

Self-reported allergy to penicillin and clindamycin administration may be risk factors for dental implant failure: A systematic review, meta-analysis and delabeling protocol

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Abstract

Objective: Growing evidence is highlighting the inefficacy of clindamycin as an effective substitute to amoxicillin in patients self-reporting a penicillin allergy. The hypothesis is that implant failure is higher in these patients, when compared to patients receiving penicillin. To test this hypothesis, a systematic review and meta-analysis was undertaken and a protocol for delabeling penicillin allergic patients was presented.

Materials and Methods: A systematic review was undertaken by searching across three different databases, namely PubMed, Scopus and Web of Science.

Results: Out of 572 results, four studies were eligible to be included. Fixed-effects meta-analysis showed a higher number of failed implants in patients who were administered clindamycin, because of a self-reported allergy to penicillin. Results showed that these patients are over three times more likely (OR=3.30, 95% C.I. 2.58–4.22, p -value < .00001) to undergo implant failure with an average cumulative proportion of 11.0% (95% C.I. 3.5–22.0%) versus 3.8% (95% C.I. 1.2–7.7%) of patients not requiring clindamycin and administered amoxicillin. A protocol for penicillin allergy delabeling is proposed.

Conclusions: Current evidence is still limited and based on retrospective observational studies, it is difficult to state if penicillin allergy, clindamycin administration or a combination of both is responsible for the current trends and reported findings.

KEYWORDS

clindamycin, dental implants, meta-analysis, penicillins, peri-implantitis

1 | INTRODUCTION

The patient population receiving dental implants has increased significantly over the last decade. While the success rate of dental implants remains very high, there are surgical, prosthetic, and biological factors that can adversely affect outcomes (Basma & Misch, 2021; Canullo et al., 2016; Pjetursson et al., 2014). Among the biological factors where clinicians may help reduce the rate of implant failure

(French et al., 2015), the administration of antibiotics in the peri-operative setting has emerged as an important variable (Block et al., 2021; French et al., 2016; Salomo-Coll et al., 2018; Zhurakivska et al., 2022). The oral cavity hosts over 600 bacterial species which could contribute to implant contamination and surgical site infection leading to implant treatment failure (Canullo et al., 2021). Therefore, administration of antibiotics has acquired both a preventive and therapeutic role in implant patient management (Duval et al., 2019;

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Salgado-Peralvo et al., 2021). Currently, the most used antibiotic in dentistry is amoxicillin (Bongaerts & Lyster, 1994; Mainjot et al., 2009). As with any antibiotic, the clinician should be aware of potential adverse effects such as hypersensitivity reactions, dermatological and allergic disorders (Rodriguez Sanchez et al., 2020). Approximately 7% of the population have a penicillin allergy label in their electronic health record. Of this patient population, less than 5% will experience an active clinically significant immunologically mediated hypersensitivity (Liang et al., 2020; Shenoy et al., 2019). The rate of unconfirmed penicillin allergy rises with increasing age and increasing levels of healthcare utilization, reaching up to the 10% range (Shenoy et al., 2019). Despite this, most importantly, only 0.01% of patients will experience a life-threatening adverse effect (Bhattacharya, 2010).

When patients requiring dental implants present with penicillin allergy, the normal course of action taken by most clinicians has been to give a substitute antibiotic, usually clindamycin (Deniz-Sungur et al., 2020; Ireland et al., 2012; Santamaria Arrieta et al., 2022; Segura-Egea et al., 2017; Yingling et al., 2002). Indeed, the recently published Consensus Report by the Italian Academy of Osseointegration recommends the administration of 600mg of clindamycin, 1h before the intervention in straightforward cases, in patients with penicillin allergy (Caiazzo et al., 2021). However, the consensus report on preventive antibiotic therapy with dental implants from Spanish Society of Implants does not recommend the same (Salgado-Peralvo, Garcia-Sanchez, et al., 2022). This regimen emerged as the most used among clinicians in the United Kingdom (Ireland et al., 2012) Spain (Camacho-Alonso et al., 2019) and Belgium (Santamaria Arrieta et al., 2022). Despite the widespread use of clindamycin as a substitute, current evidence is based only on retrospective studies about the clinical efficacy of clindamycin and only one randomized clinical trial has been published on this topic. (Romandini et al., 2019; Salgado-Peralvo et al., 2021; Salgado-Peralvo, Pena-Cardelles, et al., 2022; Santamaria Arrieta et al., 2022). Arrieta et al. found that pre-operative 600mg clindamycin did not reduce implant failure or post-surgical complications; however, patients allergic to clindamycin were originally excluded and allergy testing was not performed on included patients (Santamaria Arrieta et al., 2022). Similarly, clindamycin use was ineffective in third molar surgery patients (Arteagoitia et al., 2022), while exhibiting a higher adverse-effects profile (Arteagoitia et al., 2022; Azher & Patel, 2021). The American Dental Association advised against the use of clindamycin in patients with penicillin allergy due to serious reported adverse effects, such as pseudomembranous colitis induced by *C. difficile* (Azher & Patel, 2021; Santamaria Arrieta et al., 2022). Moreover, Salomo-Coll et al. (2018) reported that penicillin allergic patients treated with clindamycin had a fourfold higher risk of implant failure; Basme and Mitch reported in 2021 that the use of clindamycin after socket graft and ridge augmentation procedures was associated with a higher rate of infection and complications (Basma & Misch, 2021). Numerous other publications have documented that the use of beta-lactam antibiotics, including amoxicillin, when

used as the antibiotic of choice for a variety of bacterial infections and clinical settings, are associated with improved outcomes (Blumenthal et al., 2015; Elliott et al., 2009; Koliscak et al., 2013; MacFadden et al., 2016; Murphy et al., 2017). Moreover, it is now known that penicillin allergy delabeling is easy to accomplish, safe, effective and reduces healthcare utilization and patient morbidity (Chua et al., 2021; Macy & Shu, 2017; Staicu et al., 2020).

In this complex scenario, the aim of this systematic review and meta-analysis is to test the hypothesis that implant failure is higher in patients receiving clindamycin as a substitute to penicillins because of a self-reported allergy, when compared to patients receiving penicillin; and to present a protocol for delabeling penicillin allergic patients, thereby improving clinical outcomes with dental implant placement.

2 | REVIEW

The present systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al., 2021). The protocol was submitted and registered in the PROSPERO database: CRD42022343716.

2.1 | Search strategy and database screening

PubMed, Scopus and Web of Science were screened to identify fitting articles using the following search terms, in combination or alone. The PubMed database was searched as follows: (("dental implants" OR "implant dentistry") AND ("implant failure" OR failure OR "implant loss") AND ("antibiotic prophylaxis" OR amoxicillin OR penicillin OR preventive OR "self-reported allergy") AND ("drug hypersensitivity" OR "adverse effects" OR "antibiotics allergy" OR "penicillin allergy" OR complications)). The Scopus database was searched as follows: TITLE-ABS-KEY (((("dental implants" OR "implant dentistry") AND ("implant failure" OR failure OR "implant loss") AND ("antibiotic prophylaxis" OR amoxicillin OR penicillin OR preventive OR "self-reported allergy") AND ("drug hypersensitivity" OR "adverse effects" OR "antibiotics allergy" OR "penicillin allergy" OR complications))). The Web of Science database was set to "All databases" and topic input was as follows: (("dental implants" OR "implant dentistry") AND ("implant failure" OR failure OR "implant loss") AND ("antibiotic prophylaxis" OR amoxicillin OR penicillin OR preventive OR "self-reported allergy") AND ("drug hypersensitivity" OR "adverse effects" OR "antibiotics allergy" OR "penicillin allergy" OR complications)). The first search was performed on 22nd June 2022 and the last search was performed on 19th September 2022. In addition, a hand search was performed by screening of references of included studies. EndNote reference software program (Endnote X9.3.2, Clarivate Analytics) was used to automatically discard duplicates, which were verified manually in the resulting list.

2.2 | Eligibility criteria

2.2.1 | Inclusion criteria

For the above-mentioned search, no restriction for year of publication was set. Studies were screened based on the following inclusion criteria: (1) English language; (2) Cohort, case-control and observational retrospective studies; (3) Patients aged over 18 years old, healthy, in need of non-traumatic tooth extraction, followed by dental implant treatment; (4) For the test group, patients had to self-report a penicillin allergy.

2.2.2 | Exclusion criteria

The exclusion criteria were as follows: (1) Case reports, case series, systematic review and meta-analysis and studies not including information outcomes for patients reporting penicillin allergy; (2) Studies with patients undergoing radiotherapy of head and neck; (3) Patients with bone disease, and with uncontrolled systemic diseases for which implant therapy is not suitable in a clinical setting; (4) Cell-line or animal model studies; (5) Cases with multi-antibiotics administration.

2.3 | Focused PICO question and effect measure

Participants: patients undergoing dental implant treatment with a self-reported penicillin allergy, who were administered peri-operative antibiotics.

Intervention: peri-operative penicillin.

Comparison: peri-operative clindamycin.

Outcome: implant failure.

To be eligible for inclusion in the meta-analysis, the outcome had to be reported as number of implant failures in both the intervention and comparison group over total number of implant treatments in each group.

2.4 | Studies screening and inclusion

Two authors (NE and AILP) independently screened for retrieved citations, by reading of title and abstract. Both authors ended up with a list to screen for full-text eligibility assessment, following inclusion and exclusion criteria. Kappa coefficient was calculated to quantify the reviewers' agreement. The third author (VCAC) was involved in making a final decision in case of disagreements. Kappa coefficient was 0.88 which showed excellent agreement. This coefficient was calculated after full-text assessment of eligible studies (24 studies).

2.5 | Data extraction

Similarly, data extraction was undertaken by two reviewers (NE and VCAC), independently and results were compared and merged

by using an ad hoc extraction sheet. In case of discrepancy, articles were re-screened in a joint meeting with the third reviewer (AILP). The extraction sheet in Excel format included the following fields: first author surname, year of publication and country in which the study was performed; percentages of implant failures in both groups; followed by the antibiotic prescription therapy in both groups.

2.6 | Assessment of risk of bias

Newcastle–Ottawa scale was employed for cohort studies included in this systematic review and meta-analysis. Newcastle–Ottawa scale for cohort studies includes eight domains with different items content. Each item was scored 1 point, while the item comparability was scored a maximum of 2 points. A study rated from 6 to 9 points is considered as low risk of bias, from 3 to 5 points with medium risk of bias, while 0–2 is considered as high risk of bias (Forte et al., 2022; Stang, 2010). Two authors (NE and AILP) independently performed such assessment and discrepancies were resolved in a joint meeting with the third reviewer (VCAC).

2.7 | Statistical analysis

Data were matched by the number of failed implants in the total number of implants placed for the penicillin allergic group administered clindamycin versus the number of failed implants in the total number of implants placed for patients administered penicillins. Data were input as dichotomous and inverse variance method was applied to weight studies and to estimate their 95% confidence interval odds ratio (OR) and overall effect. To graphically display each study and their pooled proportions, a forest plot was generated by the fixed effects model. Heterogeneity between studies was assessed by Cochran's Q test and quantified by I^2 index. Since I^2 resulted in 0%, absence of heterogeneity was assumed and a fixed effects model was set for running the meta-analysis (Higgins & Thompson, 2002). Meta-regression was performed to inspect the impact of total follow-up time and publication year on effect size. The leaving one out strategy was used to examine how individual studies affected the overall standardized mean difference (Willis & Riley, 2017). Furthermore, a funnel plot was created to visually depict publication bias and was combined with trim and fill analysis, Egger's test, and the safe N test (Duval & Tweedie, 2000; Egger et al., 1997; Persaud, 1996).

By setting an acceptable risk of type one errors (α) at 5% with a power of 80%, trial-sequential analysis (TSA) was performed to explore the power of the meta-analysis result. Dichotomous data were input as number of events and total number between the two groups. OR was used as a measure in a fixed effects model (Wetterslev et al., 2017). Trial sequential monitoring boundaries were displayed with the cumulative sample size. Variance-based model was used to correct for heterogeneity. TSA generated a graphical view of the

required information size (RIS) and the cumulative Z-curve in relation to the monitoring and futility boundaries according to one and two error values. RIS was estimated based on user input % incidence in intervention and control arms, which was respectively 0.2% and 0.05%.

MedCalc® Statistical Software version 20.218 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2023) was employed for proportional meta-analysis to summarize the overall proportion of failed implants in patients with self-reported penicillin allergy and administered clindamycin versus patients who were administered amoxicillin. Events and total sample for each group were input separately on the online platform of the software. Freeman–Tukey transformation test was set as the statistical method to retrieve 95% confidence intervals in a random effects model.

3 | RESULTS

3.1 | Study selection

The last updated search reported 572 results and each study reference was downloaded from each database (PubMed=329, Scopus=145, Web of Science=98) and imported into EndNote reference software program (Endnote X9.3.2, Clarivate Analytics). Of all the references included, 197 were automatically discarded by the software as duplicates, and the resulting 375 references were screened manually for duplicates. Eleven duplicates were deleted, giving 364 articles to be screened for title and abstract. Of these studies, 340 were removed, resulting in 24 articles screened by full-text; 20 studies were excluded (list and reason for exclusion are summarized in Table S1) and four were deemed fit to be included in the systematic review and meta-analysis. A graphical representation of the search strategy and screening is shown in Figure 1.

3.2 | Risk of bias assessment

Risk of bias results were low for all the included studies (Table S2). Even though Zahra et al. (2022) did not report posology, it was clearly indicated that patients were administered amoxicillin and clindamycin properly, based on current clinical standards. For this reason, the item “ascertainment of exposure” was scored 1 point; since attributing a 0 score to that item would not have changed the overall score, resulting in an overall low risk of bias.

3.3 | Study characteristics

Four studies (French et al., 2016; Salomo-Coll et al., 2018; Wagenberg & Froum, 2006; Zahra et al., 2022) were included, investigating differences about implant failure percentages between patients administered amoxicillin versus self reported penicillin allergic patients administered clindamycin. One study was published

in 2006 (Wagenberg & Froum, 2006), while the other three studies were published between 2016 and 2022 (Table 1). Two studies were performed in the USA (Wagenberg & Froum, 2006; Zahra et al., 2022), one in Canada (French et al., 2016) and one in Europe (Salomo-Coll et al., 2018). In all the studies, patients had self-reported allergy to penicillins and no clinical or laboratory test was used for confirmation. Two studies reported follow-up data of 16 and 10 years (French et al., 2016; Wagenberg & Froum, 2006) while Salomo-Coll et al. (2018) and Zahra et al. (2022) had follow-up of 1 year. All the included studies had a retrospective cohort nature of design (French et al., 2016; Salomo-Coll et al., 2018; Wagenberg & Froum, 2006; Zahra et al., 2022).

A total of 10,853 implants were evaluated, of which, 9643 (88.85%) implants were placed in patients who were administered amoxicillin and 1210 (11.15%) implants were placed in patients who self-reported an allergy to penicillins and were prescribed clindamycin. In all the studies, amoxicillin was prescribed to non-penicillin allergic patients, while clindamycin was prescribed to all the patients with self-reported allergy to penicillins. Amoxicillin administration was commonly prescribed prior and/or after implant treatment. The most common posology was 2g prior to implant placement which was reported in three studies (French et al., 2016; Salomo-Coll et al., 2018; Zahra et al., 2022); while in the Wagenberg & Froum (2006) study, 500mg every 6h for 2 days were prescribed. Post treatment posology for amoxicillin followed different protocols, from a single postoperative dose (French et al., 2016) to 7 (Salomo-Coll et al., 2018; Zahra et al., 2022) – 10 days (Wagenberg & Froum, 2006). Posology in penicillin-allergic patients was heterogeneous. Zahra et al. did not report the posology for clindamycin (Zahra et al., 2022). Administration of 600mg prior to implant treatment was administered in two studies (French et al., 2016; Salomo-Coll et al., 2018), followed by no postoperative antibiotics in the French et al study; and 300mg of clindamycin every 6h for 7 days post operatively in the Salomo-Coll et al study (Table 1). A total of 114 implants failed in the clindamycin group, for 1210 implants placed, versus 252 failed implants in the amoxicillin group, for 9643 implants placed.

3.4 | Meta-analysis and trial-sequential analysis

All the included studies were eligible for the meta-analysis. Weighted proportional meta-analysis for failed implants in the amoxicillin group reported a cumulative percentage of 3.8 (95% C.I. 1.2–7.7%). Of 9643 implants placed in patients prescribed amoxicillin, 252 failed, with heterogeneity I^2 among studies of 98.3%. Highest number of failed implants was 8.4% (95% C.I. 5.9–11.5%) in the Zahra et al study (Zahra et al., 2022), while the lowest number was 0.8% (95% C.I. 0.5–1.0%) in the French et al study. (French et al., 2016) (Figure 2).

Similarly, proportional meta-analysis for implant failure in patients with self-reported allergy to penicillins and prescribed clindamycin reported a cumulative percentage of 11.0 (95% C.I.

FIGURE 1 PRISMA 2020 flow diagram of the screening process. In total, 4 studies were included in the present systematic review and meta-analysis.

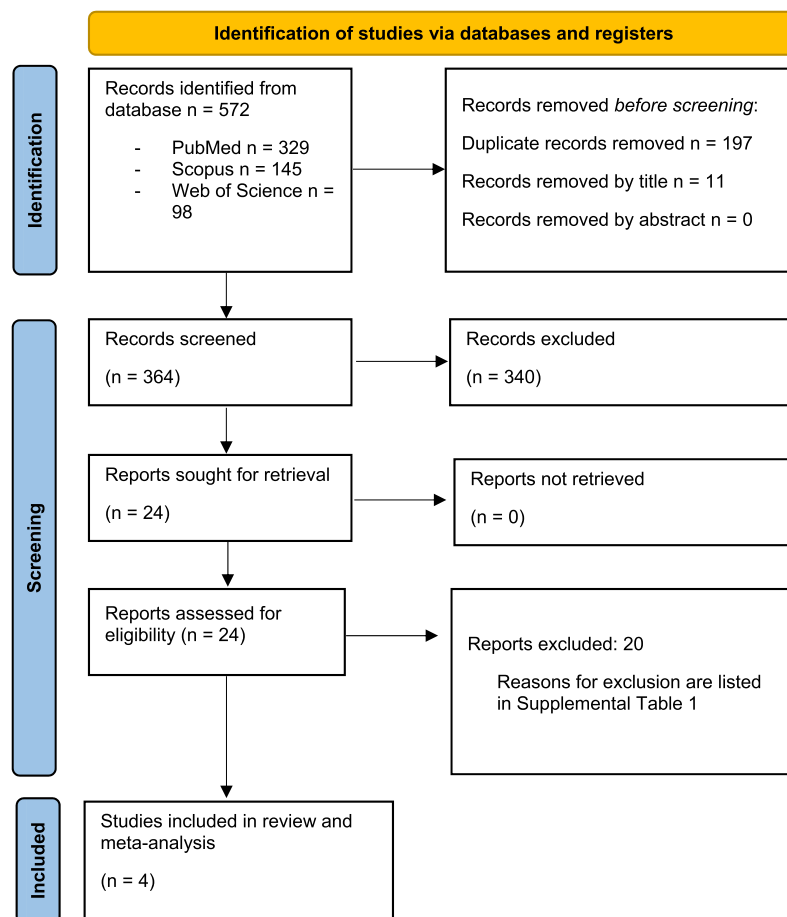


TABLE 1 Characteristics of the included studies.

Author Year, Nationality	No of implants test/ Control	Failed in test	Failed in control	Antibiotics prescription test	Antibiotics prescription control	Follow-up	Study design
Wagenberg & Froum, 2006, USA	364/1561	8.52%	2.95%	300mg every 6 h for 2 days prior and after for 10 days	500mg amoxicillin every 6 h for 2 days prior and after for 10 days	16 years	Retrospective cohort study
French et al., 2016, Canada	470/5106	2.10%	0.80%	600mg clindamycin 1 h prior and no postoperative dose	2g amoxicillin 1 h prior and 500mg 8 h as a single postoperative dose	10 years	Retrospective cohort study
Salomo-Coll et al., 2018, Spain	175/2572	18.86%	5.17%	600mg clindamycin 1 h prior and 300mg every 6 h for 7 days	2g amoxicillin 1 h prior and 750mg three times a day for 7 days	1 year	Retrospective cohort study
Zahra et al., 2022, USA	201/404	19.90%	8.40%	Clindamycin not specified regimen	2g amoxicillin 1 h prior and 500mg three times a day for 7 days	1 year	Retrospective cohort study

3.5–22.0%). Of 1210 implants placed in these patients, 114 failed with heterogeneity I^2 among studies of 96.2%. Highest percentage of failures (19.9%) was reported by Zahra et al. (2022) (95% C.I. 14.6–26.1%) while, French et al. (2016) reported the lowest at 2.1% (95% C.I. 1.0–3.8%; Figure 3).

Meta-analysis was also performed to pool single study proportions and estimate the overall OR. For the administration of clindamycin, these patients were 3.30 times (95% C.I. 2.58–4.22) more likely to experience implant failure compared to patients administered penicillin, p -value < .00001. Absence of heterogeneity among

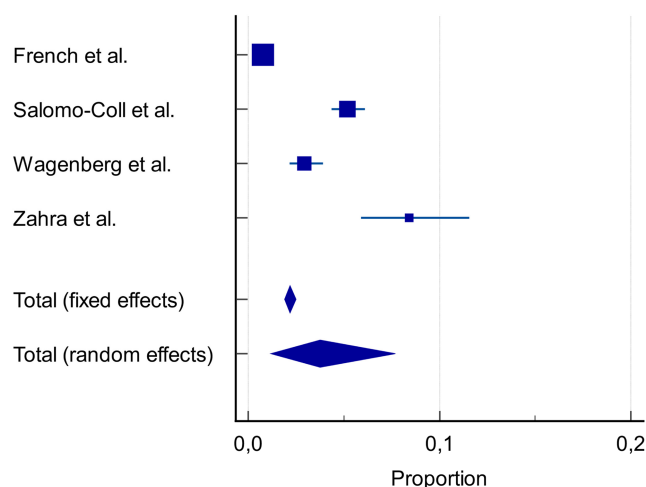


FIGURE 2 Proportional meta-analysis for number of failed implants in patients administered amoxicillin.

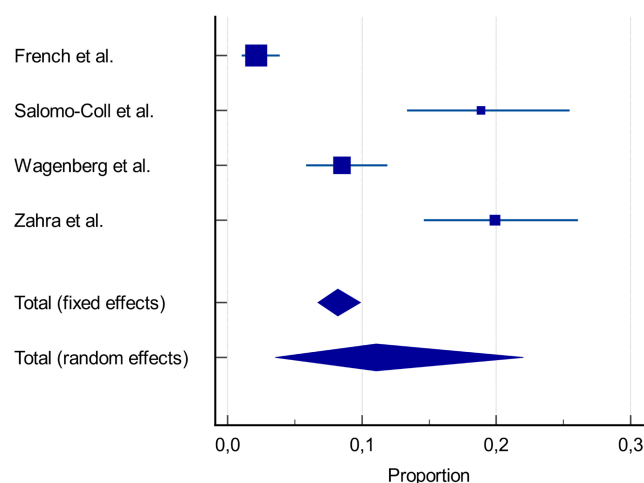


FIGURE 3 Proportional meta-analysis for number of failed implants in patients self-reporting allergy to penicillins and administered clindamycin.

studies was confirmed by $I^2=0\%$ (Figure 4). Sensitivity analysis (leave one out) did not show particular changes in estimated ORs (Figure S1). Meta-regression (fixed effects model) did not find statistically significant correlation between estimated effect size and both clinical follow-up (p -value=0.629) and publication year (p -value=.931). Zero studies were trimmed (Figure S2), and Egger's linear regression test failed to show publication bias (p -value=.379). Results were further supported by Fail Safe N 83 studies needed to reverse the statistically significant association. However, these results should be taken with caution, since the presence of small-study effects on the prevalence of implant failure on patients with self-reported allergy should be considered; the above mentioned methods may lack statistical power when the number of included studies is <10 (Sterne et al., 2011). Furthermore, simulation analyses pointed out a high type 1 error rate (i.e., false positives) assessing publication bias in meta-analysis of proportion studies with rare

	ES	95% CI	W	
French 2016	2.82	1.40 . 5.69	12.39%	■
Salomó-Coll 2018	4.26	2.81 . 6.47	35.04%	■
Wagenberg 2006	3.07	1.92 . 4.91	27.51%	■
Zahra 2022	2.70	1.65 . 4.43	25.05%	■
Overall (fixed-effect model)	3.30	2.58 . 4.22	100.00%	◆

FIGURE 4 Comparative meta-analysis for number of failed implants in patients self-reporting allergy to penicillins and administered clindamycin, versus patients who had taken amoxicillin (OR=3.30, 95% C.I. 2.58–4.22, p -value < .00001).

outcomes, despite it being suggested that funnel plots of study size against odds may be a more accurate way of publication bias assessment in these studies (Hunter et al., 2014). In these meta-analyses, the effect size although in the same direction, varied widely across the studies. So, instead of admitting a precise mean effect size, we consider essential the research carried out to discover the origin of this variation (i.e., search for sources of heterogeneity and study subpopulations). Nonetheless, primary data prevented to produce a proper subgroup analysis. In this vein, further studies should focus on improving knowledge about these aspects, and we hope that the results of our meta-analysis can serve as a guideline.

Results from this meta-analysis were confirmed by the TSA. The RIS for this meta-analysis was 17,421 (versus 10,853). Trial sequential significance boundary was crossed by the cumulative Z curve after the second study, by French et al.'s study and was added to the meta-analysis (French et al., 2016). Administering clindamycin was related to a higher implant failure rate compared to amoxicillin, even if the sample size of this meta-analysis did not reach the RIS. Additional studies are required in order to reach the RIS (Chai-Adisaksopha et al., 2016; Wetterslev et al., 2008) (Figure S3).

4 | DISCUSSION

This is the first meta-analysis demonstrating a higher number of failed implants in patients who were administered clindamycin because of a self-reported allergy to penicillin than in patients who were administered penicillin. Results showed that patients will be over three times more likely (OR=3.30, 95% C.I. 2.58–4.22, p -value < .00001) to undergo an implant failure with an average cumulative proportion of 10.5% (95% C.I. 4.6–18.5%) if they were administered clindamycin.

In 2006, Wagenberg & Froum (2006) reported in their retrospective study that there was an increased risk of implant treatment failures and surgical complications in patients who were administered clindamycin. Clindamycin is traditionally the drug of choice in patients self-reporting allergy to penicillins (Deniz-Sungur et al., 2020; Ireland et al., 2012; Santamaria Arrieta et al., 2022;

Segura-Egea et al., 2017; Yingling et al., 2002) and only recently some concerns have emerged in the scientific community about the detrimental effects of clindamycin as related to implant success. Indeed, most of the evidence is based only on retrospective studies. However, all the studies included in this meta-analysis found higher rates of implant failures in patients administered clindamycin compared to patients who were given amoxicillin (French et al., 2016; Salomo-Coll et al., 2018; Wagenberg & Froum, 2006; Zahra et al., 2022). Similar results were also found by Arteagoitia et al. They performed a systematic review and meta-analysis of randomized controlled trials using clindamycin in oral surgery. Poor evidence emerged and the meta-analysis was only possible for patients undergoing third molar extraction. Even in this procedure, clindamycin resulted ineffective in preventing post-operative complications (Arteagoitia et al., 2022). Basma and Mitch reported in 2021 that the use of clindamycin after socket graft and ridge augmentation procedures was associated with a higher rate of infection and complications [2]. Similar results were obtained in other studies with different applications in oral and maxillofacial surgery and oncology (Block et al., 2021; Langerman et al., 2016; Murphy et al., 2017; Roistacher et al., 2022; Weber et al., 1992). In June 2022, in a letter to the editor, Salgado-Peralvo et al. highlighted the worrying scenario of prescribing clindamycin in patients self-reporting allergy to penicillins; calling for future clinical trials to assess the role of both the allergic profile and the action of clindamycin itself (Salgado-Peralvo, Pena-Cardelles, et al., 2022). A recently published clinical trial by Arrieta et al. paved the way for this scenario. In their study, using clindamycin as prophylaxis in oral implant surgery resulted in no reduction of oral implant failures. Of great interest, they excluded patients self-reporting allergy to penicillins, trying to solve the controversy in implant failure (Santamaria Arrieta et al., 2022). The biological mechanisms behind higher failure rates in patients allergic to penicillin taking clindamycin is still unknown (French et al., 2016; Zahra et al., 2022). Clindamycin has been found to impact osteoblasts viability in vitro, hypothetically causing a disturbance in osteointegration (Düwelhenke et al., 2007; Naal et al., 2008; Zahra et al., 2022). Some authors found higher rates of post-operative infections in clindamycin administered patients, and infection is a major factor for implant failure (French et al., 2016; Wagenberg & Froum, 2006). The quantities of resistant *Prevotella* species in saliva may rise as a result of clindamycin administration (Rashid et al., 2015), and are frequently discovered in implants with peri-implantitis (Lafaurie et al., 2017). In this regard, an in vitro investigation discovered that more pathogenic species, including *Prevotella intermedia*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans*, are resistant to clindamycin at therapeutic concentrations (Rams et al., 2013). Moreover, few studies have connected the use of antibiotics other than beta-lactams in prescriptions to a rise in methicillin-resistant *Staphylococcus aureus* (Wyles et al., 2019). These clindamycin-resistant bacteria have been discovered in high concentrations in implants with peri-implantitis (Persson & Renvert, 2014). For example, *Staphylococcus*

aureus is involved in the early colonization process of implant, and could still be there even a year later, increasing the chance of developing peri-implantitis in the future and explaining late failures (Charalampakis et al., 2012; Salvi et al., 2008). A connection between genetic polymorphisms in penicillin-allergic patients and an increased risk of implant failure has not yet been explored.

In this meta-analysis of 10,853 implant treatments, 1210 (11.15%) were placed in patients self-reporting allergy to penicillins and were prescribed clindamycin. In this context, penicillin allergy delabeling can be an important part of antibiotic stewardship (Roistacher et al., 2022). However, current evidence is based on retrospective studies, lacking proper methodological assessment of penicillin allergy. Further investigations are needed to address the role of penicillin allergy, clindamycin administration and the reliability and validity of allergy delabeling protocols. There is an increase of studies addressing penicillin allergy testing in hospitalized patients. These studies demonstrate that penicillin allergy testing may be done safely on hospitalized patients, being feasible and an easy measure to delabel a large proportion of patients (Steenvoorden et al., 2021), and point to better results, such as a reduction in the need for vancomycin, and financial savings (Macy & Contreras, 2014; Sacco et al., 2017; Sousa-Pinto et al., 2021). In both inpatient and outpatient settings, formal penicillin allergy evaluation programs are becoming more prevalent and dental offices may be a crucial location for this purpose (Vivo et al., 2022). Amoxicillin is the antibiotic that dentists most frequently recommend, and medications based on penicillin are still the first line of defense for the majority of tooth infections (Roberts et al., 2017). Nowadays, there is a lack of simple decisional algorithms to guide and assist dentists in penicillin allergy delabeling; while dentists' precise function in a penicillin allergy program is still unknown. Dentists with a busy practice might not want to take on more clinical duties, or they might not have much training or experience in performing allergy evaluations. Also, it is unknown how patients may react to an oral amoxicillin challenge or a skin test for penicillin allergies in a dental setting (Wanat et al., 2018). Future studies should look into these concerns (Vivo et al., 2022).

We therefore propose a protocol for penicillin allergy delabeling in patients who need dental implant placement, which could be employed in future investigations (Table 2). Penicillin allergy delabeling is defined as the removal of the designation of penicillin allergy from the patient's health record, after testing.

If testing is carried out in a clinical setting, then it should be performed by a qualified allergist or a clinician experienced in drug challenges and managing acute hypersensitivity reactions. A thorough drug allergy history is essential. There are two risk profiles: low risk and higher risk. Low-risk patients include those who have had any clearly non-allergic symptoms such as gastrointestinal symptoms, headaches, anxiety, pruritis without rash, benign rashes of any kind more than 1 year ago, any unknown reactions, individuals with a family history of penicillin allergy who have never been exposed to penicillin, or who have tolerated penicillin after their index reaction and this index reaction did not require any testing to confirm current

Risk profile	Low risk	High risk
History	Nonallergic symptoms such as gastrointestinal symptoms, other benign symptoms, delayed onset benign rashes, hives more than 1 year ago, patients with a family history of penicillin allergy, pruritis without rash or any unknown reactions (>10 years ago) which do not indicate an IgE-mediated reaction	Anaphylaxis or any other IgE mediated reaction, urticarial eruptions within 1 h of the 1st dose and regression within 1 day (1-1-1 criterion) of any beta lactam antibiotic, compromised hemodynamic status, pregnancy
Test	Amoxicillin 250mg oral challenge with 1 h of observation	Skin testing and if negative proceed to Amoxicillin 250mg oral challenge with 1 h of observation

TABLE 2 Protocol for penicillin allergy delabeling in patients requiring dental implants in research setting environment.

tolerance (Shenoy et al., 2019). The vast majority of patients are low risk and would only need an oral challenge with a single therapeutic dose, amoxicillin 250mg and 1 h of observation. If no reaction is observed, then these patients can be safely delabeled. The clinician should inform the patient of a small risk (2–3%) of a delayed onset, benign, often non-itchy rash over the next 2–5 days. If the patient develops this kind of rash and has already started a typical post implant therapeutic course of amoxicillin, then the course may be completed. If a blistering rash or systemic symptoms occur, the antibiotic should be stopped, and the allergist informed immediately.

Higher risk patients will need skin testing with an approved skin test, such as benzylpenicilloyl polylysine injection USP (Pre-Pen®, ALK-Abello). If the skin test is negative, an oral challenge is given with a single therapeutic amoxicillin 250mg dose and 1 h of observation to confirm current acute tolerance. Penicillin skin testing can serve as a useful test to exclude hypersensitivity, with a negative predictive value close to 100% (Roistacher et al., 2022).

An acute-onset hypersensitivity reaction (IgE-mediated) typically occurs within 1 h of the exposure and is manifested by hives and sometimes hypotension or anaphylaxis, and completely clears within 1 day (Sabato et al., 2021). These relatively rare higher risk individuals constitute the majority of individuals who may benefit from penicillin skin testing prior to an oral amoxicillin challenge with a single 250mg dose to confirm current tolerance. Most patients, however, are low risk and can be delabeled with only a single oral 250mg amoxicillin challenge and 1 h of observation to confirm current tolerance (Banks et al., 2019; Gateman et al., 2021; Goh et al., 2021; Livirya et al., 2022; Macy & Poon, 2009; Macy & Vyles, 2018). Any patient who has had urticarial eruptions within 1 h of the 1st dose and regression within 1 day (1-1-1 criterion) (Sabato et al., 2021) of any beta lactam antibiotic is a higher risk patient. Patients who are pregnant and with any compromised hemodynamic status are also considered higher risk. Patients with a history of any severe cutaneous adverse reaction (SCAR) syndromes such as Stevens–Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS) cannot undergo skin testing or oral challenges, outside of a protected research setting environment. Such patients account for less than 1 in 10,000 reported penicillin allergies (Liang et al., 2020; Shenoy et al., 2019).

5 | CONCLUSION

Growing evidence is highlighting the inefficacy of clindamycin as an effective substitute to amoxicillin in patients self-reporting a penicillin allergy. Current evidence is still limited and based on retrospective observational studies, and it is difficult to state if penicillin allergy, clindamycin administration or a combination of both are responsible for the current trends and reported findings. In light of this, new prospective clinical trials should be performed to better elucidate underlying mechanisms. While it is worth noting that antibiotic prescription aims to reduce early failures, the studies included in this meta-analysis reported both early and late failures. Authors reported that most failures occurred early; and in most cases it was not possible to discern between early and late failures. Future studies should aim at investigating early and late implant failures separately.

Penicillin allergy delabeling is currently rarely performed in dentistry. Many clinicians may not get a more detailed history of the allergy when they encounter a penicillin allergy label in the patient's chart, thereby continuing to inadvertently validate the self-reported penicillin allergy claim. Therefore, a paradigm shift is required in the management of such patients. The focus should be on penicillin allergy delabeling rather than selecting an alternative antibiotic regimen. Even though the protocol presented here relates to patients receiving dental implant therapy, we suggest the same protocol be applied to all penicillin allergic patients by testing in a protected research setting environment. This would not only reduce the risk of implant failure but could also potentially improve outcomes for patients, should they require healthcare utilization or hospitalization in the future.

AUTHOR CONTRIBUTIONS

Naushad R. Edibam: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); investigation (equal); supervision (equal). **Alejandro Ismael Lorenzo-Pouso:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); investigation (equal); software (equal). **Vito Carlo Alberto Caponio:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); investigation (equal); software (equal).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This does not apply to the current study design. Please refer to the original publications included in the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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