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Antibiotic Prophylaxis for Thyroid and Parathyroid Surgery: A Systematic Review and Meta-analysis

Fabio Medas, MD[1], Gian Luigi Canu, MD[1], Federico Cappellacci, MD[1], Giorgio Romano, MD[2], Giuseppe Amato, MD[3], Enrico Erdas, MD[1], and Pietro Giorgio Calò, MD[1]

Abstract

Objective. Although thyroid and parathyroid surgery is considered a clean procedure with a low incidence of surgical site infections (SSIs), a great number of endocrine surgeons use antibiotic prophylaxis (AP). The aim of this study was to assess whether AP is significantly effective in reducing the incidence of SSIs in this kind of surgery.

Data Sources. A systematic literature search was performed with PubMed, Scopus, and ISI–Web of Science. Studies addressing the efficacy of AP in reducing the incidence of SSIs in thyroid and parathyroid surgery were included in the systematic review and meta-analysis.

Review Methods. The random effects model was assumed to account for different sources of variation among studies. The overall effect size was computed through the inverse variance method. Heterogeneity across studies, possible outlier studies, and publication bias were evaluated.

Results. A total of 6 studies with 4428 patients were included in the quantitative analysis. The incidence of SSI was 0.6% in the case group and 0.4% in the control group (odds ratio, 1.07; 95% CI, 0.3-3.81; P = .915). There was no evidence of heterogeneity among the studies (Q = 8.36, P = .138; I^2 = 40.17). The analysis of several continuous moderators, including age, use of drain, and duration of surgery, did not generate any significant result.

Conclusion. AP is not effective in reducing the incidence of SSI in thyroid and parathyroid surgery and should be avoided, notwithstanding the negative impact on social costs and the risk of development of antibiotic resistance.

Keywords

thyroidectomy, parathyroidectomy, antibiotic prophylaxis, surgical site infection

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According to the Centers for Disease Control and Prevention (CDC), thyroid and parathyroid surgery is considered a clean head and neck surgical procedure due to the absence of contact with the upper aerodigestive tract. The reported incidence of surgical site infection (SSI) in this kind of surgery is low, ranging from 0.09% to 2%.[1-11] However, antibiotic prophylaxis (AP) seems to be employed on a discretionary basis, depending on the clinical practice and the behaviors of each center. According to an international survey conducted among 275 endocrine surgeons, 26% administered AP "almost always," with a peak among Asian surgeons using AP in 58.3% of cases.[12] In Italy, a large national study of nearly 3000 thyroidectomies demonstrated the use of AP in 38.7% of interventions.[13]

Only a few controlled trials, randomized or not, have tried to assess the efficacy of AP on the reduction of SSIs, whereas most published studies on this issue represent the experience of a single center without a control group, with limited scientific value.

Currently, there is a lack of indication about AP in the major guidelines about thyroid disease: no mention of AP is made in the guidelines of the American Thyroid Association guidelines[14] or the National Comprehensive Cancer Network.[15] Only a recent guideline of the American Association of Endocrine Surgeons for the management of thyroid disease in adults indicates that AP is not necessary in most cases of standard transcervical thyroid surgery (strong recommendation, high-quality evidence); indeed, this recommendation is based on only 1 randomized controlled trial (RCT).[16]

In light of this, it is essential to consider that the inappropriate use of antibiotics not only has a negative impact on social costs but also contributes to the rise of antibiotic resistance, which is one of the main causes of antibiotic failure in human infections.

[1]Department of Surgical Sciences, University of Cagliari, Cagliari, Italy
[2]Department of Surgical, Oncological, and Oral Sciences, Section of General and Urgent Surgery, University of Palermo, Palermo, Italy
[3]Postgraduate School of General Surgery, University of Cagliari, Cagliari, Italy

Corresponding Author:
Fabio Medas, MD, Department of Surgical Sciences, University of Cagliari, Cittadella di Monserrato, SS 554–Km 4,500, Monserrato, CA 09042 Italy.
Email: fabiomedas@gmail.com

As a result, we think that acquiring stronger evidence on this topic is crucial; as such, we performed a systematic literature review, including in our meta-analysis RCTs and non-RCTs regarding this issue. The primary outcome of our study was to assess whether AP significantly reduces the incidence of SSIs in thyroid and parathyroid surgery.

Material and Methods

The work has been reported in line with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews).

Eligibility Criteria

The review methods were established prior to conducting this study, and no deviations from the initial protocol were made.

Characteristics of Primary Study: PICOS.

Participants: patients undergoing thyroid or parathyroid surgery for benign or malignant disease; studies including other clean head and neck procedures were included if extrapolation of data regarding only thyroid and parathyroid surgery was possible. Studies including thyroidectomies or parathyroidectomies performed with remote extracervical access were excluded.

Intervention: any type of AP administrated intravenously or orally before surgery to reduce the risk of postoperative wound infections

Comparisons: no treatment or placebo

Outcomes (dependent variable): overall incidence of postoperative SSI detected at follow-up

Study design: RCTs or non-RCTs

Characteristics of Publications. To ensure rigorous methodology, only studies published in peer-reviewed journals were included in the research. No a priori exclusion based on language or year of the publication was made.

Search Strategy and Selection Study

The literature search was performed in January 2020 by 2 independent researchers. The following databases were screened: PubMed, Scopus, and ISI–Web of Science. The search strategy included the following string:

> (antibiotic* OR antimicrob* or anti-infect* or anti infect*) and (prophyla* or prevent*) and (thyroid* or parathyroid* or neck*) and (surger*).

A further search was performed in the reference lists of the selected articles.

The study was performed in accordance with the PRISMA statement.[17]

Coding

A coding protocol was prepared and used by the first 2 authors to independently extract relevant information from the selected primary studies. The accordance between the researchers was very high (Cohen's kappa = 0.83).

The following information was coded for each primary study:

Characteristics of the publication: first author's name, year of publication, language, randomization, country, number of centers involved, result of the study

Characteristics of the sample: total sample size, mean age, rate of male sex, type of operation, neck dissection, use of drain, mean length of surgery

Preoperative management: type of preoperative asepsis, type, dose, mode and timing of antibiotic administration

Postoperative management: duration and modality of follow-up, criteria used for SSI diagnosis

Data necessary for effect size calculation: number of patients and number of postoperative SSIs in case and control groups

Statistical Analysis

Statistical analyses were performed with meta-analytic software (ProMeta 2.0). First, the effect size was calculated as odds ratio and 95% CI from the data extracted from each study. Following this, the overall effect size was computed through the inverse variance method. Furthermore, the odds ratio was considered statistically significant at the 5% level if the 95% CI did not include the value 1. The random effects model was assumed to account for different sources of variation among the studies.[18] Heterogeneity across studies was evaluated through Q and I^2 examination. A significant Q value indicates heterogeneity of results among the studies; I^2 values of 25%, 50%, and 75% can be considered as low, moderate, and high real differences among the effect sizes of the studies, respectively.[19] An additional study of heterogeneity was performed on continuous moderators testing the means of meta-regression analysis, including the incidence of SSI in the control group, rate of male sex, mean age of the patients, mean operative time, and rate of use of suction drainage.

The standardized residual of each study and its statistical significance were used to identify possible outlier studies. If ≥ 1 outlier study was identified, a further meta-analysis was conducted after exclusion of the outlier studies, to evaluate their incidence on the overall effect size.

Finally, publication bias was analyzed with a funnel plot, representing a scatter plot of the effect sizes from primary studies against a measure of their standard error, and with Egger's linear regression analysis: a significant result of the test indicates the presence of an asymmetric funnel plot and a publication bias.[20] In addition, the trim-and-fill method was employed to evaluate the effect of potentially missing

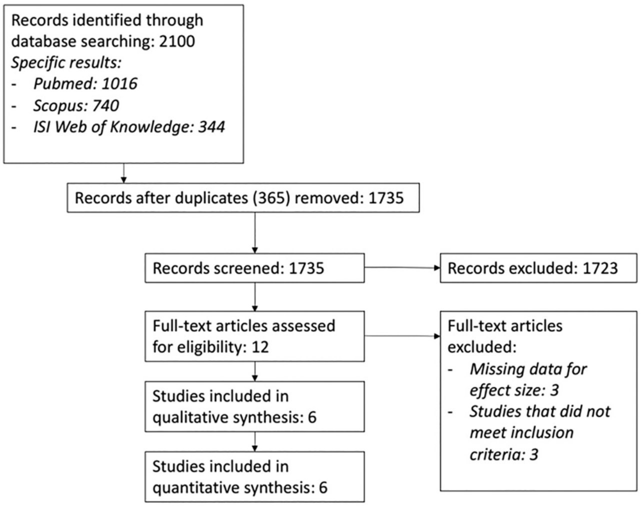

Figure 1. Selection process of studies according to the PRISMA statement.

studies due to publication bias to adjust the overall effect: in case of the absence of publication bias, any study is trimmed; otherwise, the overall effect size was calculated by excluding the trimmed studies.[21]

Results

Initial research identified 2100 results from all databases. As reported in **Figure 1**, after duplicates were removed and titles and abstracts screened, 12 studies were assessed for eligibility. Three were excluded because inclusion criteria were not met and another 3 due to missing data for effect size calculation. Therefore, 6 studies were included in the meta-analysis.[5-10]

The main characteristics of the studies are reported in **Tables 1** to **4**. Only 1 study was published before 2000,[6] whereas the others were published in the 2008-2017 period. Accordingly, 3 studies were RCTs[5,6,9] and 3 were non-RCTs.[7,8,10] Furthermore, 3 studies were conducted in Europe, 2 in Asia, and 1 in the United States; none of the studies had been published in Africa or South America. Only 1 study was multicentric,[5] involving 4 centers, whereas the others were based on a single center. None of the included studies demonstrated a significant efficacy of AP in reducing SSIs. The sample size ranged from 113 to 2164 patients, with the mean age ranging from 46.3 to 60.5 years; as expected, the male sex was poorly represented, with the highest prevalence being 22.1%.[8] Moreover, 3 studies included only thyroidectomies, and another 3 also included parathyroidectomies; furthermore, 2 studies included neck dissections,[9,10] whereas in the others this feature was not clearly defined. The use of the drain was slightly heterogeneous: it was always used in 2 studies[5,6]; it was employed in 46.5% of the patients in 1 study[7]; it was used in only 2.1% of the patients in 1 study [8]; and 2 studies did not report whether the drain was used. The mean duration of surgery ranged from 83.5 to 157.9 minutes. Preoperative skin preparation was reported in 3 studies,[5,8,9] where povidone-iodine or chlorhexidine was used. AP was administrated intravenously, with the most

Table 1. Characteristics of the Publication.

Study [a]	Year	Language	Study design	Country	Centers, No.
Avenia[5]	2009	English	RCT	Italy	4
De Salvo[6]	1998	Italian	RCT	Italy	1
Jen[7]	2007	Chinese	Retrospective	China	1
Moskalenko[8]	2018	English	Retrospective	USA	1
Uruno[9]	2015	English	RCT	Japan	1
Vamvakidis[10]	2017	English	Retrospective	Greece	1

Abbreviation: RCT, randomized controlled trial.
[a]Result of each study: antibiotic prophylaxis did not demonstrate significant efficacy in reducing surgical site infections.

Table 2. Characteristics of the Sample.

Study	Sample size, No.	Mean age, y	Male, %	Type of operation	Radical neck dissection, %	Use of drain, %	Mean length of surgery, min
Avenia[5]	500	47.0	NA	Thyroidectomy	NA	100	NA
De Salvo[6]	113	50.6	15.0	Thyroidectomy	NA	100	83.5
Jen[7]	310	46.3	21.0	Thyroidectomy	NA	46.5	NA
Moskalenko[8]	534	60.5	22.1	Thyroidectomy, parathyroidectomy	NA	2.1	97
Uruno[9]	2164	52.0	15.3	Thyroidectomy, parathyroidectomy	8.9	NA	75.4
Vamvakidis[10]	807	NA	20.3	Thyroidectomy, parathyroidectomy	8.8	NA	157.9

Abbreviation: NA, not available.

Table 3. Preoperative Management and Follow-up.

Study	Preoperative asepsis	Antibiotic	Administration		Follow-up, d	SSI criteria
			Route	Timing		
Avenia[5]	Povidone-iodine / chlorhexidine	Sulbactam/ampicillin, 3 g	IV	30 min before surgery	30	NA
De Salvo[6]	NA	Ceftriaxone, 1 g	IV	30 min before surgery	NA	NA
Jen[7]	NA	NA	IV	30 min before surgery	30	CDC
Moskalenko[8]	Povidone-iodine (96%)	Cefazolin or vancomycin or clindamycin	NA	NA	30	NSQIP
Uruno[9]	Chlorhexidine	Piperacillin, 2 g; or cefazolin, 1 g	IV	Immediately after endotracheal intubation	30	CDC
Vamvakidis[10]	NA	Cefuroxime	IV	NA	NA	NA

Abbreviations: CDC, Centers for Disease Control and Prevention; IV, intravenous; NA, not available; NSQIP, National Surgical Quality Improvement Program.

Table 4. Incidence of SSI in the Primary Studies.

Study	Events, No. (%)					ES	95% CI	*P* value	Residuals	*P* value
	Cases	Total	Controls	Total	Overall					
Avenia[5]	2 (0.8)	250	1 (0.4)	250	3 (0.6)	2.01	0.18-22.29	.570	0.38	.708
De Salvo[6]	1 (1.7)	57	2 (3.4)	56	3 (2.6)	0.48	0.04-5.47	.556	−0.53	.594
Jen[7]	6 (3.8)	160	0	150	6 (1.9)	12.66	0.71-226.76	.085	1.79	.073
Moskalenko[8]	1 (0.7)	141	0	393	1 (0.2)	8.40	0.34-207.45	.193	1.20	.232
Uruno[9]	1 (0.1)	1082	3 (0.3)	1082	2 (0.2)	0.33	0.03-3.20	.341	−0.81	.416
Vamvakidis[10]	2 (0.4)	518	4 (1.4)	289	6 (0.7)	0.28	0.05-1.52	.139	−1.23	.217

Abbreviations: ES, effect size; SSI, surgical site infection.

Table 5. Meta-analytic Results.

	k	Patients, No.	SSIs/patients, No. (%)		OR (95% CI)	*Q*	I^2	Egger	Trim and fill
			Cases	Control					
SSI	6	4428	13/2208 (0.6)	10/2220 (0.4)	1.07 (0.3-3.81)[a]	8.36[b]	40.17	3.39[c]	0[d]

Abbreviation: OR, odds ratio; SSI, surgical site infection.
[a]Not significant, *P* = .915.
[b]Not significant, *P* = .138.
[c]Significant, *P* = .028.
[d]No studies were trimmed, and the OR (95% CI) results remain 1.07 (0.3-3.81).

antibiotic employed being cephalosporin of the first, second, or third generation. The timing of antibiotic administration was reported in 4 studies: it was administrated 30 minutes before surgery in 3 cases[5-7] and immediately after endotracheal intubation in 1 case.[9] The length of follow-up was reported in 4 studies, and 3 studies clearly indicated the adopted criteria for SSI diagnosis.[7-9]

As reported in **Table 5** and summarized in **Figure 2**, the overall rate of SSIs was 0.6% in the case group (range, 0.1%-3.8%) and 0.4% in the control group (range, 0.3%-3.4%); this difference was not statistically significant. There was no evidence of heterogeneity (Q = 8.36, P = .138; I^2 = 40.17, indicating low grade of heterogeneity).

The Egger test revealed asymmetry in the funnel plot (**Figure 3**), suggesting potential publication bias; however, no studies were trimmed with the trim-and-fill method.

The analysis of continuous moderators (**Table 6**) produced no significant results.

Potential outlier studies were searched with the analysis of standardized residuals, which did not demonstrate their

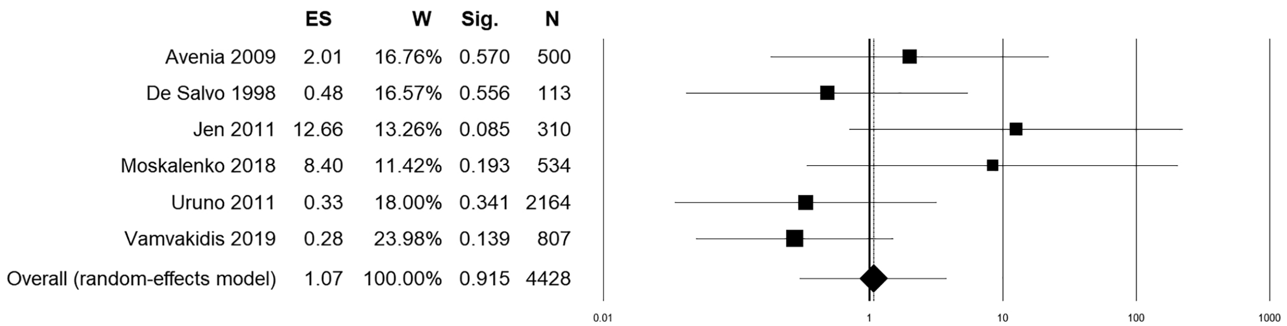

Figure 2. Forest plot of effect sizes from meta-analysis on the effectiveness of antibiotic prophylaxis in reducing incidence of surgical site infection after thyroidectomy and parathyroidectomy. ES, effect size.

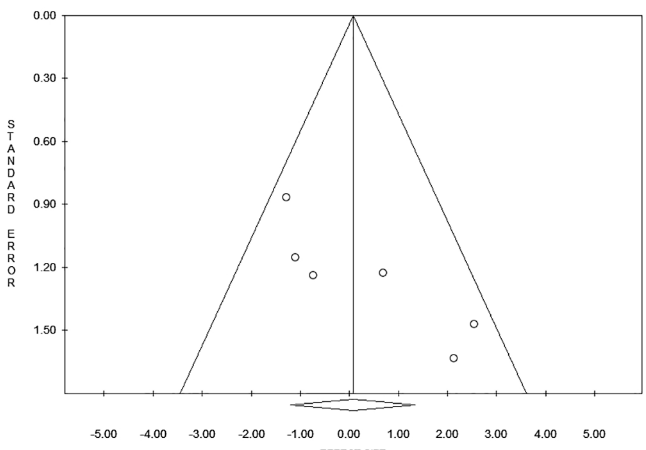

Figure 3. Funnel plot of effect sizes from meta-analysis on the effectiveness of antibiotic prophylaxis in reducing incidence of surgical site infection after thyroidectomy and parathyroidectomy.

presence, as reported in **Table 4**. In addition, the sensitivity analysis—which represents a meta-analysis conducted by excluding 1 study to evaluate the incidence of each study on the overall effect size—demonstrated the absence of outlier studies (**Figure 4**).

A subset analysis was conducted on the 3 RCTs in our study (Supplemental Figure S1): 2777 patients were included in the meta-analysis, and no significant effect of AP in reducing SSIs was found (overall effect size, –0.22; 95% CI, –0.98 to 0.53; $P = .560$).

The symmetry of the forest plot was also evaluated by ordering primary studies according to sample size, but no sign of publication bias was found (Supplemental Figure S2); in fact, in case of publication bias, it is common to find an asymmetrical forest plot with the small-sample studies reporting systematically significant results.

Table 6. Continuous Moderator Analysis.

		Patients, No.				
Moderator	k	Total	Cases	Control	B (slope)	P value
SSI in control group, %	6	4428	2208	2220	−0.67	.273
Male, %	5	3928	1958	1970	0.33	.281
Age	5	3621	1690	1931	0.01	.967
Operative time	4	3618	1798	1820	−0.01	.699
Drainage, %	4	1457	608	849	−0.03	.199

Abbreviation: SSI, surgical site infection.

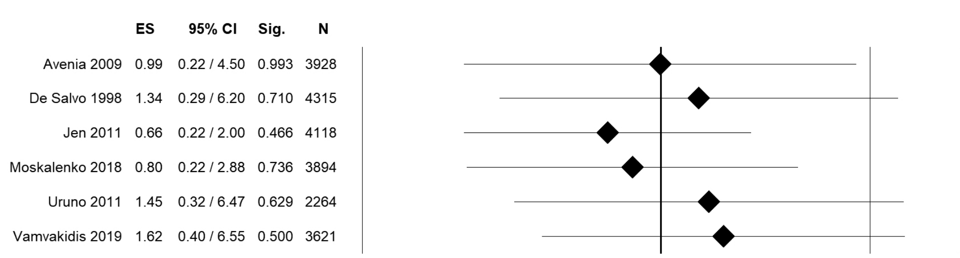

Figure 4. Sensitivity analysis of effect sizes from meta-analysis on the effectiveness of antibiotic prophylaxis in reducing incidence of surgical site infection after clean neck surgery. ES, effect size.

Discussion

Thyroid and parathyroid surgery is considered a clean surgical procedure. A survey conducted by the CDC in >1500 US hospitals during the 2006-2008 period found that the incidence of SSI in thyroid and parathyroid surgery is <1%.[22] Furthermore, many centers have reported their experience without the routine use of preoperative AP, reporting a low incidence of SSIs.[11,23-25] In addition, it is important to consider that in the last decades, thyroid and parathyroid surgery has undergone several changes, with the introduction of new devices and techniques that allow for reduced skin incision, tissue manipulation, surgical time, bleeding, and use of sutures[25-28]; it is likely that these innovations have contributed to a further reduction of SSIs.

However, even if no evidence supports the use of AP in thyroid and parathyroid surgery, many surgeons still use it routinely, with an approach that appears to be more dogmatic than evidence based. This attitude may be dangerous because it increases the possibility of raising antibiotic resistance and increasing medical costs.

A few controlled trials tried to assess whether AP is efficient in reducing SSIs, resulting in poor evidence in the literature. The aim of this study was to achieve stronger evidence for this argument.

The present study examined the results of 6 studies (3 RCTs and 3 non-RCTs) addressing the efficacy of AP in thyroid and parathyroid surgery, and it is the first meta-analysis on this topic. Overall, 4428 patients were included in our study; the incidence of SSIs after thyroid and parathyroid surgery was 0.5% (0.6% in the case group and 0.4% in the control group). Our quantitative analysis demonstrated that AP was not significantly effective in reducing SSIs.

In our study, the analysis of several continuous moderators, such as age, duration of surgery, and use of drain, did not indicate any significant correlation with the pooled effect size; this seems to be in accordance with the previously mentioned survey of the CDC, where the incidence of SSIs is not influenced by the duration of surgery.[22]

In our meta-analysis, a publication bias was suspected from a significant Egger test, but the trim-and-fill method did not trim off any study. This finding seems contradictory, but it is important to consider that in case of a low number of primary studies, Egger's test has low statistical power.[20]

The low number of RCTs found in the literature probably reflects the fact that this kind of surgery is considered clean and the administration of AP is not perceived as a problem, but as already stated, this is in contrast with the literature suggesting that 26% to 58% of the surgeons still routinely use AP.

However, we found several limitations in our study. First, this meta-analysis was conducted on only 6 studies, and among these, just 3 were RCTs, while the others were retrospective observational studies. The geographic distribution of the studies was not homogenous; in fact, 3 studies were performed in Europe, 2 in Asia, and 1 in the United States, whereas no studies were conducted in Africa or South America. In some cases, the definition of SSI was not well defined. We found heterogeneity among the antibiotics used in the case group in the different studies, including cephalosporin of the first, second, and third generation, as well as piperacillin and ampicillin. Another limitation is that an analysis of some risk factors for SSIs, including diabetes mellitus and obesity, was not possible due to a lack of data.

Finally, in our meta-analysis, we did not include thyroidectomies performed with remote extracervical access. In these patients, there is an increase in surgical trauma, duration of surgery, and dissection area, and particularly in the case of a transoral approach with vestibular access, there is a contamination of the surgical field with oral bacteria. We think that further studies are required to assess the usefulness of AP in this case.

Conclusion

Even considering the limits of the primary studies, on the basis of the findings of our meta-analysis, we think that AP should be avoided in thyroid and parathyroid surgery. It is essential to emphasize the importance of preoperative patient preparation and the observance of the rules of asepsis. In case of a higher-than-expected incidence of SSIs, a careful analysis of the procedures, including pre-, intra-, and postoperative strategies for asepsis, should be performed, rather than routine administration of AP.

Author Contributions

Fabio Medas, study conception and design, literature search, acquisition, interpretation and analysis of data (statistical expertise); drafting and critically revising the article for important intellectual content; and final approval of the version to be published; **Gian Luigi Canu**, study conception and design, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; editing and revising the English for the final version to be published; and final approval of the version to be published; **Federico Cappellacci**, study conception and design, literature search, acquisition, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published; **Giorgio Romano**, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published; **Giuseppe Amato**, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published; **Enrico Erdas**, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published; **Pietro Giorgio Calò**, study conception and design, literature search, acquisition, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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