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SYSTEMATIC REVIEWS

Cost-analysis of inpatient and outpatient parenteral antimicrobial therapy in orthopaedics: A systematic literature review

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Abstract

BACKGROUND

Increasing numbers of total joint arthroplasties and consecutive revision surgery are associated with the risk of periprosthetic joint infections (PPJI). Treatment of PPJI is complex and associated with immense socio-economic burden. One treatment aspect is parenteral antiinfective therapy, which usually requires an inpatient setting [Inpatient parenteral antibiotic therapy (IPAT)]. An alternative is outpatient parenteral treatment [Outpatient parenteral antibiotic therapy (OPAT)]. To conduct a health economic cost-benefit analysis of OPAT, a detailed cost analysis of IPAT and OPAT is required. So far, there is a lack of knowledge on the health economic effects of IPAT and OPAT for PPJI.

AIM

To review an economic comparison of IPAT and OPAT.

METHODS

A systematic literature review was performed through Medline following the PRISMA guidelines.

RESULTS

Of 619 identified studies, 174 included information of interest and 21 studies were included for quantitative analysis of OPAT and IPAT costs. Except for one study, all showed relevant cost savings for OPAT compared to IPAT. Costs for IPAT were between 1.10 to 17.34 times higher than those for OPAT.

CONCLUSION

There are only few reports on OPAT for PPJI. Detailed analyses to support

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economic or clinical guidelines are therefore limited. There is good clinical evidence supporting economic benefits of OPAT, but more high quality studies are needed for PPJI.

Key words: Antibiotic therapy; Outpatient parenteral antibiotic therapy; Inpatient parenteral antibiotic therapy; Cost analysis; Periprosthetic joint infection; Parenteral

Core tip: Periprosthetic joint infection of total joint replacement poses a significant socio-economic burden. One factor is the need for prolonged parenteral antibiotic therapy. Outpatient parenteral antibiotic therapy (OPAT) might reduce costs compared to inpatient (IPAT) settings. A systematic literature review was performed to compare economic impact of OPAT and IPAT. Twenty-one articles were identified of which 20 reported economic benefits of OPAT. While the heterogeneity of studies limited the interpretation and generalization, overall beneficial cost effects of OPAT were shown. Future studies should focus on specific economic outcomes of OPAT for PPJI.

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INTRODUCTION

There is a continuous increase in numbers of total joint arthroplasties (TJA) and an expansion of indications has been noted in recent years[1,2]. In addition, predictions show a growing demand for the coming years[1,2]. On the one hand, more older and multi-morbid patients undergo TJA, on the other hand, indications have been extended to younger and more active patients with high functional demands and longer life expectancy[1,2]. Due to a general increase in life expectancy the consecutive risk for revision surgery rises. Every revision surgery is associated with a risk for infections as are co-morbidities (*e.g.*, diabetes mellitus, obesity, immune suppression)[3]. Due to increasing numbers of joint replacements, a subsequent increase in numbers of periprosthetic joint infections (PPJI) can be expected. Treatment of PPJI usually consists of surgical intervention and a long-term antimicrobial therapy[4]. Surgical intervention includes one-stage revision with either retention or revision of components in combination with debridement and irrigation. Alternatively, patients can undergo a staged revision with explantation of the prosthesis combined with debridement and irrigation and potentially reimplantation after several weeks to months. Both surgical principles are combined with antimicrobial treatment – mostly antibiotics[4,5].

Empiric antimicrobial therapy is followed by calculated therapy as soon as the pathogenic agent is identified and a resistogram is available. In PPJI, a bone-infection must be assumed and therefore antiinfective therapy lasts for several weeks (usually 6-12 wk)[4]. Initially, antimicrobial therapy is started as parenteral therapy to achieve high plasma concentrations as well as sufficient concentrations in the targeted bone and joint as fast as possible (*e.g.*, time to peak serum concentration and peak serum concentration). Additionally, there are reports indicating an increase in multi-resistant bacteria. Here, extended parenteral antiinfective therapy is often required and no oral antibiotics are available. Another advantage of parenteral therapy is the fast (immediate) absorption and bio-availability of the drug. Potential risks of mal-absorption do not occur. Usually, parenteral therapy requires an inpatient setting [Inpatient parenteral antibiotic therapy (IPAT)] due to monitoring, need for intravenous lines and administration of detergents by healthcare providers. This inpatient therapy goes along with high direct as well as indirect costs for the health system[6]. An alternative to IPAT is outpatient parenteral treatment [Outpatient parenteral antibiotic therapy (OPAT)]. To conduct a health economic cost-benefit analysis of OPAT, a detailed cost analysis of IPAT and OPAT is required. While calculation of direct costs hospital and outpatient settings is generally possible, there

are no standards for methods and reporting. Additionally, exact cost-benefit analyses are a difficult endeavour as they should take into account direct cost savings (*e.g.*, hospital stay, physician visits, drugs and supplies, childcare, housekeeping, transportation, *etc.*) as well as indirect benefits (lost wages, both for patient and family members, *etc.*)[7]. So far, there is a lack of knowledge regarding health economic effects of IPAT and OPAT for PPJI.

The aim of this study is an economic comparison of IPAT and OPAT. A systematic literature review was performed for this purpose.

MATERIALS AND METHODS

Systematic literature review

A systematic literature review was performed. Medline was searched *via* PubMed after a previous pilot-search to identify relevant search terms and strategies. The literature search and presentation of results followed the most recent version of the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A PRISMA checklist was used in a modified form for this study. This systematic literature review was registered in the international, prospective registry for systematic literature reviews (PROSPERO) at the Centre for Reviews and Dissemination of the University of York (York, United Kingdom) (No. 71005).

Search strategy and screening

The exact search strategy using Medical Subject Headings (MeSH) is presented in Figure 1. Identified hits were entered into proprietary literature management software (EndNote v. 7.7.1 for Mac). All articles were subsequently screened based on titles and abstracts.

Inclusion and exclusion criteria (screening/eligibility)

All studies reporting comparative costs of OPAT and IPAT were deemed eligible for inclusion in the systematic review. Exclusion was performed based on criteria outlined in Table 1. After screening, the full texts of all included articles were subjected to an in-depth analysis for inclusion and exclusion criteria. Finally, all eligible articles were stratified into five groups (Table 2). Studies were grouped into the highest possible category (A to E). Only category A studies were included into quantitative data analysis. Category B to E studies were used for background analysis and discussion. The inclusion process is depicted in Figure 2.

Statistical analysis

Extraction of data followed a standardized protocol. First authors, publication year, country of origin, study design, sample size, diagnosis, anti-infective therapy, costs of IPAT and OPAT and differences were extracted and entered into a digital spreadsheet.

RESULTS

The systematic literature search resulted in 524 hits for "outpatient parenteral antibiotic therapy", 570 hits for "outpatient parenteral anti-infective therapy", and 514 for "outpatient parenteral antimicrobial therapy". After deleting duplicates, 619 potential studies of interest remained. Of these, 328 were excluded based on title and abstract during screening. For the rest, 215 full texts were available for in-depth analysis and 174 were categorized into group A-E. For quantitative analysis of OPAT and IPAT cost, 21 studies were included (Table 3[8-28]). A detailed description of these studies can be found in Table 4[8-28].

Comparisons were performed based costs per day and costs per case. Table 5[8-28] shows costs per day and per case of IPAT and OPAT of included studies.

Five (24%) of the studies were performed in the United States, six (29%) in the United Kingdom, another five in the rest of Europe (24%) and the remainder in other countries. Except for one study, all showed relevant cost savings by OPAT compared to IPAT. Costs for IPAT were between 1.10 to 17.34 times higher than those for OPAT (Table 6[8-28]).

DISCUSSION

PPJI of large joints remains a multidisciplinary challenge. They are associated with

(("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) AND ("parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields] OR "parenteral"[All Fields]) AND ("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) AND ("parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields] OR "parenteral"[All Fields]) AND ("anti-infective agents"[Pharmacological Action] OR "anti-infective agents"[MeSH Terms] OR ("anti-infective"[All Fields] AND "agents"[All Fields]) OR "anti-infective agents"[All Fields] OR "antiinfective"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields]) AND ("parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields] OR "parenteral"[All Fields]) AND ("anti-infective agents"[Pharmacological Action] OR "anti-infective agents"[MeSH Terms] OR ("anti-infective"[All Fields] AND "agents"[All Fields]) OR "anti-infective agents"[All Fields] OR "antimicrobial"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]))

Figure 1 Exact search strategy using Medical Subject Headings. MeSH: Medical Subject Headings.

significant socio-economic costs. Haddad *et al*[6] estimate the costs of PPJI to be approximately $1.62 billion (approx. €1.4 billion). Additionally, Parisi *et al*[29] used a Markov model including direct and indirect costs, and calculated costs per case to be $390000 to $474000 (circa €337000 to €409700). An increase in PPJI in recent years could be shown by the Nationwide Inpatient Sample[30]. While 1104 cases were documented in 1990, a continuous increase was noted and reached 5838 cases in 2004. Interestingly, direct costs were stable at $55.000 per case. However, in the same timeframe, the length of hospital stay was significantly reduced from 22.2 to 7.6 d[30]. Kurtz *et al*[31] performed a follow-up study and calculated costs of infected total knee arthroplasties until the year 2020. The authors estimated costs of $330 billion in 2011; reaching $527 billion in 2020. Interestingly, the costs per case were stable in the calculation. This estimation was supported by the study and thus highlights the relevance of PPJI[30,31].

While avoiding PPJI is the best method to reduce costs, increasing numbers of total joint replacements makes this an illusionary aspiration. Occurrence of PPJI is associated with high costs and long-term therapy. By replacement of inpatient treatment with outpatient treatment, a significant cost reduction seems possible[32-34]. Already in the 1970s, studies showed higher levels of patient satisfaction with OPAT in comparison to IPAT[8,35]. Furthermore, no increase in risks and complications was noted by OPAT[36,37].

The first identified cost analysis with potential cost reduction were reported in the 1970s[9,38]. Antoniskis *et al*[9] reported the first detailed outpatient antibiotic therapy in 1978. Cost structures of OPAT as well as IPAT showed significant variability. This may result from the large timeframe of the included studies. For example, studies of Antoniskis *et al*[9] and Grizzard *et al*[15] were much older than comparable studies from 2000 to 2017. To allow for a better comparison of studies, therapy costs were calculated for per-day-costs and transformed using the exchange rate for the mid of the year of publication. Correction for inflation was not performed. Additionally, analysis and interpretation of costs per case are severely influenced by individual cases and as such demonstrate immense heterogeneity. Thus, the analysis of costs per day was deemed more suitable for comparison. Costs per day ranged from €110 to €1125 for IPAT and from €28 to €269 for OPAT. Comparability is, however, restricted by specific peculiarities of each healthcare system. The complexity of the healthcare system in the United States adds to these limitations as does reimbursement in each of the included countries. The highest comparability was probably achieved in United Kingdom studies. Here, the NHS National Institute for Health Research supports OPAT research and therapy. This is highlighted by "The Community Intra Venous Antibiotic Study" (CIVAS) by Minton *et al*[39]. One part of this research project was a systematic literature review on economic aspects of OPAT[39]. Cost-effectiveness was one of the five main research questions of the project and showed potential reduction in costs. Good acceptance of OPAT by patients and treating healthcare personnel was identified. Furthermore, safety and clinical effectiveness of OPAT were shown to be acceptable and comparable to IPAT. So far, no other comprehensive systematic literature review has been performed on cost comparisons of OPAT and IPAT. The aim of this study was the identification of costs of IPAT compared to OPAT. This systematic literature review identified 21 studies with sufficient information on costs of IPAT and OPAT. While the studies were published over a long time period (1978-2017) with wide geographical distribution, some generalized conclusions may be drawn. Here, the IPAT costs per day ranged from €110 to €1125 since 2001, OPAT costs were between €28 to €228. More comparable might be the ratio between IPAT and OPAT costs for each study. As shown in Table 6[8-28], the mean cost ratio was 3.6

Table 1 Exclusion criteria for systematic literature review

Exclusion criteria
No relation to OPAT
No bacterial infections
Only prophylactic antibiotic therapy
No distinction between oral and parenteral outpatient antibiotic therapy
Parenteral therapy with orally available antibiotics
Non-English language publication
No original study (*e.g.*, comments, letters, *etc.*)
Combination of IPAT and OPAT
Only patients < 18 yr
Case reports and case series with < 15 cases
Poster-publications/Congress abstracts *etc.*
"Specific infections" or tropical diseases
Study protocols (without original clinical data)
Simulations (without original clinical data)
CME publications (without original clinical data)
Non-peer-reviewed journals
No full text available

OPAT: Outpatient parenteral antibiotic therapy.

(1.0-10.4) per case and 4.8 (1.1-17.3) per day. Thus, the assumption of cost reduction by OPAT seems reasonable. Additional effects by indirect opportunity costs were not included in this study and might therefore increase the beneficial effect of OPAT.

Notably, all studies had some limitations in design and data analysis. Overall, all studies used simplified methods to calculate IPAT costs. OPAT costs were mostly calculated in a more complex fashion. Cost reductions were beneficial in most cases and most publications did not differentiate between cost-effects for payers/insurances and hospitals. Therefore, it cannot be conclusively demonstrated whether cost reductions led to reduced costs to the health care system (*e.g.*, insurance) or increased profit to the hospitals; mixed effects are possible as well. Additionally, the information regarding to PPJI was limited. Thirteen publications mentioned treatment of bone and joint infections (Table 7[9-11,13-15,17,18,20,21,23,25-28]). Of those, only two defined the affected bones or joints in detail. One study (Sims *et al*[25]) specifically looked at PPJI of the hip and knee. Therefore, it was the only study to provide economic information for this particular subset of patients.

In the United States and the United Kingdom, OPAT is already well accepted. Efficacy and safety of OPAT was comparable to IPAT and associated with higher patient satisfaction (11, 18-21). Still, in many countries (*e.g.*, Germany) there is none or only very limited availability of facilities to support OPAT.

In conclusion, a large number of publications on OPAT is available. Notably, there are only few reports on the specific subject of PPJI. Detailed analyses to support economical or clinical guidelines are therefore limited. This systematic literature review could identify only three studies that explicitly covered PPJI (category C)[32-34]. Overall, OPAT showed comparable efficacy, safety and success rates as did IPAT.

Table 2 Classification of publications

A	Original research with health economic data on OPAT (costs)
B	Secondary literature with health economic data on OPAT in PPJI
C	Pro-/Retrospective study on OPAT (PPJI of hip or knee)
D	Pro-/Retrospective study on OPAT (other infections)
E	Guidelines, reviews on OPAT with health economic data
F	Exclusion of publication

OPAT: Outpatient parenteral antibiotic therapy; PPJI: Periprosthetic joint infections.

Table 3 Details of included studies

ID	First author	Ref.	Year	Country	Design	Diagnosis	Cases/Patients (*n*)	Antibiotic agent
1	Al Alawi	[8]	2015	Bahrain	Retrospective	Bacterial tonsillitis	97	Ceftriaxon
2	Antoniskis	[9]	1978	United States	Retrospective	Endocarditis + Osteomyelitis	13/7 (Controls)	Multiple
3	Bernard	[10]	2001	Switzerland	Prospective	Osteomyelitis (incl. 10 PPJI)	39	Multiple
4	Chapman	[11]	2009	United Kingdom	Retrospective	multiple	334/296	Multiple
5	Connors	[12]	2017	Canada	Prospective	Dental	110/.	Multiple
6	Gonzales	[13]	2017	Spain	Retrospective	Multiple	1324/1190	Multiple
7	Gray	[14]	2012	United Kingdom	Retrospective	Multiple	291/.	Multiple
8	Grizzard	[15]	1991	United States	Retrospective	Multiple	46/.	Multiple
9	Harrison	[16]	2015	United Kingdom	Retrospective	Kidney transplant	12/9	n. a.
10	Heintz	[17]	2011	United States	Prospective	Multiple	569/536	Multiple
11	Kieran	[18]	2009	Ireland	Retrospective	Multiple	60/56	Multiple
12	Lacroix	[19]	2014	France	Retrospective	Endocarditis	18/.	Multiple
13	Malone	[20]	2015	Australia	Retrospective	Diabetic foot	59/.	n. a.
14	Nathwani	[21]	2003	United Kingdom	Retrospective	Bone and joint	55/.	Teicoplanin
15	Nguyen	[22]	2010	United States	NA	Cellulitis	80/.	Multiple
16	Ruh	[23]	2015	United States	Retrospective	Multiple	96/85	Multiple
17	Seaton	[24]	2014	United Kingdom	Retrospective	MRSA skin and soft tissue	173/.	Multiple
18	Sims	[25]	2013	United Kingdom	Retrospective	PPJI	96/85	Multiple
19	Theocharis	[26]	2012	Greece	Retrospective	Multiple	173/.	Multiple
20	Wai	[27]	2000	Canada	Retrospective	Multiple	80/.	Multiple
21	Yong	[28]	2009	Singapore	Retrospective	Multiple	96/85	Multiple

OPAT: Outpatient parenteral antibiotic therapy; PPJI: Periprosthetic joint infections.

Table 4 Detailed description of costs of outpatient parenteral antibiotic therapy and inpatient parenteral antibiotic therapy depending on available information

ID	First author	Ref.	Cost IPAT	Cost OPAT	Cost-difference	Comment
1	Al Alawi1	[8]	€43152.41/ € 50343.67 €143.37/d2	€ 17261.45 €57.35/d2	€ 25890.96 €86.02/d2	301 bed days were saved by OPAT; Exact cost reduction not clear in text
2	Antoniskis	[9]	US $234.22/d US $10022.23 /pat	US $69.35/d US $6357.52/pat	US $229.70/d US $3664.71/pat	Historical data/prices from 1977/78; Average day costs
3	Bernard	[10]	US $710/d US $2233945	US $129/d US $360060	US $581/d US $1873885	2.147 patient-days of 39 patients
4	Chapman	[11]	£372.53/d £1502769	£151.79/d £612306	£220.74/d £890463	Calculation based on 4034 bed-days
5	Connors1	[12]	CAN $1720.70 / d CAN $717530 € 1063451.21	CAN $1094/d CAN $120096 € 177994.28	CAN $288/d CAN $597434 € 884919.24	110 patients with 417 bed-days; Average: 3.8 d with CAN $1094 / case
6	Gonzales	[13]	€4357/pat	€2350/pat		Very detailed calculation; Methods presented; IPAT for an average of 8.4 days; OPAT included IPAT for readmission within 30 d
7	Gray	[14]	€518.70/d	€98.30/d	€420.40/d £192635	Simulation of cost analysis based on potentially saved bed
8	Grizzard	[15]	US $159.54/d	US $112.68/d	£662/patient US $112.68/d	Historical data (1988); Cost-Charge Ratio; Additional
9	Harrison	[16]	US $101314 £264 / d	US $29763	US $71551	Simplified calculation; 320 bed days
10	Heintz	[17]	£84480	£35070	£49410	Simplified calculation with relevant limitations; 228 bed
11	Kieran	[18]	US $658.50/visit € 342862	€167.60/d € 558912	-€ 216.05	Prospective study on 60 cases. 1289 bed days saved; Community nurses included in OPAT calculation
12	Lacroix	[19]	€1125/d € 335250	€228/d € 67943	€897/d €14850/pat	Simulated cost analysis; 298 bed days saved
13	Malone	[20]	US $829/d US $1143.957	US $278848	€ 267307 US $14661/pat US $864997	IPAT costs based on Council of Australian Governments; 1569 bed days saved
14	Nathwani	[21]	£300 / d £11400 / pat £627000	£1749.15/pat £96203.25	£9650.85/pat £530796.75	Three groups: IPAT, OPAT (Teicoplanin) and outpatient oral therapy (Linezolid); Oral group not included
15	Nguyen	[22]	US $1180/d	US $385/d	US $795/d	472 OPAT visits
16	Ruh	[23]	US $556960 US $7540135.35	US $181720 US $607583.32	US $375240 US $6932552.03	Complex cost calculation with multiple factors
17	Seaton	[24]	£13019.57/pat	£6532.89/pat £228651	£6487/pat	Three groups: IPAT, OPAT (Teicoplanin) and outpatient
18	Sims	[25]	£250/d £14500/pat	£24/d 1392/pat	£24/d £13108/pat	For two weeks OPAT cost reduction of 2108 £/Pat
19	Theocharis	[26]	€167.50-195.50/d	€164/d €637/pat		Re-admission rates (14.2%) and costs not included in OPAT calculation
20	Wai	[27]	€20728/pat € 2901983	€2774/pat € 388402	€17954/pat € 2513580	Very detailed cost analysis for IPAT and OPAT;
21	Yong	[28]	US $457/d US $12403/pat	US $278/d US $12736/pat		Includes calculation for opportunity-costs

Table 5 Daily costs calculated in Euro for inpatient parenteral antibiotic therapy and outpatient parenteral antibiotic therapy (exchange rate based on mid of publication year)

ID	First author	Year	Ref.	IPAT		OPAT	
				€ per case	€ per day	€ per case	€ per day
1	Al Alawi	2015	[8]		143.361		57.351
2	Antoniskis	1978	[9]		251.26		74.09
3	Bernand	2001	[10]		755.88		137.34
4	Chapman	2009	[11]	-	418.92		170.71
5	Connors	2017	[12]	2550.69		1621.42	
6	Gonzales	2017	[13]	4357	519	2350	98
7	Gray	2012	[14]				
8	Grizzard	1991	[15]		110.29		77.89
9	Harrison	2015	[16]		337.26		140.53
10	Heintz	2011	[17]		492.12		28.38
11	Kieran	2009	[18]				168
12	Lacroix	2014	[19]		1125		228
13	Malone	2015	[20]		68524		
14	Nathwani	2003	[21]	17502.42	460.59	2685.24	
15	Nguyen	2010	[22]		823.73		268.76
16	Ruh	2015	[23]				
17	Seaton	2014	[24]	15670.97		7863.77	
18	Sims	2013	[25]	17881.4	308.3	1716.61	29.6
19	Theocharis	2012	[26]		180	637	164
20	Wai	2000	[27]	20278		9188	
21	Yong	2009	[28]	8873.23	326.94	9111.46	198.88

[1]Calculation simplified based on limited data. Calculations not applicable for two studies. IPAT: Inpatient parenteral antibiotic therapy; OPAT: Outpatient parenteral antibiotic therapy.

Table 6 Cost comparison (ratio) per case of outpatient parenteral antibiotic therapy *vs* inpatient parenteral antibiotic therapy

ID	First author	Year	Ref.	IPAT/OPAT	
				Ratio per case	Ratio per day
1	Al Alawi	2015	[8]		2.50[1]
2	Antoniskis	1978	[9]		3.39
3	Bernand	2001	[10]		5.50
4	Chapman	2009	[11]		2.45
5	Connors	2017	[12]	1.57	
6	Gonzales	2017	[13]	1.85	5.30
7	Gray	2012	[14]		
8	Grizzard	1991	[15]		1.42
9	Harrison	2015	[16]		2.40
10	Heintz	2011	[17]		17.34
11	Kieran	2009	[18]		
12	Lacroix	2014	[19]		4.93
13	Malone	2015	[20]		
14	Nathwani	2003	[21]	6.52	
15	Nguyen	2010	[22]		3.06
16	Ruh	2015	[23]		
17	Seaton	2014	[24]	1.99	
18	Sims	2013	[25]	10.42	10.42
19	Theocharis	2012	[26]		1.10
20	Wai	2000	[27]	2.21	

21	Yong	2009	[28]	0.97	1.64

[1]Calculation simplified based on limited data. Calculations not applicable for two studies. A ratio above 1.0 indicates higher cost of inpatient parenteral antibiotic therapy in comparison to outpatient parenteral antibiotic therapy. IPAT: Inpatient parenteral antibiotic therapy; OPAT: Outpatient parenteral antibiotic therapy.

Table 7 Literature details on bone and joint infections

ID	First author	Ref.	Year	Diagnosis	
2	Antoniskis	[9]	1978	5 acute OM, 6 chronic OM	No information regarding affected joints
3	Bernard	[10]	2001	39 OM (13 non-union fracture; 16 chronic OM; 10 PPJI)	Sites of OM: femur (n = 11), hip (n = 9); tibia (n = 5), ankle (n = 4), mastoid, calcaneum, vertebra, knee (each n = 2), wrist and phalange (each n = 1). No information on outcome per affected joints
4	Chapman	[11]	2009	Of 334 infections, approx. 20 (6%) were bone and joint associated; bed days saved were approx. 481 of 4034 (12%)	No information regarding affected joints
6	Gonzales	[13]	2017	Underlying diagnosis not mentioned	No information regarding affected joints
7	Gray	[14]	2012	291 cases; 14 in orthopaedics (4.8%)	No information regarding affected joints
8	Grizzard	[15]	1991	OM and septic arthritis most frequent diagnosis in OPAT (30% of patient days)	No information regarding affected joints
10	Heintz	[17]	2011	569 cases; 190 (33.4%) bone and joint associated	No information regarding affected bones or joints
11	Kieran	[18]	2009	60 cases; OM (n = 25, 41.7%), PPJI (n = 2; 3.3%) and septic arthritis (n = 3, 5.1%) accounting for 50%	No information regarding affected bones or joints
13	Malone	[20]	2015	Diabetic foot syndrome. Cellulites with OM (n = 14; 24%) and OM alone (n = 11; 19%) were documented (n = 25; 43%)	No information regarding affected bones or joints
14	Nathwani	[21]	2003	4 septic arthritis; 3 acute and 48 chronic OM (40%/19 = PPJI)	No information regarding affected bones or joints
16	Ruh	[23]	2015	96 cases; bone and joint infection in 14 (39.5%)	No information regarding affected bones or joints
18	Sims	[25]	2013	10 primary total knee replacements and 4 primary total hip replacement	No economic analysis was performed by affected joint
19	Theocharis	[26]	2012	No bone or joint infection mentioned	No information regarding affected bones or joints
20	Wai	[27]	2000	140 cases; 55 bone/joint (39%) infections	No information regarding affected bones or joints
21	Yong	[28]	2009	7/72 cases of OPAT and 9/93 IPAT patient bone and joint associated	No information regarding affected bones or joints

OM: Osteomyelitis; PPJI: Periprosthetic joint infections; IPAT: Inpatient parenteral antibiotic therapy; OPAT: Outpatient parenteral antibiotic

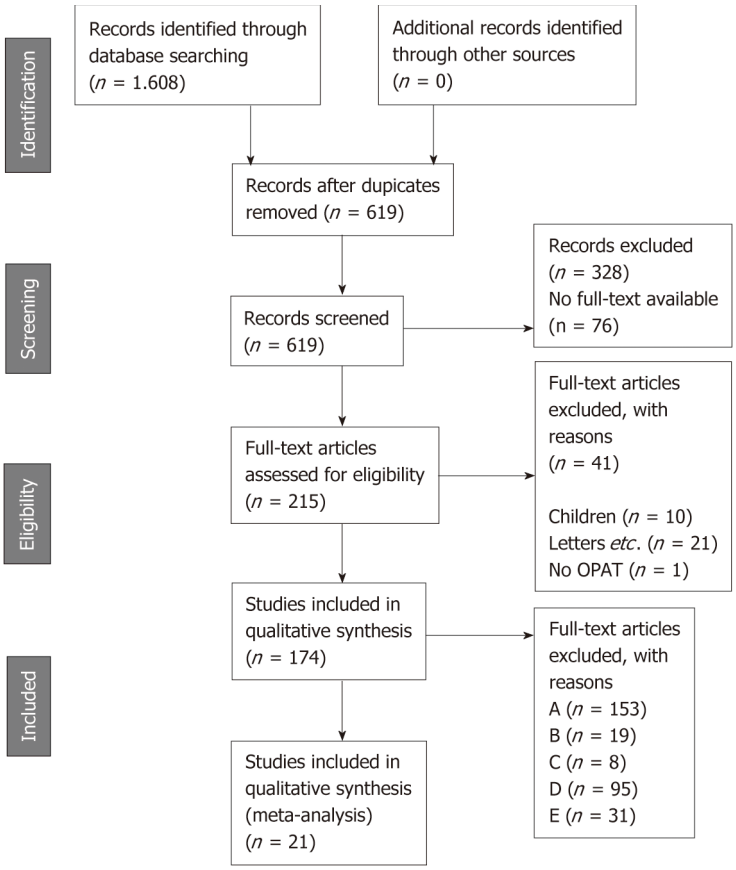

Figure 2 Inclusion process depicted using the PRISMA Flowchart.

ARTICLE HIGHLIGHTS

Research background

Increasing numbers of total joint arthroplasties worldwide are noted. This is associated with rising risk for revision surgery. Periprosthetic joint infections (PPJI) play a significant role in revisions. Treatment of PPJI often requires long-term antimicrobial therapy. In PPJI, a bone-infection must be assumed and therefore antiinfective therapy lasts for 6-12 wk or longer. Parenteral antiinfective therapy is often required. Usually, parenteral therapy requires an inpatient setting [Inpatient parenteral antibiotic therapy (IPAT)] and goes along with high direct as well as indirect costs. An alternative is outpatient parenteral treatment [Outpatient parenteral antibiotic therapy (OPAT)]. So far, there is a lack of knowledge regarding health economic effects of IPAT and OPAT in general and for PPJI specifically.

Research motivation

To identify the proposed economical benefits of OPAT in comparison to IPAT health economic cost-benefit analysis are needed. While various publications dealt with OPAT, generalization of assumptions requires input from multiple studies. We aimed to perform a systematic literature review of published literature on cost comparisons of OPAT and IPAT to better delineate the effects. The motivation was generating evidence to support OPAT for PPJI and create awareness for this alternative treatment option.

Research objectives

The aim of this study was an economic comparison of IPAT and OPAT. A systematic literature review was performed for this purpose.

Research methods

For this purpose, a search strategy was developed and we performed a systematic review of published literature by searching the Medline database via PubMed. All abstracts meeting the inclusion criteria were identified, and relevant articles were analyzed in detail. Relevant data was extracted and homogenized.

Research results

The literature search identified 619 potential studies of interest. 328 were excluded during screening. 215 full texts were available for in-depth analysis. For quantitative analysis of OPAT and IPAT cost, 21 studies were included. Costs for IPAT were between 1.10 to 17.34 times higher

than those for OPAT. Only one study showed marginally lesser costs for IPAT. Only one study focused specifically on PPJI.

Research conclusions

To the best of our knowledge, this is the first comprehensive systematic literature review outside the CIVAS report on cost effectiveness of OPAT. The review provides a wide overview over the exiting literature with minimal exclusion criteria. The presentation of extracted data allows for detailed understanding of included studies. Limitations of the study were the heterogeneity of studies from different health care systems and a wide time interval. Still, this open inclusion allows for better understanding of the available data worldwide.

Research perspectives

While the beneficial cost effect of OPAT has been shown, there is need to provide more specific studies. In particular, there is need to analyze cost structures for PPJI treatment in different health care systems. With such studies, guidelines to implement OPAT into the standard of care might be created.

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