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Review

A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ)

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SUMMARY

Objectives: The clinical management of bisphosphonate-related osteonecrosis of the jaw (BRONJ) remains controversial. Since universally accepted guidelines have not been released yet, clinicians usually chose the type of treatment according to position papers based on expert opinion, or on empirical experience. The aim of this systematic review is to identify different therapeutical approaches for BRONJ that have been described in literature and to describe their effectiveness. *Materials and Methods:* A Medline via Pubmed and Scopus database literature search was conducted and all publications fulfilling the inclusion and exclusion criteria were included in eligibility assessment. The full texts of 146 retrieved articles were then screened and 40 studies were included in the quality assessment process. *Results:* After quality assessment, 22 full text articles were selected for the final review. 14 articles out of 22 were screened for stage-related outcomes. The overall outcome results and results for every disease stage were the highest when patients were treated with extensive surgery or extensive laser assisted surgery.

Introduction

Since bisphosphonate-related osteonecrosis of the jaw (BRONJ) was first reported in the early 2000s, it is now a well-established entity [1,2]. Bisphosphonates (BPs) are powerful inhibitors of osteoclastic activity leading to suppression of bone turnover. They also have anti-angiogenic properties, activate T-cells and have direct tumoricidal effects [3]. While the exact etio-pathogenetic mechanism of BRONJ has still to be established, it is clear that infection, trauma and reduced vascularity play important roles. The use of denosumab (an antibody against RANK-ligand that also leads to inhibition of osteoclastic activity) has also been associated with the development of jaw osteonecrosis, strengthening the hypothesis that osteoclast inhibition and suppression of bone turnover plays a central role in the etio-pathogenesis [4]. Unfortunately, the exact mechanism remains unclear and there are still a lot of questions that need to be answered.

In 2009, the American Association of Oral and Maxillofacial Surgeons (AAOMS) published an update of their position paper that provided diagnostic and staging criteria associated to treatment recommendations for BRONJ (Table 1). According to the position paper, patients may be considered to have BRONJ if all of the following three characteristics are present: (1) current or previous treatment with a BP (2) exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks (3) no history of radiation therapy to the jaws [5]. These criteria are widely accepted although they continue to be revised as new data become available. Wilde et al. [6] proposed a modification to this staging system adding a Stage 4 which connotes more severe disease. Since a clinical variant of BRONJ that presents without exposed bone has been recognized referred to as "Stage 0" or "non-exposed BRONJ" [7], this definition has also been incorporated into the AAOMS BRONJ diagnostic criteria. Recently, in a letter to the editor, members of the Expert Panel of the Italian Society for Maxillofacial Surgery (SICMF) and of the Italian Society of Oral Pathology and Medicine (SIPMO) submitted a proposal for an updated definition of BRONJ as follows: "Bisphosphonate related osteonecrosis of the jaw (BRONJ) is an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible or maxilla of patients exposed to the treatment with nitrogen-containing bisphosphonates, in the absence of a previous

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radiation treatment" and for a new combined clinical and radiological staging system [8].

BRONJ treatment has been challenging from the beginning as treatment protocols for similar diseases like osteomyelitis or osteoradionecrosis, including surgical debridement, resection and hyperbaric oxygen therapy, led to scarcely predictable and not always effective outcomes [2,9]. Many different therapeutic approaches for BRONJ have been reported including anti-microbial rinses, antibiotics, local debridement and surgical resection, or a combination thereof. Clinicians chose their therapies based on their own empirical experience as well as guidelines from position papers from professional societies. According to the 2009 AAOMS position paper [5], the goal of treatment should be conservative with a focus on palliation since healing rates for surgical treatment are fairly low. However, since several recent studies have shown durable disease-free status after surgical resection of lesions of BRONJ, the goal of therapy may not only be palliation. Up to date, there are no universally accepted treatment protocols and no systematic reviews or meta-analyses have been published on this issue. The aim of this systematic review is to identify different treatment approaches for BRONJ that are reported in literature and to assess healing rates for each category of treatment and for each BRONJ stage.

Materials and methods

A systematic review of the evidence available in the literature was performed following PRISMA statement [10] to answer the following clinical question: "Which therapeutical approaches for BRONJ are more effective overall and basing on the disease stage?". An electronic research was performed using Medline via PubMed and Scopus. Studies published in literature from January 2005 to February 2013 have been screened, as this condition is recent and no older studies about treatment modalities were available. The search strategy used the following keywords: bisphosphonates AND osteonecrosis AND jaw AND treatment. After duplicates removal, the yielded titles and abstracts of potentially relevant articles were screened by two independent reviewers (KR and MG) according to the following inclusion and exclusion criteria:

Inclusion criteria:

- Studies describing BRONJ treatment strategies.

Exclusion criteria:

- Articles not in English.
- Review articles.
- Animal-model based studies.

Full texts of articles meeting the inclusion/exclusion criteria were then obtained. If a relevant citation was found in the screened full texts, the full article was also retrieved and included in the selection phase. The full texts of all articles retrieved from the database search and from the manual reference list search were evaluated by the two reviewers considering the following eligibility criteria for inclusion in the quality assessment phase and final review:

- Studies with a minimum of 5 patients.
- Staging criteria according to 2009 AAOMS guidelines; if another staging system was used, the BRONJ stages were converted to the AAOMS system.
- Exhaustively described therapeutic protocols.
- Healing described as stabile complete mucosal healing of lesions.
- Overall outcome documented.
- Outcome by stage documented (for the inclusion in the stage-dependent analysis).
- Minimum follow-up period of 3 months; if patients with less follow-up periods were present, those were excluded from the outcome data.

The following data were abstracted from each article and reported in a Microsoft Word Excel table: (1) number of patients/lesions, (2) type of treatment, (3) outcome of treatment overall, (4) outcome of treatment by stage, (5) period of follow-up.

Performing quality assessment is challenging when there is a high heterogeneity of study designs involved as in the present review, and considering that majority of the studies are observational. Since there is not a specific tool to be recommended among others [11], the Authors chose three parameters:

- The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [12] checklist was used to ensure the reporting of the studies; only studies with assessed quality of reporting underwent further quality assessment.
- The level of evidence for every paper has been assigned based on the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence [13].
- The Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields [14] checklist for quantitative studies, which allows a quality evaluation of different types of study designs, was used for quality assessment. The studies that reached a value of 0.7 or more were then considered for the final analysis. Quality assessment was performed by two independent reviewers (KR and MG).

Any differences during the overall process of study selection and quality assessment were discussed and disagreement managed by consultation with a third party (MB).

Results

The electronic database search last updated on February 2013 yielded 1183 hits from Medline and 925 hits from Scopus. 1216 titles and/or abstracts were obtained after duplicates removal and then screened according to inclusion and exclusion criteria

Table 1
AAOMS staging system from the updated 2009 position paper.

Staging system (AAOMS position paper 2009)	
BRONJ stage	Description
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms
Stage 1	Exposed and necrotic bone in asymptomatic patients without evidence of infection
Stage 2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (ie, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor

and 145 articles were considered relevant to the topic. A manual reference list search of the 145 selected articles yielded one further article. Full texts of these 146 articles were then assessed for eligibility leading to the selection of 40 full text articles that met STROBE criteria for proper reporting and therefore underwent further quality assessment procedures. The flow chart for study selection adapted from PRISMA statement [10] is showed in Fig. 1. Considering levels of evidence, level 2 was assigned to one study (RCT), level 3–16 non-randomized cohort studies, level 4–23 studies (22 observational interventional basic research studies and 1 case-control study). Following The Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields [14] checklist for quantitative studies, a numerical value has been assigned to every study. 22 Studies reached a cut-off value $\geqslant 0.7$ and were included in quantitative synthesis for treatment outcomes. 14 studies out of 22 were included in quantitative synthesis for stage-dependent treatment outcomes. Data including study type, level of evidence, quality assessment value, number of patients/lesions with documented outcome, types of treatment, outcome and follow-up for all 40 studies included following eligibility criteria are reported in Table 2.

One of the main deals concerning the present study has been the high heterogeneity among studies, that would lead to an inappropriate combination of data (which is a frequent problem when reporting observational studies). Potential biases such as publication bias in original studies make the calculation of a single summary estimate of effect of exposure potentially misleading. For these reasons, Authors decided to combine data limiting statistics only to descriptive analysis and not providing a statistical evidence for treatment effects. Therefore, the present systematic review does not contain meta-analysis.

Total treatment outcome synthesis

The full text paper screening and quality assessment process led to the identification of 14 different combinations of treatments performed on 858 BRONJ patients described in 22 studies. Treatments can be clustered into two general approaches: nonsurgical and surgical.

Nonsurgical approaches

200 Patients were treated with nonsurgical approaches. Studies and results are reported in Table 3. Medical therapy focused on reinforcing oral hygiene, regular dental follow-up, mouth rinse administration (chlorhexidine 0.12% or 2%) and antibiotic and/or antiflogistic therapy in case of pain and inflammation. The antibiotics mostly prescribed in the studies have been amoxicillin 500 mg/1 g with or without clavulanic acid, azitromicin 500 mg and clindamicin 300 mg. Some studies associated metronidazole 250 mg to β-lactam antibiotics. We observed a low rate of overall success in terms of healing when only medical therapy was performed, even if the range of outcome among studies is very wide. In the majority of studies this kind of approach led only to stabilization of necrosis or minor improvement [16,19,20], whether in others led to a low rate of healing [24–27], and in two studies healing reached over the half of patients involved [28,29]. One study performed LLLT (Low level laser therapy) [27] using with Nd:YAG laser appliances, reaching a healing rate after last follow-up of 30%. Freiberger et al. [26] performed the only randomized controlled trial available in literature and evaluated the role of adjunctive HBO (Hyperbaric Oxygen) administered at 2 atm twice a day for 40 treatments as an adjunct to conventional therapy of surgery and antibiotics versus conventional therapy alone. Healing rate in patients that underwent HBO was 52%, while in those who underwent conventional/antibiotic therapy alone was 33%, but the difference was not significant ($P = 0.203$).

Surgical approaches

A total of 658 patients underwent surgical therapies, which can be clustered into three different surgical approaches: conservative surgery, extensive surgery and laser surgery. Studies and results are reported in Table 4.

Conservative surgical approach. When only sequestrectomy and/or superficial surgical debridement of necrotic bone associated to antibiotic therapy was performed, the Authors defined it as a conservative surgical approach. All the studies considered have healing rates over 50% [20,24,27–29,36], with the exception of two studies [16,19]. In two studies, BP therapy was suspended before surgery [37,38]. One study associated LLLT to conservative surgery [27], increasing the healing rate to 74%. Even higher healing rates were observed when conservative surgery was performed adding PRP (Protein Rich Plasma), in addition to [24] LLLT applications. Total healing rate after conservative surgical approaches was 75%.

Extensive surgical approach. When resection of jawbone was performed, the Authors defined it as an extensive surgical approach often performed under general anesthesia. A marginal jawbone resection is the removal of necrotic bone usually including the whole alveolar process, extending to bloody viable margins. A segmental jawbone resection is the removal of a segment of mandible thereby interrupting its continuity due to extended necrosis. Although in one study none of the patients healed [19], the other selected studies report high success rates [43,44,46–48]. The addition of HBO prior to surgery provides controversial results: both low [19] and very high healing rates [49] when also BP therapy was suspended. Further approaches with high healing outcome are fluorescent-guided bone resection [50] and the use of PRP (Protein Rich Plasma) to enhance healing after surgery [51,52]. Total healing rate after extensive surgical approaches was 84%.

Laser surgery. When used in surgery, laser provides the capability to ablate bone effectively without producing major thermal side effects to adjacent tissues. It also has bactericidal, detoxification and biostimulating effects that may potentially enhance bone regeneration and help wound healing after surgery. All the considered studies that used laser surgery (ErCrYSGG and Er:YAG lasers) to perform ablation of necrotic tissue extended to bloody viable margins provided high healing rates, ranging from 60% to 100% [18,27,38,53,54]. Total healing rate after laser surgical approaches was 85%.

Stage-dependent outcome synthesis

To identify which types of treatment may be more effective for each BRONJ stage, 14 papers out of 22 containing the treatment outcomes for each disease stage have been selected and screened. The results are reported in Tables 5 and 6. 13 Treatments or combinations of treatments have been identified and clustered into four major types of approaches: nonsurgical, conservative surgical, extensive surgical and laser surgical approaches.

Nonsurgical approaches

Nonsurgical approaches described in the selected papers include antibiotic therapy [19,20,24,27] and antibiotic therapy associated to LLLT [27]. Total healing rates for nonsurgical approaches were 33% in Stage 1, 24% in Stage 2 and 0% in Stage 3.

Conservative surgical approaches

When only sequestrectomy and/or superficial surgical debridement of necrotic bone associated to antibiotic therapy was performed, we defined it as a conservative surgical approach. Conservative surgical approaches described in the selected papers

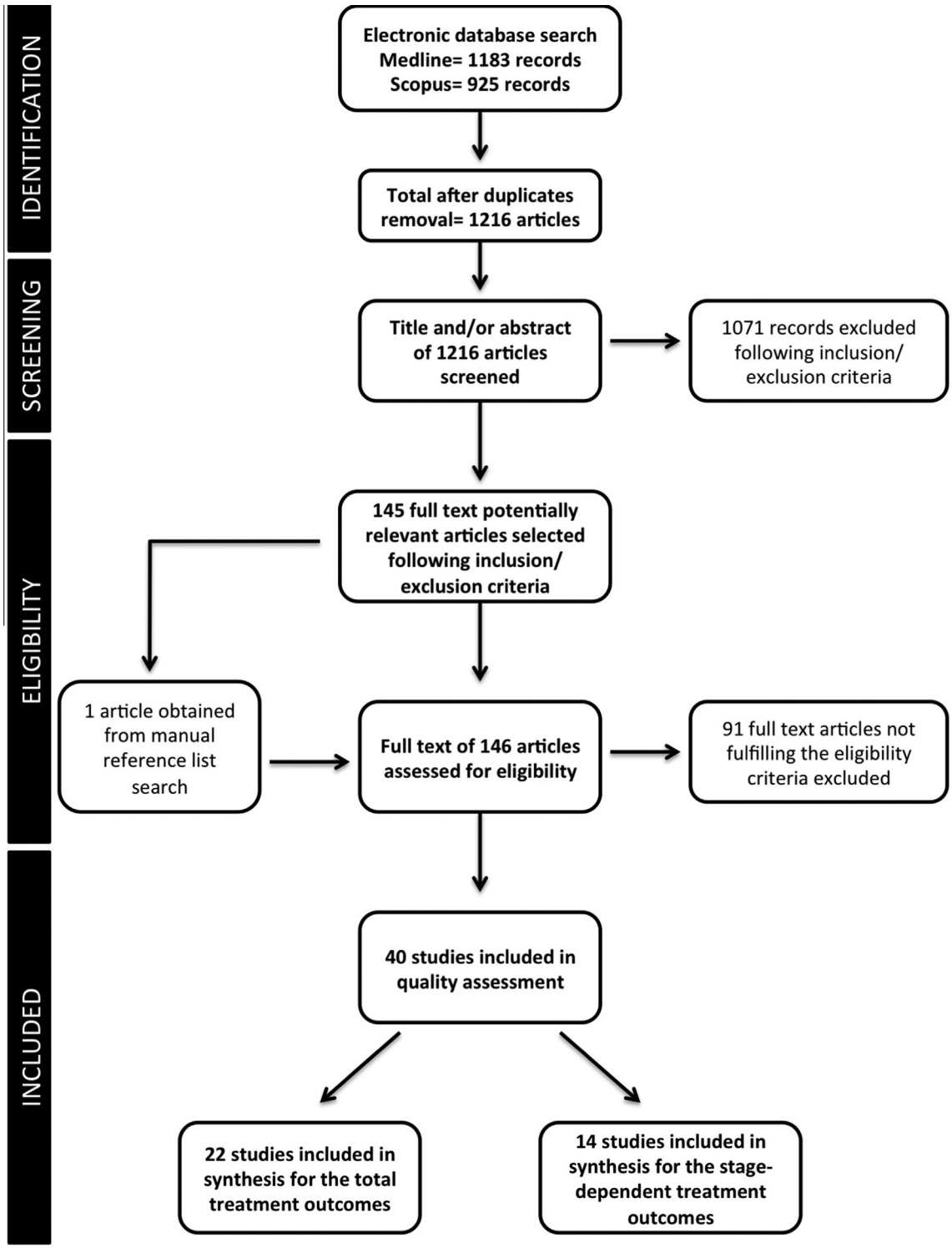

Fig. 1. Flow-chart of the review process modified from PRISMA statement [10].

include conservative surgical procedures associated to antibiotic therapy [19,24,27], conservative surgical procedures associated to long term antibiotic therapy [20], conservative surgical procedures associated to antibiotic therapy and suspension of BP treatment [37,38], conservative surgical procedures associated to antibiotic therapy and LLLT [27], conservative surgical procedures associated to antibiotic therapy, LLLT and PRP [24]. Total healing rates for conservative surgical approaches were 72% in Stage 1, 79% in Stage 2, and 27% in Stage 3.

Extensive surgical approaches

When a marginal or segmental resection of jawbone was performed, we defined it as an extensive surgical approach. Extensive surgical approaches described in the selected papers include extensive surgical procedures associated to antibiotic therapy [19,43,45–48], extensive surgical procedures associated to antibiotic therapy and HBO [19], extensive surgical procedures associated to antibiotic therapy, HBO and suspension of NBP treatment [49], fluorescence-guided extensive surgical procedures associated

Table 2
Total treatment outcomes of studies with proper reporting following STROBE statement undergoing quality assessment procedure. *QA* quality assessment, *Obs* observational, *Coh* cohort, *RCT* randomized controlled trial, *Npts* number of patients, AB antibiotic therapy, *Susp* suspension of BP treatment, *HBO* hyperbaric oxygen, *LLLT* low level laser therapy, O_3 medical ozone in oil suspension, *PαT* Pentoxifylline and tocopherol, *NSd* non surgical debridement, *CS* conservative surgery, *stAB* short term preoperative antibiotic therapy, *ltAB* long term preoperative antibiotic therapy, *PRP* protein rich plasma, *ES* extensive surgery, *fgES* fluorescence-guided extensive surgery, *LS* laser surgery, *Terip* teriparatide therapy, *h* healing.

Study/year	Study type	Level of evidence	QA score	Npts	Type of treatment (*n*)	Outcome (% h)	Follow-up (months)
Marx et al. (2005) [15]	Obs	4	0.5	119 (91 outcome)	91/91 AB	0	12
Eckert et al. (2007) [40]	Obs	4	0.6	24 (14 with f-up)	14/14 AB, ES	79	3–13
Montebugnoli et al. (2007) [16]	Obs	4	0.75	16	7/16 AB	0	3–24 (10)
					9/16 AB, CS	22	
Yarom et al. (2007) [17]	Obs	4	0.5	11 (9 treated)	2/9 AB	0	6–38
					5/9 AB, CS	22	
					2/9 AB, ES	0	
Boonyapakorn et al. (2008) [31]	Obs	4	0.6	22	3/22 Susp, AB	0	Min 3
					3/22 Susp, AB, NSd	67	
					2/22 AB, CS	0	
					13/22 Susp, AB, CS	70	
Wutzl et al. (2008) [37]	Coh	3	0.8	58 (41 treated)	41/41 Susp, AB, CS	59	6
Alons et al. (2009) [35]	Obs	4	0.55	7	7/7 AB, CS	86	5–52
Angiero et al. (2009) [18]	Obs	4	0.7	49	19/49 AB	0	12–80 (39)
					20/49 AB, CS	0	
					10/49 AB, LS	60	
Carlson et al. (2009) [41]	Obs	4	0.68	74 (95 sites)	74/74 AB, ES	92	
Junquera et al. (2009) [21]	Obs	4	0.55	21	9/21 AB	10	6–30
					12/21 AB, CS	100	
Lazarovici et al. (2009) [22]	Obs	4	0.6	101 (87 outcome)	87/87 AB	18	6–54
Markose et al. (2009) [42]	Coh	3	0.65	15	15/15 AB, ES	100	24
Stubinger et al. (2009) [53]	Coh	3	0.65	8 (10 sites)	8/8 LS	100	12
Thumbigere-Math et al. (2009) [19]	Coh	3	0.75	26	2/26 AB	0	6
					19/26 AB, CS	15	
					1/26 AB, ES	0	
					4/26 HBO, AB, ES	25	
Epstein et al. (2010) [32]	Coh	3	0.5	6	6/6 PαT, AB	17	3–19 (11)
Rugani et al. (2010) [54]	Obs	4	0.7	5	5/5 AB, LS	100	12
Scoletta et al. (2010) [28]	Coh	3	0.78	37	24/37 AB	87	24
					13/37 AB, CS	56	
Stockmann et al. (2010) [43]	Coh	3	0.75	50 (44 outcome)	44/44 AB, ES	89	12
Williamson et al. (2010) [36]	Coh	3	0.7	40	40/40 AB, CS	100	6–48 (20)
Atalay et al. (2011) [38]	Case-Control	4	0.77	20	10/20 Susp, AB, CS	40	3–28 (17)
					10/20 Susp, AB, LS, LLLT	70	
Bedogni et al. (2011) [49]	Coh	3	0.75	30	30/30 Susp, HBO, AB, ES	90	6–24 (21)
Curi et al. (2011) [51]	Obs	4	0.65	25	25/25 AB, ES, PRP	80	12
Ferlito et al. (2011) [20]	Obs	4	0.75	94	3/94 AB	0	6
					91/94 ltAB, CS	100	
Hoefert et al. (2011) [44]	Obs	4	0.8	47	16/47 stAB, ES	36	1–59 (17)
					31/47 ltAB, ES	96	
Lemound et al. (2011) [45]	Coh	3	0.7	20	20/20 AB, ES	90	3–33 (20)
Manfredi et al. (2011) [23]	Obs	4	0.65	25 (22 treated)	4/22 AB	25	6–36 (15)
					1/22 Susp, AB	100	
					5/22 AB, LLLT	80	
					2/22 Susp, AB, LLLT	0	
					3/22 AB, CS	100	
					2/22 Susp, AB, CS	100	
					4/22 AB, CS, LLLT	100	
					2/22 Susp, AB, CS, LLLT	100	
Martins et al. (2011) [24]	Obs	4	0.7	22	3/22 AB	33	6
					5/22 AB, CS	60	
					14/22 AB, CS, PRP, LLLT	86	
Moretti et al. (2011) [25]	Coh	3	0.8	34 (33 outcome)	33/33 AB	24	3–40 (16)
Mucke et al. (2011) [29]	Coh	3	0.8	108	6/108 AB	100	6–84 (44)
					102/108 AB, CS	71	
Pautke et al. (2011) [50]	Coh	3	0.6	15 (20 lesions)	20/20 AB, fgES	85	1
Ripamonti et al. (2011) [34]	Cohort	3	0.65	10	10/10 AB, O_3	100	8
Wilde et al. (2011) [46]	Obs	4	0.75	24 (33 lesions)	33/33 AB, ES	88	16.5
Bocanegra-Perez et al. (2012) [39]	Cohort	3	0.65	8	8/8 AB, CS, PRP	100	12–26 (14)
Freiberger et al. (2012) [26]	RCT	2	0.79	46	21/46 AB	33	3–24
					25/46 HBO, AB	52	
Jabbour et al. (2012) [30]	Obs	4	0.55	14 (19 lesions)	7/19 AB	71	4–27 (13)
					4/19 AB, CS	50	
					8/19 AB, ES	63	
Kwon et al. (2012) [33]	Obs	4	0.4	6	6/6 Susp, Terip, M/S	100	3
Mozzati et al. (2012) [52]	Obs	4	0.75	32	32/32 AB, ES, PRP	100	45–60 (50)
Schubert et al. (2012) [47]	Obs	4	0.75	54	54/54 AB, ES	87	6
Vescovi et al. (2012) [27]	Obs	4	0.8	190 (166 treated)	32/166 AB	19	6–54 (16)
					37/166 AB, LLLT	30	

(*continued on next page*)

Table 2 (*continued*)

Study/year	Study type	Level of evidence	QA score	Npts	Type of treatment (*n*)	Outcome (% h)	Follow-up (months)
					17/166 AB, CS	65	
					39/166 AB, CS, LLLT	74	
					41/166 AB, LS	93	
Voss et al. (2012) [48]	Cohort	3	0.75	21	21/21 AB, ES	95	12–24 (16)

Table 3
Outcomes after nonsurgical approaches *AB* antibiotic therapy, *LLLT* low level laser therapy, *HBO* hyperbaric oxygen.

Type of treatment	Author, year	NPts healed/NPts treated	
Antibiotic therapy	Montebugnoli et al. (2007) [16]	0/7 0%	AB 50/138 36%
	Thumbigere-Math et al. (2009) [19]	0/2 0%	
	Scoletta et al. (2010) [28]	21/24 87%	
	Ferlito et al. (2011) [20]	0/3 0%	
	Martins et al. (2011) [24]	1/3 33%	
	Moretti et al. (2011) [25]	8/33 24%	
	Mucke et al. (2011) [29]	6/6 100%	
	Freiberger et al. (2012) [26]	7/21 33%	
	Vescovi et al. (2012) [27]	7/39 19%	
Antibiotic therapy LLLT	Vescovi et al. (2012) [27]	11/37 30%	AB LLLT 11/37 30%
Antibiotic therapy HBO	Freiberger et al. (2012) [26]	13/25 52%	AB HBO 13/25 52%

Table 4
Outcomes after surgical approaches *NPts* number of patients, *HBO* hyperbaric oxygen, *NBP* Nitrogen-containing bisphosphonate therapy, *PRP* platelet rich plasma, *LLLT* low level laser therapy.

Type of treatment	Author, year	NPts healed/NPts treated	
Conservative surgery	Montebugnoli et al. (2007) [16]	2/9 22%	Conservative surgery 298/400 75%
	Thumbigere-Math et al. (2009) [19]	3/19 15%	
	Scoletta et al. (2010) [28]	7/13 56%	
	Williamson et al. (2010) [36]	40/40 100%	
	Ferlito et al. (2011) [20]	91/91 100%	
	Martins et al. (2011) [24]	3/5 60%	
	Mucke et al. (2011) [29]	72/102 71%	
	Vescovi et al. (2012) [27]	11/17 65%	
Conservative surgery Suspension NBP	Wutzl et al. (2008) [37]	24/41 59%	
	Atalay et al. (2011) [38]	4/10 40%	
Conservative surgery LLLT	Vescovi et al. (2012) [27]	29/39 74%	
Conservative surgery PRP LLLT	Martins et al. (2011) [24]	12/14 86%	
Extensive surgery	Thumbigere-Math et al. (2009) [19]	0/1 0%	Extensive surgery 172/204 84%
	Stockmann et al. (2010) [43]	39/44 89%	
	Hoefert et al. (2011) [44]	36/47 77%	
	Wilde et al. (2011) [46]	29/33 88%	
	Schubert et al. (2012) [47]	47/54 87%	
	Voss et al. (2012) [48]	20/21 95%	
Extensive surgery HBO	Thumbigere-Math et al. (2009) [19]	1/4 25%	
Extensive surgery Suspension NBP HBO	Bedogni et al. (2011) [49]	27/30 90%	
Extensive surgery PRP	Curi et al. (2011) [51]	20/25 80%	
	Mozzati et al. (2012) [52]	32/32 100%	
Fluorescence-guided extensive surgery	Pautke et al. (2011) [50]	17/20 85%	
Laser surgery	Angiero et al. (2009) [18]	6/10 60%	Laser surgery 46/54 85%
	Stubinger et al. (2009) [53]	8/8 100%	
	Rugani et al. (2010) [54]	5/5 100%	
	Vescovi et al. (2012) [27]	20/21 95%	
Laser surgery Suspension NBP LLLT	Atalay et al. (2011) [38]	7/10 70%	

to antibiotic therapy [50], extensive surgical procedures associated to antibiotic therapy and PRP [52]. Total healing rates for extensive surgical approaches were 89% in Stage 0, 87% in Stage 1, 96% in Stage 2, and 81% in Stage 3.

Laser surgical approaches

Laser surgical approaches performed with ErCrYSGG or Er:YAG lasers include laser surgical procedures associated to antibiotic therapy [27,54], and laser surgical procedures associated to

Table 5
Stage-dependent treatment outcomes of studies selected after quality assessment. *AB* antibiotic therapy, *Susp* suspension of BP treatment, *HBO* hyperbaric oxygen, *LLLT* low level laser therapy, *CS* conservative surgery, *PRP* protein rich plasma, *ES* extensive surgery, *LS* laser surgery. Results reported as number of patients with complete healing at last follow-up/total number of patients treated with a treatment or combination of treatments.

Study/year	Stage	Npts	AB	AB LLLT	AB CS	ltAB CS	Susp AB CS	AB CS LLLT	AB CS PRP LLLT	AB ES	HBO AB ES	Susp AB HBO ES	AB ES PRP	AB LS	Susp AB LS LLLT
Wutzl (2008) [37]	1	7					7/7								
	2	27					17/27								
	3	7					0/7								
Thumbigere-Math (2009) [19]	1	2	0/2												
	2	19			4/19										
	3	5								0/1	1/4				
Rugani (2010) [54]	1	0													
	2	5												5/5	
	3	0													
Stockmann (2010) [43]	1	12								10/12					
	2	20								19/20					
	3	12								10/12					
Atalay (2011) [38]	1	6					0/5								1/1
	2	14					4/5								6/9
	3	0													
Bedogni (2011) [49]	0	9										8/9			
	1	1										0/1			
	2	9										8/9			
	3	11										11/11			
Ferlito (2011) [20]	1	8				8/8									
	2	86	0/3			83/83									
	3	0													
Lemound (2011) [45]	1	11								10/11					
	2	9								8/9					
	3	0													
Martins (2011) [24]	1	9	1/3		3/4				1/2						
	2	10			0/1				8/9						
	3	3							3/3						
Wilde (2011) [46]	1	6								6/6					
	2	12								12/12					
	3	15								11/15					
Mozzati (2012) [52]	1	0													
	2	32											32/32		
	3	0													
Schubert (2012) [47]	1	13								11/13					
	2	22								21/22					
	3	14								12/14					
Vescovi (2012) [27]	1	36	1/4	3/6	3/3			4/7						16/16	
	2	118	5/22	8/30	8/13			25/32						18/21	
	3	12	0/6	0/1	0/1									4/4	
Voss (2012) [48]	1	0													
	2	15								13/15					
	3	5								5/5					
Total healings (healings/treated)															
0												8/9			
1			2/9	3/6	6/7	8/8	7/12	4/7	1/2	27/31		0/1		16/16	1/1
2			5/25	8/30	12/33	83/83	21/32	25/32	8/9	74/78		8/9	32/32	23/26	6/9
3			0/6	0/1	0/1		0/7		3/3	38/47	1/4	11/11		4/4	

antibiotic therapy, suspension of BP treatment and LLLT [38]. Total healing rates for laser surgical approaches were 100% in Stage 1, 83% in Stage 2, and 100% in Stage 3.

Discussion

Systematic reviews exhaustively search for, identify, and summarize the available evidence on clinical topics, especially controversial ones. Initial reports and some latter studies regarding BRONJ treatment reporting that surgical therapy could not provide complete healing [15,28,2,55] led to the assumption that patients should undergo palliative therapies rather than pursue complete healing with more aggressive interventions. According to these results, the 2009 AAOMS position paper provided the following raccomandations for the clinical management of patients with BRONJ: Stage 1 patients should control infection of exposed bone

Table 6
Cumulative results of treatment outcomes for the selected studies for each disease stage basing on AAOMS staging system [5].

Stage (AAOMS [5])	Nonsurgical approach	Conservative surgery	Extensive surgery	Laser surgery
0			8/9 89%	
1	5/15 33%	26/36 72%	27/31 87%	17/17 100%
2	13/55 24%	149/189 79%	114/119 96%	29/35 83%
3	0/7 0%	3/11 27%	50/62 81%	4/4 100%

with antimicrobial rinses (Chlorhexidine 0,12%) and improving and maintaining oral hygiene; Stage 2 lesions require antibiotic therapy in combination with oral antimicrobial rinses; patients in Stage 3 should undergo surgical debridement to smooth the exposed bone surface to minimize traumatic ulceration of the adjacent soft tissue, or resection of the necrotic bone fragments in combination with antibiotic therapy for long-term palliation with resolution of acute infection and pain [5]. Since several recent studies have proposed other types of therapeutical approaches, the Authors performed a systematic review of the available literature to evaluate their effectiveness. Unfortunately, as reported in the review results there is high heterogeneity among study designs and protocols, and most of the studies regarding BRONJ treatment are non-randomized cohort, case-control or observational interventional basic research studies. Such studies are more exposed to potential biases such as publication bias, selection bias, systematic and nonsystematic errors, and interferential errors, which makes combining data and performing meta-analysis of observational studies is challenging and controversial, potentially leading to problematic interpretation of exposure effects [56]. Therefore, the main limit of the present review is the restriction of statistics to descriptive analysis only. Although, risk of bias has been reduced through quality assessment procedures.

Considering the limitations of the present study, the results show how it seems possible to reach high rates of stabile complete mucosal healing. When treatment modalities were not divided basing on disease stages, medical therapy resulted to be the less effective, LLLT or HBO. Conservative surgery provided healing to more than half of the patients treated in almost all the included studies. Extensive surgery and laser surgery seem to provide the highest healing results. When treatment modalities for single stages were evaluated, the results were very similar. Despite of the AAOMS treatment recommendations, healing seems to be an attainable outcome in all stages. Furthermore, the outcome results for every BRONJ stage were low when patients were treated with nonsurgical therapies, higher when treated with conservative surgery and the highest when treated with extensive surgery or extensive laser assisted surgery. The healing outcomes vary between stages when nonsurgical and conservative surgical procedures were performed, decreasing from Stage 0 to 3. On the other hand, healing outcomes are very similar in all stages when extensive or extensive laser surgical procedures were performed.

In conclusion, a surgical approach to BRONJ lesions seems to be the more effective overall and in every disease stage, but more randomized controlled studies are needed to confirm this statement providing higher levels of evidence.

Conflict of interest statement

None of the authors have any commercial affiliations or consultant roles that could be construed as a conflict of interest.

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