in the community with outpatient parenteral antimicrobial therapy. *QJM* 2014; 107: 207-
453 211. <https://doi.org/10.1093/qjmed/hct239>.
454
- 455 25. Batayneh O, Mahfouz R, Rabinovich D, et al. Peripherally inserted central catheters and upper
456 extremity deep venous thrombosis: incidence and risk factors. *Arch Intern Med Res* 2022; 5: 71-76.
457
- 458 26. Bernard L, El-Hajj, Pron B, et al. Outpatient parenteral antimicrobial therapy (OPAT) for the
459 treatment of osteomyelitis: evaluation of efficacy, tolerance and cost. *J Clin Pharm Ther* 2001; 26:
460 445-51. <http://doi.org/10.1046/j.1365-2710.2001.00380.x>.
461
- 462 27. Bhagat H, Sikka MK, Sukerman ES, et al. Evaluation of opportunities for oral antibiotic therapy in
463 bone and joint Infections. *Ann Pharmacother* 2023; 57:156-162.
464 <https://doi.org/10.1177/10600280221101105>.
465
- 466 28. Bodycot J, Mashonganyika L, Kucziw N, et al. Maximising the opportunity of a self-administration
467 outpatient parenteral antimicrobial therapy pathway. *Br J Nurs* 2021; 30: S4-S10.
468 <https://doi.org/10.12968/bjon.2021.30.2.S4>.
469
- 470 29. Browning S, Loewenthal MR, Freeland I, et al. Safety of prolonged outpatient courses of
471 intravenous antibiotics: a prospective cohort study. *Clin Microbiol Infect* 2022; 28: 832-837.
472 <https://doi.org/10.1016/j.cmi.2021.12.020>.
473

- 474 30. Chambers S, Gallagher K, Metcalf S, et al. Home intravenous antimicrobial service - twelve months
475 experience in Christchurch. *N Z Med J* 2002; 115: 216-218.
476
- 477 31. Chambers ST, Basevi A, Gallagher K, et al. Outpatient parenteral antimicrobial therapy (OPAT) in
478 Christchurch: 18 years on. *N Z Med J* 2019; 132: 21-32.
479
- 480 32. Chemaly RF, de Parres JB, Rehm SJ, et al. Venous thrombosis associated with peripherally inserted
481 central catheters: a retrospective analysis of the Cleveland Clinic experience. *Clin Infect Dis* 2002;
482 34: 1179-1183. <http://doi.org/10.1086/339808>.
483
- 484 33. Coursen J, Roth P, Schrank C, et al. The outpatient parenteral antimicrobial therapy (OPAT)
485 experience in a referral hospital in South Carolina. *Int J Infect Dis Ther* 2020; 5: 112-117.
486 <https://doi.org/10.11648/j.ijidt.20200504.12>.
487
- 488 34. Cox AM, Malani PN, Wiseman SW, Kauffman CA. Home intravenous antimicrobial infusion therapy:
489 a viable option in older adults. *J Am Geriatr Soc* 2007; 55: 645-650. [http://doi.org/10.1111/j.1532-](http://doi.org/10.1111/j.1532-5415.2007.01133.x)
490 [5415.2007.01133.x](http://doi.org/10.1111/j.1532-5415.2007.01133.x).
491
- 492 35. Dargan S, Zvonar RK, Saginur R. A review of outpatient parenteral antimicrobial therapy practices
493 and experience at the Ottawa hospital. *Can J Hosp Pharm* 2007; 60: 177-183.
494 <https://doi.org/10.4212/cjhp.v60i3.172>.
495
- 496 36. Duggal A, Barsoum W, Schmitt SK. Patients with prosthetic joint infection on IV antibiotics are at
497 high risk for readmission. *Clin Orthop Relat Res* 2009; 467: 1727-1731.
498 <https://doi.org/10.1007/s11999-009-0825-7>.
499
- 500 37. Erba A, Beuret M, Daly ML, et al. OPAT in Switzerland: single-center experience of a model to treat
501 complicated infections. *Infection* 2020; 48: 231-240. <https://doi.org/10.1007/s15010-019-01381-8>.
502
- 503 38. Farry JK, Miles CD, Collins CD, et al. Adverse events among renal transplant recipients receiving
504 outpatient parenteral antimicrobial infusion therapy. *Transpl Infect Dis* 2009; 11: 284-285.
505 <https://doi.org/10.1111/j.1399-3062.2009.00377.x>.

- 506
- 507 39. Gardiol C, Voumard R, Cochet C, et al. Setting up an outpatient parenteral antimicrobial therapy
508 (OPAT) unit in Switzerland: review of the first 18 months of activity. *Eur J Clin Microbiol Infect Dis*
509 2016; 35: 839-845. <https://doi.org/10.1007/s10096-016-2606-z>.
- 510
- 511 40. Gross ND, McInnes RJ, Hwang PH. Outpatient intravenous antibiotics for chronic rhinosinusitis.
512 *Laryngoscope* 2002; 112: 1758-1761. <https://doi.org/10.1097/00005537-200210000-00009>.
- 513
- 514 41. Hase R, Yokoyama Y, Suzuki H, et al. Review of the first comprehensive outpatient parenteral
515 antimicrobial therapy program in a tertiary care hospital in Japan. *Int J Infect Dis* 2020; 95: 210-215.
516 <https://doi.org/10.1016/j.ijid.2020.03.033>.
- 517
- 518 42. Kaul CM, Haller M, Yang J, et al. Assessment of risk factors associated with outpatient parenteral
519 antimicrobial therapy (OPAT) complications: A retrospective cohort study. *Antimicrob Steward*
520 *Healthc Epidemiol* 2022; 2: e183. <https://doi.org/10.1017/ash.2022.313>.
- 521
- 522 43. Keller SC, Dzintars K, Gorski LA, et al. Antimicrobial agents and catheter complications in
523 outpatient parenteral antimicrobial therapy. *Pharmacotherapy* 2018; 38: 476-481.
524 <https://doi.org/10.1002/phar.2099>.
- 525
- 526 44. Keller SC, Wang NY, Salinas A, et al. Which patients discharged to home-based outpatient parenteral
527 antimicrobial therapy are at high risk of adverse outcomes? *Open Forum Infect Dis* 2020; 7: ofaa178.
528 <https://doi.org/10.1093/ofid/ofaa178>.
- 529
- 530 45. Lai A, Tran T, Nguyen HM, et al. Outpatient parenteral antimicrobial therapy at large veterans
531 administration medical center. *Am J Manag Care* 2013; 19:e317-324.
- 532
- 533 46. Larioza J, Girard A, Brown RB. Clinical experience with daptomycin for outpatient parenteral
534 antibiotic therapy. *Am J Med Sci* 2011; 342: 486-488.
535 <https://doi.org/10.1097/MAJ.0b013e31821e1e6b>.
- 536

- 537 47. Lin JW, Kacker A, Anand VK, et al. Catheter- and antibiotic-related complications of ambulatory
538 intravenous antibiotic therapy for chronic refractory rhinosinusitis. *Am J Rhinol* 2005; 19: 365-369.
539 <https://doi.org/10.1177/194589240501900408>.
540
- 541 48. Marsh N, Larsen E, Tapp S, et al. Management of Hospital in the Home (HITH) peripherally inserted
542 central catheters: a retrospective cohort study. *Home Health Care Management & Practice* 2020;
543 32: 34-39. <https://doi.org/10.1177/1084822319873334>.
544
- 545 49. Matthews PC, Conlon CP, Berendt AR, et al. Outpatient parenteral antimicrobial therapy (OPAT): is
546 it safe for selected patients to self-administer at home? A retrospective analysis of a large cohort
547 over 13 years. *J Antimicrob Chemother* 2007; 60: 356-362. <https://doi.org/10.1093/jac/dkm210>.
548
- 549 50. Ng N, Bailey P, Pryor R, et al. Experiences in outpatient parenteral antimicrobial therapy (OPAT):
550 Barriers and challenges from the front lines. *Antimicrob Steward Healthc Epidemiol* 2021; 1: e42.
551 <https://doi.org/10.1017/ash.2021.213>.
552
- 553 51. O'Callaghan K, Tapp S, Hajkowicz K, et al. Outcomes of patients with a history of injecting drug use
554 and receipt of outpatient antimicrobial therapy. *Eur J Clin Microbiol Infect Dis* 2019; 38:575-580.
555 <https://doi.org/10.1007/s10096-018-03461-3>.
556
- 557 52. Ong BS, Ngian VJJ, Yeong C, et al. Out of hospital and in hospital management of cellulitis requiring
558 intravenous therapy. *Int J Gen Med* 2019; 12: 447-453. <https://doi.org/10.2147/IJGM.S230054>.
559
- 560 53. Price CN, Solomon DA, Johnson JA, et al. Feasibility and safety of outpatient parenteral antimicrobial
561 therapy in conjunction with addiction treatment for people who inject drugs. *J Infect Dis* 2020;
562 222(Suppl 5): S494-S498. <https://doi.org/10.1093/infdis/jiaa025>.
563
- 564 54. Seo H, Altshuler D, Dubrovskaya Y, et al. The safety of midline catheters for intravenous therapy at
565 a large academic medical center. *Ann Pharmacother* 2020; 54: 232-238.
566 <https://doi.org/10.1177/1060028019878794>.
567

- 568 55. Shrestha NK, Shrestha J, Everett A, et al. Vascular access complications during outpatient parenteral
569 antimicrobial therapy at home: a retrospective cohort study. *J Antimicrob Chemother* 2016; 71: 506-
570 512. <https://doi.org/10.1093/jac/dkv344>.
- 571
- 572 56. Shrestha NK, Blaskewicz C, Gordon SM, et al. Safety of outpatient parenteral antimicrobial therapy
573 in nonagenarians. *Open Forum Infect Dis* 2020; 7: ofaa398. <https://doi.org/10.1093/ofid/ofaa398>.
- 574
- 575 57. Sriskandarajah S, Ritchie B, Eaton V, et al. Safety and clinical outcomes of hospital in the home. *J*
576 *Patient Saf* 2020; 16: 123-129. <https://doi.org/10.1097/PTS.0000000000000617>.
- 577
- 578 58. Suleyman G, Kenney R, Zervos MJ, Weinmann A. Safety and efficacy of outpatient parenteral
579 antibiotic therapy in an academic infectious disease clinic. *J Clin Pharm Ther* 2017; 42: 39-43.
580 <https://doi.org/10.1111/jcpt.12465>.
- 581
- 582 59. Tice AD, Hoaglund PA, Nolet B, et al. Cost perspectives for outpatient intravenous antimicrobial
583 therapy. *Pharmacotherapy* 2002; 22: 63S-70S. <https://doi.org/10.1592/phco.22.4.63s.33653>.
- 584
- 585 60. Underwood J, Marks M, Collins S, et al. Intravenous catheter-related adverse events exceed drug-
586 related adverse events in outpatient parenteral antimicrobial therapy. *J Antimicrob Chemother*
587 2019; 74:787-790. <https://doi.org/10.1093/jac/dky474>.
- 588
- 589 61. Upton A, Ellis-Pegler RB, Woodhouse A. Outpatient Parenteral Antimicrobial Therapy (OPAT): a
590 review of experience at Auckland Hospital. *N Z Med J* 2004; 117: U1020.
- 591
- 592 62. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients:
593 Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest
594 Physicians Evidence-Based Clinical Practice Guidelines. *Chest*; 141: e227S-e277S.
595 <https://doi.org/10.1378/chest.11-2297>.
- 596
- 597 63. Stubbs JM, Assareh H, Curnow J, et al. Incidence of in-hospital and post-discharge diagnosed
598 hospital-associated venous thromboembolism using linked administrative data. *Intern Med J* 2018;
599 48:157-165. <https://doi.org/10.1111/imj.13679>.

- 600
- 601 64. Neeman E, Liu V, Mishra P, et al. Trends and risk factors for venous thromboembolism among
602 hospitalized Medical Patients. *JAMA Netw Open* 2022; 5: e2240373.
603 <https://doi.org/10.1001/jamanetworkopen.2022.40373>.
- 604
- 605 65. Jordan Bruno X, Koh I, Lutsey PL, et al. Venous thrombosis risk during and after medical and
606 surgical hospitalizations: the medical inpatient thrombosis and hemostasis (MITH) study. *J Thromb*
607 *Haemost* 2022; 20:1645-1652. <https://doi.org/10.1111/jth.15729>.
- 608
- 609 66. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of
610 hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J*
611 *Thromb Haemost* 2010; 8: 2450-2547. <https://doi.org/10.1111/j.1538-7836.2010.04044.x>.
- 612
- 613 67. Piper R, Carr PJ, Kelsey LJ, et al. The mechanistic causes of peripheral intravenous catheter failure
614 based on a parametric computational study. *Sci Rep* 2018; 8: 3441.
615 <https://doi.org/10.1038/s41598-018-21617-1>.
- 616
- 617 68. Zwicker JI, Connolly G, Carrier M, et al. Catheter-associated deep vein thrombosis of the upper
618 extremity in cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2014; 12: 796-
619 800. <https://doi.org/10.1111/jth.12527>.
- 620
- 621 69. Wall C, Moore J, Thachil J. Catheter-related thrombosis: A practical approach. *J Intensive Care Soc*
622 2016; 17: 160-167. <https://doi.org/10.1177/1751143715618683>.
- 623
- 624 70. Nemeth B, Lijfering WM, Nelissen RGHH, et al. Risk and risk factors associated with recurrent
625 venous thromboembolism following surgery in patients with history of venous
626 thromboembolism. *JAMA Netw Open* 2019; 2:e193690.
627 <https://doi.org/10.1001/jamanetworkopen.2019.3690>.
- 628
- 629 71. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients:
630 Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest

631 Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e278S-e325S.
632 <https://doi.org/10.1378/chest.11-2404>.

633

634 72. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines
635 for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized
636 medical patients. *Blood Adv* 2018; 2: 3198-3225.
637 <https://doi.org/10.1182/bloodadvances.2018022954>.

638

639 73. Lederle FA, Zylla D, MacDonald R, Wilt TJ. Venous thromboembolism prophylaxis in hospitalized
640 medical patients and those with stroke: a background review for an American College of Physicians
641 Clinical Practice Guideline. *Ann Intern Med* 2011; 155: 602-615. [https://doi.org/10.7326/0003-4819-](https://doi.org/10.7326/0003-4819-155-9-201111010-00008)
642 [155-9-201111010-00008](https://doi.org/10.7326/0003-4819-155-9-201111010-00008).

643

644 74. Luciani A, Clement O, Halimi P, et al. Catheter-related upper extremity deep venous thrombosis in
645 cancer patients: a prospective study based on Doppler US. *Radiology* 2001; 220: 655-60.
646 <http://doi.org/10.1148/radiol.2203001181>.

647

648 75. National Institute for Health and Care Excellence (NICE). Venous thromboembolic diseases:
649 diagnosis, management and thrombophilia testing. NICE guideline. NICE: London, UK, 2020.
650 Available from: <https://www.nice.org.uk/guidance/ng158>.

651

652 76. Metelli S, Chaimani A. Challenges in meta-analyses with observational studies. *Evid Based Ment*
653 *Health* 2020; 23: 83-87. <https://doi.org/10.1136/ebmental-2019-300129>.

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TABLES**Table 1.** Results of random-effects meta-analysis of the incidence of non-catheter-related thromboembolic events in outpatient parenteral antimicrobial therapy

Study	n/N	VTE Incidence, %	95% CI
Barr et al 2014	2/780	0.3	0.0 - 0.9
Keeley et al 2020	0/214	0.0	0.0 - 1.7
Kenyon et al 2011	0/94	0.0	0.0 - 3.8
Ong et al 2019	0/52	0.0	0.0 - 6.8
Population-averaged estimate	2/1140	0.2	0.0 - 0.7

CI, confidence interval; n/N, number of non-catheter-related thromboembolic events over the total number of patients at risk in each study; VTE, venous thromboembolism.

Table 2. Multivariable meta-regression analysis of the associations between study-level characteristics and the incidence of catheter-related venous thromboembolism in outpatient parenteral antimicrobial therapy

Study characteristic	Levels	n	CRT incidence (CI; PI), %	Adjusted OR (CI)	P-value	R ²
Year of publication	≤2019	22	1.3 (0.8 - 1.9; 0.3 - 6.0)	Ref.	0.942	0.0%
	≥2020	17	0.9 (0.5 - 1.4; 0.1 - 5.6)	0.98 (0.51 - 1.88)		
Region	Europe	8	0.7 (1.9 - 2.9; 1.9 - 3.0)	Ref.	0.657	6.5%
	N. America	22	1.3 (1.9 - 2.9; 1.9 - 2.9)	1.45 (0.66 - 3.16)		
	Western Pacific	9	0.9 (1.9 - 2.9; 1.9 - 3.0)	1.27 (0.52 - 3.12)		
Study design	Descriptive (single arm)	25	1.0 (0.7 - 1.4; 0.3 - 3.6)	Ref.	0.282	9.0%
	Comparative non-randomised	14	1.1 (0.6 - 2.0; 0.1 - 9.3)	1.39 (0.77 - 2.49)		
Risk of bias	Low/moderate	26	0.8 (0.5 - 1.2; 0.1 - 4.5)	Ref.	0.019	21.2%
	High	13	2.4 (1.9 - 2.9; 1.9 - 2.9)	2.48 (1.20 - 5.14)		

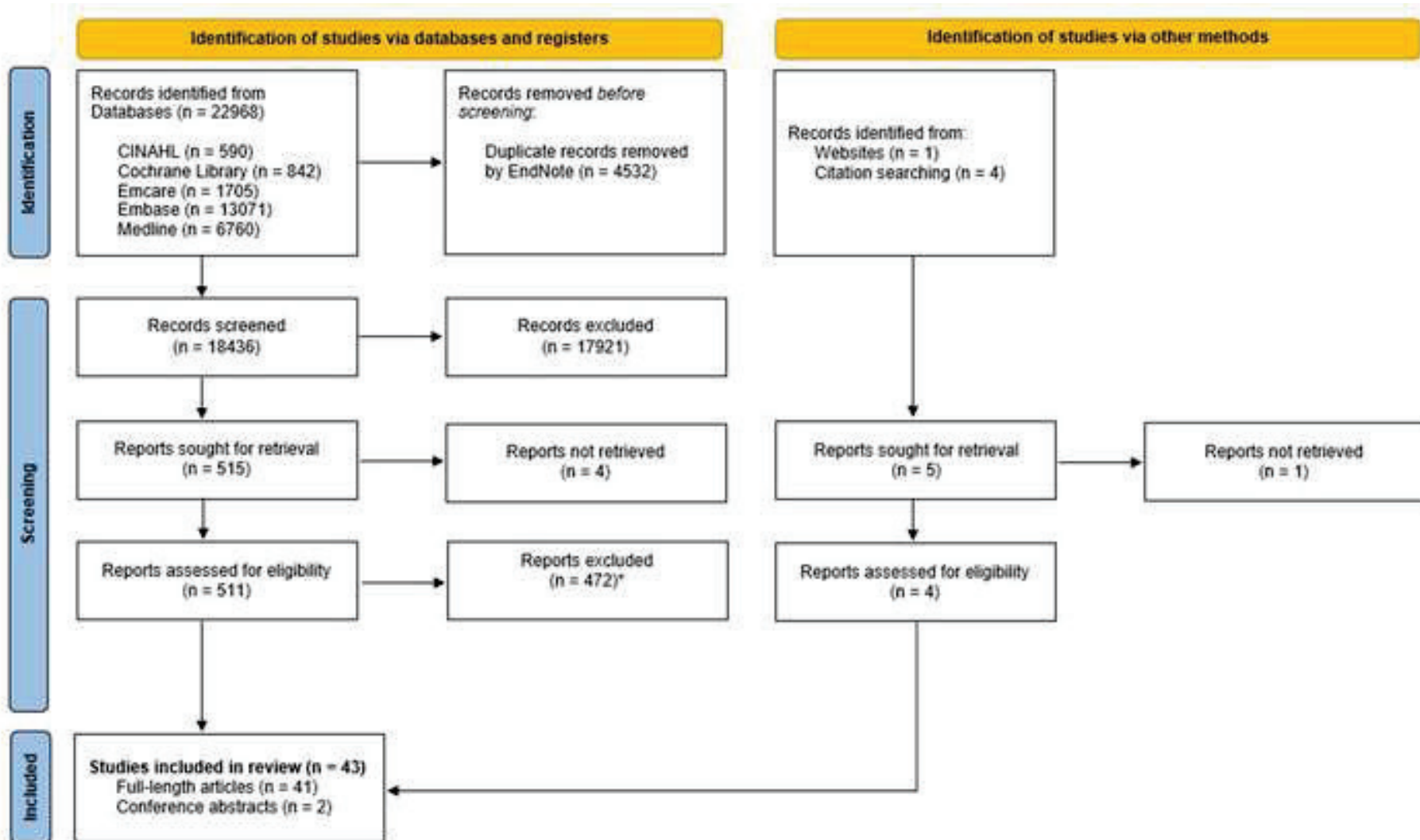
CI, 95% confidence interval; CRT, catheter-related venous thromboembolism; n, number of studies; OR, odds ratio; PI, 95% prediction interval.

FIGURE CAPTIONS

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of the systematic review process [13].

Fig. 2. Forest plot of the results of the random-effects meta-analysis of the risk of catheter-related venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT). n/N denotes the number of catheter-related thromboembolic (CRT) events over the total number of patients at risk in each study. The diamond's centre is the population-averaged CRT incidence proportion. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled average estimate. The extended blue line continuing through the confidence interval and the respective bluish-grey vertical area indicate the 95% prediction interval of CRT incidence expected in new studies. Abbreviations: CI, confidence interval; CRT, catheter-related venous thromboembolism.

Fig. 3. Forest plot of the results of the random-effects meta-analysis of the incidence density rate of catheter-related venous thromboembolism in outpatient parenteral antimicrobial therapy. n/N denotes the number of CRT cases over the total number of OPAT/IV catheter-days in each study. The diamond's centre is the population-averaged CRT incidence rate. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled average estimate. The extended blue line continuing through the confidence interval and the respective bluish-grey vertical area indicate the 95% prediction interval of CRT incidence expected in new studies. Abbreviations: CI, confidence interval; CRT, catheter-related venous thromboembolism



*Reasons for exclusion are stated in Supplementary Material S3.

