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Manuscript NO: 47167

Manuscript Type: SYSTEMATIC REVIEWS

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

Please find the following

- Letter to the editor
- Point-by-point answers to editorial requests
- Additional changes
- Point-by-point response to reviewer comments

Letter to the editor

Dear Editor,

Thank you very much for the positive feedback to our manuscript. We have made the requested changes to the manuscript and attached the required files. All changes to the manuscript were highlighted with yellow colour.

Please find the following point-by-point responses to all requests.

The authors

Point-by-point answers to editorial requests

Editor: Please provide the author contributions. The format of this section should be like this:

Answer: Author contributions were added.

Editor: Please add those statements. (p.1)

Answer: COI and PRISMA statements were added.

Editor: Please add an aim for the abstract..

Answer: Aim was added to the abstract.

Editor: Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Answer: A core tip has been added to the manuscript.

Editor: Please write the article highlight section according to the guidelines listed below. Please don't copy from the main text.

Answer: The ARTICLE HIGHLIGHTS section has been added to the manuscript. As requested, the section was newly written and not copied from the main manuscript.

Editor: Please add the reference number for each author. (Table 4)

Answer: The respective reference numbers were added to table 4 as requested.

Editor: We found that the content of the figures cannot be edited by our staff. Authors have to provide the figures as separate electronic files. Please upload the figures in the following vector or bitmap formats so that we will be able to edit them:

1) Vector art formats: *bw, Illustrator, EPS, WMF, EMF, FreeHand, CorelDraw, Color Map File, PowerPoint, Excel, IFF, etc.*

2) Bitmap formats: *Photoshop, TIFF, GIF, JPEG, etc.*

Answer: The figures were added as separate files as requested. Both figures are based on Microsoft Word documents and are thus provided as such.

Editor: Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI
(<http://www.crossref.org/SimpleTextQuery/>)

Answer: The reference list has been updated according to the recommendation. All references include the PMID.

Additional changes

Table 3: missing information for study a (Nathwani et al.) has been added and highlighted.

Table 4: missing information for study a (AL Alawi et al.) and 7 (Gray et al.) has been added and highlighted.

Table 5: missing information for study a (AL Alawi et al.) has been added and highlighted. Additional information to legend added.

Table 6: missing information for study a (AL Alawi et al.) has been added and highlighted. Additional information to legend added.

Point-by-point response to reviewer comments

Reviewer 1

Reviewer's code: 02444715

SPECIFIC COMMENTS TO AUTHORS

*the paper: Cost-analysis of inpatient and outpatient parenteral antimicrobial therapy in orthopaedics: a systematic literature review is very important for the orthopedic community
It demonstrate the need for attention to medical economics*

Answer: We thank the reviewer for the positive comments. As the esteemed reviewer mentioned, we strongly believe that the economic effects of OPAT need further research and understanding and one of the most important aspects of the current manuscript is generating awareness for OPAT.

No changes to the manuscript were required.

Reviewer 2

Reviewer's code: 02444795

SPECIFIC COMMENTS TO AUTHORS

An interesting study. Please comment in greater detail on breakdown of which joints were infected eg hip, knee, shoulder etc

Answer: The reviewer highlights an important aspect of OPAT in orthopedics. For periprosthetic joint infections and osteomyelitis, the affected joints may play a relevant role. The systematic literature review included studies for varying indications (see **table 1** for exclusion criteria). Due to the small number of articles on orthopedic infections included in the systematic literature review, a joint specific subgroup analysis is limited. In **table 3** the underlying diagnosis for antiinfective treatment is presented.

We reviewed all included article full texts to provide comprehensive information on affected joints. We added **Table 7** to the manuscript and the discussion section was expanded accordingly:

Thirteen publications mentioned treatment of bone and joint infections. Of those, only two defined the affected bones or joints in detail. One study (Sims et al.) 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.

The following articles included information on bone and joint infections:

Table 7. Literature details on bone and joint infections.

OM = osteomyelitis

ID	First author	Ref.	Year	Diagnosis	
2	Antoniskis	[19]	1978	5 acute OM, 6 chronic OM	No information regarding affected joints.
3	Bernard	[22]	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	[23]	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	[25]	2017	Underlying diagnosis not mentioned.	No information regarding affected joints.
7	Gray	[26]	2012	291 cases; 14 in orthopaedics (4.8%)	No information regarding affected joints.
8	Grizzard	[20]	1991	OM and septic arthritis most frequent diagnosis in OPAT (30% of patient days).	No information regarding affected joints.
10	Heintz	[28]	2011	569 cases; 190 (33.4%) bone and joint associated.	No information regarding affected bones or joints.
11	Kieran	[29]	2009	60 cases; OM (n = 25, 41.7%), PPJI (n = 2; 3.3%) and septic arthritis (n = 3, 5.1%)	No information regarding affected bones or joints.

				accounting for 50%.	
13	Malone	[31]	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	[32]	2003	4 septic arthritis; 3 acute and 48 chronic OM (40%/19 = PPJI)	No information regarding affected bones or joints.
16	Ruh	[34]	2015	96 cases; bone and joint infection in 14 (39.5%)	No information regarding affected bones or joints.
18	Sims	[36]	2013	10 primary total knee replacements and 4 primary total hip replacement	No economic analysis was performed by affected joint.
19	Theocharis	[37]	2012	No bone or joint infection mentioned.	No information regarding affected bones or joints.
20	Wai	[38]	2000	140 cases; 55 bone/joint (39%) infections.	No information regarding affected bones or joints.
21	Yong	[39]	2009	7/72 cases of OPAT and 9/93 IPAT patients bone and joint associated.	No information regarding affected bones or joints.

