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Macrolides, quinolones, and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis

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ABSTRACT

Background: We evaluated the comparative effectiveness and safety of macrolides, quinolones, and amoxicillin/clavulanic acid (A/C) for the treatment of patients with acute bacterial exacerbation of chronic bronchitis (ABECB).

Methods: PubMed, Current Contents, and the Cochrane Central Register of Controlled Trials were searched to identify relevant randomized controlled trials (RCTs).

Results: Nineteen RCTs (20 comparisons) were included. There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, A/C and quinolones or A/C and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared with quinolones (OR= 0.47, 95% CI 0.31-0.69). Less quinolone-recipients experienced a recurrence of ABECB after resolution of the initial episode compared with macrolide-recipients during the 26-week period after therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of A/C was associated with more adverse effects (mainly diarrhea) than quinolones (OR= 1.36, 95% CI 1.01-1.85).

Conclusion: Macrolides, quinolones, and A/C may be considered equivalent for the treatment of patients with ABECB in terms of short-term effectiveness. Quinolones are associated with better microbiological success and fewer recurrence of ABECB than macrolides, while A/C with more adverse effects than both comparators.

Key words: chronic obstructive pulmonary disease, *Streptococcus pneumoniae, Haemophilus influanzea, Moraxella catarrhalis, Pseudomonas aeruginosa*

INTRODUCTION

Chronic bronchitis (CB), a disease of continuously increasing prevalence (1) that is associated with considerable morbidity, mortality, and cost is characterized by intermittent exacerbations manifested with at least one of the following symptoms: increased dyspnea, sputum production, and sputum purulence (2). There is evidence that flares of CB contribute to progressive loss of lung function (3), have a major impact on the quality of life (4), and account for a significant proportion of the cost of caring for these patients (5). In addition, exacerbations of CB requiring hospitalization are associated with an inpatient mortality of 3-4% (6), while 50% of those hospitalized patients who recover are readmitted at least once in the ensuing 6 months (7, 8). Thus, appropriate treatment of CB exacerbations seems to be compulsory.

At least 50% of the CB exacerbations are not bacterial in origin and, thereby administration of antimicrobial agents must be avoided. Only for the remaining half of CB exacerbations, which are presumably caused by bacteria, use of antibiotics seems to be of value (9). Indeed, two meta-analyses of randomized controlled trials (RCTs) performed in patients with acute CB exacerbations and comparing antibiotic to placebo agreed that in CB exacerbations with increased cough and sputum purulence antibiotics, regardless of choice, are beneficial (10, 11).

Although the beneficial role of antimicrobial agents for the management of patients with acute bacterial exacerbations of CB (ABECB) is supported by adequate evidence, there remains controversy whether the choice of antibiotic has any impact on the outcomes of such patients (12). Recent guidelines recommend the use of amoxicillin, trimethoprim/sulfamethoxazole (TMP/SMX), and doxycycline for the treatment of patients with ABECB (13, 14). However, the recommended first-line agents now have limited in vitro activity against a considerable proportion of pathogens frequently implicated in ABECB (i.e. *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis)* because of emergence of antimicrobial resistance in these bacteria. Moreover, a retrospective analysis of patients with ABECB showed that the administration of a broader spectrum antimicrobial agent [azithromycin, quinolone, or amoxicillin/clavulanic acid (A/C)] was associated with fewer clinical failures compared to the use of first-line agents (mainly amoxicillin, TMP/SMX, and doxycycline) (15).

Macrolides, quinolones, and A/C have been used extensively for the management of patients with ABECB. We sought to clarify further the role of the above broader spectrum antimicrobial agents for the treatment of patients with ABECB by performing a meta-analysis of RCTs that compared macrolides with quinolones, A/C with quinolones, or A/C with macrolides in this population.

METHODS

Data sources

We conducted a systematic literature search of PubMed (until May 2006), Current Contents, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant RCTs. The search strategy was the following: (*chronic obstructive pulmonary disease* OR *chronic bronchitis)* AND (*amoxicillin/clavulanic* OR *macrolides* OR *clarithromycin* OR *azithromycin* OR *quinolones* OR *levofloxacin* OR *moxifloxacin* OR *gemifloxacin)*. Search was limited in RCTs only. In addition, we hand-searched and reviewed the references of the initially identified articles, including relevant review papers. We did not search for abstracts presented in scientific conferences.

Study selection

Two investigators (IPK and IIS) independently performed the literature search and examined the retrieved relevant articles for further evaluation of data on effectiveness and toxicity. To be included, a study had to be a RCT, to study the role of macrolides in comparison with quinolones or the role of A/C acid in comparison with macrolides or quinolones for the treatment of patients with ABECB and to report data on effectiveness, toxicity, and/or mortality in the groups of patients receiving the compared therapeutic regimens. No restriction in time of publication was set. Only RCTs written in English, French, German, or Italian were included in our analysis. Trials with both blind and unblind design were included in our analysis. Both RCTs conducted in hospitalized patients and outpatients were included in the meta-analysis. On the contrary, trials that compared macrolides, quinolones, or A/C to an antibiotic other than one from these classes of antimicrobial agents or to placebo for the treatment of patients with ABECB were excluded. RCTs in which the same antibiotic or antibiotics of the same antimicrobial class was in both study arms were excluded. Also, RCTs in which the study drug has not been commercially available or it is no more used for the treatment of patients with ABECB were excluded from our meta-analysis. Finally, we

omitted RCTs that compared a ketolide (such as telithromycin) with a quinolone or A/C for the treatment of patients with ABECB.

Data extraction

Two reviewers (IPK and IIS) independently extracted and recorded data on a predefined checklist. Discrepancies were resolved by consensus or referral to a third reviewer (MEF). Extracted data included the following: year of publication, patient population, number of patients [enrolled, intention-to treat (ITT) and clinically evaluable (CE)], use of systemic corticosteroids before ABECB, antimicrobial agents and doses administered, clinical and microbiological outcomes, mortality, and toxicity outcomes. In addition, the 2 reviewers independently evaluated the methodological quality of each RCT by assessing the following components: randomization, generation of random numbers, details of double-blinding procedure, information on withdrawals, and concealment of allocation. One point was awarded for the specification of each criterion; the maximum score for a study is 5. High-quality RCTs were considered those that scored 3 or more points (low-quality RCTs those that scored 2 or fewer points) according to a modified Jadad score (16).

Definition of CB and ABECB

The criterion used for the diagnosis of CB in all RCTs included in the meta-analysis had to be a medical history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more consecutive years. Moreover, the ABECB had to be classified according to symptoms described by Anthonisen et al (2) as type I (who met all the following criteria: increases in amount of sputum, purulence of sputum, and dyspnea), type II (who met 2 of the above 3 criteria), or type III (who met only 1 of the above 3 criteria).

Analyzed outcomes

Treatment success (cure defined as resolution of all symptoms and signs of the bacterial exacerbation with a return to baseline condition, or improvement defined as subsidence of the ABECB but with an incomplete return to baseline condition) in ITT and CE patients, need for hospitalization during the study period in ITT patients, all-cause mortality in ITT patients, and adverse effects (in ITT patients) probably or possibly related to study antibiotics were considered as primary outcome measures for this meta-

analysis. The effectiveness of the therapeutic regimen was evaluated at the test-of-cure visit, performed 6-21 days after the onset of the ABECB. Patients considered clinically evaluable in the individual RCTs who had an indeterminate clinical outcome at the test-of-cure visit were deemed unevaluable for the treatment success analysis. All-cause mortality was analyzed based on the reported data for mortality during the study period (e.g. during treatment and follow up period) in the ITT population. The number of patients without recurrence of ABECB after treatment of the initial episode of ABECB with macrolides, quinolones, or A/C over a period of at least 26 weeks, adverse effects (any adverse effect, diarrhea, and the number of patients that were withdrawn from the RCTs due to drug-related adverse effects), treatment success in the microbiologically evaluable (ME) patients, and pathogen eradication (documented or presumed) of *Haemophilus influenzae, Moraxella catarrhalis*, and *Streptococcus pneumoniae* isolates were considered as secondary outcomes.

Data analysis and statistical methods

Statistical analyses were performed using the "S-PLUS 6.1" software. The heterogeneity between RCTs was assessed by using the I-squared statistic (17). Publication (sample size) bias was assessed by the funnel plot method using Egger's test (18). Pooled odds ratios and 95% confidence intervals (CI) for all primary and secondary outcomes were calculated, by using the DerSimonian-Laird (19) random effects models.

RESULTS

Selected RCTs

In Figure 1 we present the process of identifying eligible studies. Through our search we located 157 potentially relevant RCTs; one more RCT that was not captured in the search of the electronic databases was found through the review of the references of the relevant articles. Of these 158 articles, 107 articles excluded from this meta-analysis for the reasons presented in Figure 1. In addition, 28 RCTs were not included in the analysis as the administered quinolone (i.e. ciprofloxacin, sparfloxacin, trovafloxacin, ofloxacin, gatifloxacin, and grepafloxacin) is not used for the treatment of ABECB or it was withdrawn from the market because of serious adverse effects. Another RCT was excluded because the comparison regarded telithromycin to A/C (20). Finally, from two RCTs (21, 22) that compared moxifloxacin with clarithromycin, cefuroxime/axetil

and amoxicillin, specific data regarding the clinical outcomes of the clarithromycin recipients could not be extracted. Similarly, from one RCT (23) in which azithromycin was compared to A/C for the treatment of patients with various acute lower tract respiratory infections (including ABECB), specific data on clinical outcomes of patients with ABECB could not be extracted. Thus, 19 RCTs -that compared macrolides with quinolones *(n=8)* (24-31)*,* and A/C with quinolones *(n=4)* (24, 32-34) or macrolides *(n=8)* (35-42) were included in our meta-analysis. To note that in one RCT (24) a quinolone (levofloxacin) was compared with both a macrolide (azithromycin) and A/C.

In Table 1 we summarize the characteristics of the 19 RCTs, representing 7,405 patients included in the meta-analysis. The mean quality score of the analyzed trials was 3.2 (range 1-5), which was considered good. The quality of 13 RCTs (24-26, 28-31, 34-38, 40) was high (3 or more), while the quality of the remaining 6 RCTs (27, 32, 33, 39, 41, 42) was low.

All patients enrolled in the RCTs of the meta-analysis were adults (≥ 18 years old), not hospitalized during enrollment (except from 1 RCT (41) in which both in- and outpatients were enrolled), and they could be treated in an inpatient or outpatient basis. They had a medical history of CB or CB/chronic obstructive pulmonary disease (COPD) in 16 (24-28, 31-34, 36-42) and 2 (29, 30) RCTs, respectively; in 1 RCT (26) patients with types of COPD other than CB were excluded, while in another RCT (35) only patients with COPD [at baseline: forced expiratory volume in 1 second (FEV1) <70% of predicted value] were included. Patients were presented with ABECB characterized as Anthonisen type I, II, or III in 2 RCTs (29, 30) (in these 2 RCTs a macrolide was compared with a quinolone) or Anthonisen type I or II in 10 RCTs (24-27, 31, 33, 36, 38, 40, 41). In contrast, in the remaining RCTs (28, 32, 34, 35, 37, 39, 42) only patients with an Anthonisen type I (28, 34, 35, 37, 39) or type II (32, 42) ABECB were enrolled.

In 9 RCTs data regarding the use of systemic corticosteroids before the occurrence of ABECB (26, 27, 30, 33, 37-40, 42) were not provided, while in 4 RCTs the use of systemic corticosteroids at a dose of ≥ 10 mg of prednisone (25, 41**)** or at any dose (34, 36) was an exclusion criterion. In the 6 RCTs (24, 28, 29, 31, 32, 35) in which relevant data were provided, there was no statistically significant difference regarding the use of

systemic corticosteroids at baseline between the compared groups. On the other hand, administration of systemic corticosteroids during ABECB was permitted in 4 (26, 33, 35, 37) RCTs; in 2 (33, 35) of these 4 RCTs the treatment groups were comparable with respect to the use of corticosteroids during exacerbation, while in the other 2 RCTs (26, 37) the authors reported that corticosteroids were permitted without giving more details. Thirteen (24, 28-32, 34, 36, 38-42) out of 19 RCTs included in this meta-analysis did not provide relevant data regarding use of corticosteroids during ABECB, while in the remaining 2 RCTs (25, 27) administration of systemic corticosteroids during ABECB was not permitted.

Administration of study drugs

The administration of study antibiotics prior to enrollment as well as the administration of additional antimicrobial agents during the trial was not allowed in any of the RCTs included in our meta-analysis. The dosages of the administered drugs as well as the duration of administration are shown in Table 1. All antibiotics were given *per os*. In 8 (24-31) RCTs macrolides were compared with quinolones; specifically clarithromycin was compared with levofloxacin or gemifloxacin or moxifloxacin in 2 (25, 27), 1 (28), and 2 (29, 31) RCTs, respectively, while azithromycin was compared with levofloxacin in 2 (24, 26) RCTs and with moxifloxacin in 1 (30) RCT. On the other hand, A/C was compared with quinolones in 4 (24, 32-34) and with macrolides in 8 (35-42) RCTs. In detail, the quinolone compared with A/C was levofloxacin, moxifloxacin, or gemifloxacin (1 (24), 2 (32, 33), and 1 (34) RCTs, respectively), while the macrolide compared with A/C was clarithromycin, azithromycin, dirithromycin, or roxithromycin (2 (35, 36), 4 (37, 39-41), 1 (38), and 1 (42) RCTs, respectively).

Treatment success in intention-to-treat and clinically evaluable patients

Table 2 presents the primary outcomes studied in our meta-analysis. Data regarding treatment success of the administered antimicrobial regimens for the ITT and CE patients was reported in 10 (28-31, 33, 35, 36, 39, 41, 42) and 17 (24, 26-38, 40-42) RCTs, respectively. In another RCT (25) not enough data were provided regarding the number of patients who were cured among those treated with macrolides or quinolones was reported; thus, this RCT was excluded from the analysis of treatment success. There was no difference in treatment success between patients with ABECB treated with macrolides and those treated with quinolones (ITT: 2,822 patients, OR= 1.01, 95%

CI 0.81-1.27; I^2=0, 95% CI 0-0.85, data from 4 trials (28-31); CE: 2,606 patients, OR= 0.94, 95% CI 0.73-1.21; I^2=0, 95% CI 0-0.71, data from 7 trials (24, 26-31)) or between A/C recipients and quinolones recipients (only 1 trial (33) provided data on treatment success in ITT patients; CE: 1,441 patients, OR= 0.86, 95% CI 0.55-1.34; I^2=0.28, 95% CI 0-0.73 , data from 4 trials (24, 32-34)) or between A/C recipients and macrolides recipients (ITT: 869 patients, OR= 1.09, 95% CI 0.41-2.95, I^2=0.79, 95% CI 0.52-0.91, data from 5 trials (35-36, 39, 41-42); CE: 1,082 patients, OR= 1.70, 95% CI 0.72-4.03; I^2=0.67, 95% CI 0.25-0.85, data from 7 trials (35-38, 40-42)).The odds ratios for the treatment success of the compared antibiotics for the clinically evaluable patients in the individual randomized controlled trials, as well as the pooled odds ratio, are presented in Figure 2 (2A-C).

Need for hospitalization

Only 7 (24, 27-29, 31, 32, 35) out of the 19 RCTs included in our analysis provided data dealing with the need for hospitalization of patients with ABECB. The follow-up of patients regarding the need for hospitalization was limited during the study period in 5 RCTs (27, 29, 31, 32, 35), while in the remaining 2 (24, 28) RCTs it was extended until 26 weeks (28) or until 9 months (24). In 12 other RCTs (25, 26, 30, 33, 34, 36-42) relevant data were not reported. There was no difference in patients treated with macrolides compared to patients treated with quinolones regarding this outcome (ITT: 2,581 patients, OR= 1.37, 95% CI 0.75-2.50; I^2=0.39, 95% CI 0-0.78, data from 5 trials (24, 27-29, 31)).

Unfortunately, data regarding need for hospitalization were available only in 2 (24, 32) RCTs comparing A/C with quinolones, and in 1 (35) RCT comparing A/C with macrolides (data shown in Table 2).

Recurrence of ABECB after resolution of the initial episode

Data regarding patients with recurrence(s) of ABECB after resolution of the initial episode was available only in 2 (25, 28) out of the 19 RCTs included in the meta-analysis. In both of them macrolides was compared with quinolones. In one RCT (25) a total of 48% (122/254) of macrolide-treated patients and 44% (109/250) of quinolone-treated patients exhibited no recurrence during the 12-month period after therapy (p= 0.967 by chi-squared test). Whereas, in another RCT (28) included in the meta-analysis,

more patients treated with macrolide experienced a recurrence of ABECB after resolution of the initial episode compared to quinolone recipients during a 26-week period after therapy (100/171 (58%) vs 120/169 (71%), p= 0.016 by chi- squared test).

Mortality

All-cause mortality during the study period (based on the reported data) was available in 5 (24, 29-31, 34) RCTs. There was no difference in mortality between macrolide-treated patients with ABECB and those treated with quinolones (ITT: 2,627 patients, OR= 1.96, 95% CI 0.45-8.51; I^2=0, 95% CI 0-0.85, data from 4 trials (24, 29-31)). On the other hand, data on mortality were provided only in 2 RCTs (24, 34) comparing A/C with quinolones (data shown in Table 2).

Treatment success in microbiologically evaluable patients

In Table 3 we present the microbiological outcomes of 14 (24-26, 28-37, 41) of the 19 RCTs included in our meta-analysis that provided data relevant to the treatment success in ME patients. Regarding this outcome macrolides performed worse than quinolones (ME: 1,308 patients, OR= 0.47, 95% CI 0.31-0.69; I^2=0.06, 95% CI 0-0.73, data from 7 trials (24-26, 28-31)), while there was no difference between A/C and quinolones (ME: 445 patients, OR= 0.84, 95% CI 0.49-1.42; I^2=0, 95% CI 0-0.85, data from 4 trials (24, 32-34), or between A/C and macrolides ((ME: 571 patients, OR= 1.49, 95% CI 0.51-4.39; I^2=0.75, 95% CI 0.32-0.91, data from 4 trials (35-37, 41).

On the other hand, 9 of the RCTs included in our analysis reported data on pathogens isolated at baseline and eradicated at the test-of-cure visit (24, 26, 29-31, 35-37, 41). Treatment of patients with ABECB with macrolides was associated with lower eradication rates of *Haemophilus influanzae* compared to treatment with quinolones (338 isolates, OR= 0.18, 95% CI 0.06-0.55; I^2=0.24, 95% CI 0-0.69, data from 5 RCTs (24, 26, 29-31)). However, there was no difference between the compared groups on eradication rates of *Moraxella catarrhalis* (222 isolates, OR= 1.28, 95% CI 0.32-5.19; I^2=0, 95% CI 0-0.79, data from 5 RCTs (24, 26, 29-31)) or of *Streptococcus pneumoniae* (195 isolates, OR= 1.19, 95% CI 0.27-5.24; I^2=0.14, 95% CI 0-0.82, data from 5 RCTs (24, 26, 29-31)). Only one RCT (24) comparing A/C with quinolone reported data on these outcomes (data shown in Table 3). In addition, treatment of patients with ABECB with A/C was not associated with better eradication rates of

Haemophilus influanzae (165 isolates, OR= 2.21, 95% CI 0.72-6.72, I^2=0.35, 95% CI 0-0.77, data from 4 RCTs (35-37, 41)), or of *Moraxella catarrhalis* (91 isolates, OR= 0.78, 95% CI 0.18-3.45; I^2=0, 95% CI 0-0.85, data from 4 RCTs (35-37, 41)), or of *Streptococcus pneumoniae* (149 isolates, OR= 1.96, 95% CI 0.49-7.89; I^2=0.32, 95% CI 0-0.76, data from 4 RCTs (35-37, 41)) in comparison with treatment with macrolides.

Adverse effects

Data regarding adverse effects probably or possibly related to the study drugs in ITT patients were reported for 12 RCTs (24-26, 28-36). In the remaining 7 RCTs (27, 37-42) the total (not only the drug-related) adverse effects (27, 38, 41) or the adverse effects of patients with any lower respiratory tract infection (not only ABECB) (37, 39, 40, 42) were reported. Therefore, these 7 trials were excluded from the analysis of adverse effects. Administration of macrolides in patients with ABECB was not associated with more adverse effects in general, in comparison with the administration of quinolones (ITT: 4,081 patients, OR= 1.11, 95% CI 0.94-1.32; I^2=0.13, 95% CI 0-0.75, data from 7 trials (24-26, 28-31)). This was also the case for withdrawn of participants from the RCTs (ITT: 2,920 patients, OR= 0.75, 95% CI 0.39-1.41; I^2=0.43, 95% CI 0-0.79, data from 5 RCTs (24, 25, 28, 30, 31)), but not for the development of diarrhea (ITT: 3,571 patients, OR= 1.37, 95% CI 0.99-1.87; I^2=0, 95% CI 0-0.75, data from 6 RCTs (24, 26, 28-31)).

In contrast, administration of A/C in patients with ABECB was associated with more adverse effects, in general, in comparison with the administration of quinolones (ITT: 1,699 patients, OR= 1.36, 95% CI 1.01-1.85; I^2=0.14, CI 95% 0-0.87, data from 4 trials (24, 32-34). More A/C recipients experienced diarrhea compared to quinolones recipients (ITT: 1,699 patients, OR= 3.02, 95% CI 1.75-5.21; I^2=0.07, CI 95% 0-0.86, data from 4 trials (24, 32-34)). Only 2 trials (35, 36) comparing A/C with macrolides reported data for adverse effects in general and for diarrhea; in both of them administration of A/C was associated with a higher probability of development of adverse effects in general and of diarrhea (data shown in Table 2). Data regarding the number of patients who were withdrawn from the RCTs due to drug-related adverse effects were available only in 1 (24) trial comparing A/C with quinolone (1/179 (0.5%) vs 5/183 (3%), p= 0.1 by chi- squared test), and in 1 (35) trial comparing A/C with macrolide (8/145 (6%) vs 2/142 (1%), p= 0.06 by chi-squared test). Of note, the

majority of adverse effects in patients of both study arms were mild to moderate in severity.

Sensitivity analyses

Treatment success in CE patients was an outcome analyzed in various subsets of patients, based on the design of our meta-analysis. Specifically, the subsets that we analyzed were: 1) trials that enrolled only patients with an Anthonisen type I or II ABECB [macrolides vs quinolones: 1,761 patients, OR= 0.89, 95% CI 0.67-1.18; I^2=0, 95% CI 0-0.79, data from 5 trials (24, 26-28, 31) (Figure 2D)], 2) trials in which the evaluation of the treatment success was performed up to 3 weeks from the onset of the ABECB [macrolides vs quinolones: 1,966 patients, OR= 0.97, 95% CI 0.71-1.33, I^2=0, 95% CI 0-0.79, data from 5 trials (24, 27, 29-31)], 3) trials in which use of systemic steroids before ABECB was comparable between the study arms of the individual RCTs (macrolides vs quinolones: 1,787 patients, OR= 0.92, 95% CI 0.68-1.26, I^2=0, 95% CI 0-0.85, data from 4 trials (24, 28, 29, 31)); A/C vs quinolones: 2 trials (24, 32), 17/126 (14%) vs 20/120 (17%), p= 0.49 by chi- squaredd test, in one (24) study, and 32/74 (43%) vs 38/79 (48%), p= 0.55 by chi- squaredd test, in the other (32) study), 4) trials in which >50% of the enrolled patients had at baseline a FEV1 ≤ 75% of predicted [macrolides vs quinolones: 1,381 patients, OR= 0.89, 95% CI 0.64-1.24; I^2=0, 95% CI 0-0.89, data from 3 trials (24, 28, 31)].

DISCUSSION

The results of our meta-analysis suggest that there was no difference in treatment success between patients with ABECB treated with macrolides and those treated with quinolones as well as between A/C- and quinolones-recipients, and between A/C- and macrolide-recipients. This was the case for the analyses of both intention-to-treat and clinically evaluable patients.

This finding seems to support the suggestion that, overall, there is no clinical superiority of any one class of antimicrobial agents over another (among those compared) for the treatment of patients with ABECB and, thus, the choice of antibiotic has no influence on their outcome (10). It could be also postulated that this lack of difference between the several antimicrobial classes may simply reflect the lack of effectiveness of antimicrobials at all for the management of patients with ABECB.

The results of our meta-analysis should be interpreted in the context of the design of the RCTs included in our meta-analysis. In fact, most of these RCTs were antibiotic comparison trials designed to show non-inferiority between agents for drug registration and approval purposes; thus, they may have not enough power to show clinical superiority of any one antibiotic over another. In addition, a significant proportion of the RCTs included in our meta-analysis allowed the enrollment of patients with an Anthonisen type III ABECB (i.e. mild ABECB) (29, 30) as well as the enrollment of patients without impaired lung function (i.e. without a decrease in FEV1). It may be expected that less significant differences in the effectiveness would be found between different antibiotic for the subset of patients with mild ABECB, who should not receive antibiotic therapy at all according to the recently published guidelines on this issue (14, 43, 44). Thus, the study design and the inclusion criteria of the individual RCTs included in this meta-analysis may be responsible for failing to reveal the potential superiority of one class of antimicrobial agents over another (45).

Several investigators advocate the administration of quinolones in certain subgroups of patients with ABECB (46). Specifically, the first such subgroup includes patients of older age (>65 years), FEV1<50% at baseline (in these patients *Pseudomonas aeruginosa* may also be the cause of ABECB) (47), >3 exacerbations of CB in the previous year, or with comorbid illness (especially cardiac disease); such patients are considered to be at increased risk for poor outcome (22). Patients requiring admission to an intensive care unit due to the severity of their ABECB and patients at high risk for infection with an antibiotic-resistant pathogen are also included in the subgroups of patients with ABECB in whom quinolones should be considered for the initial treatment. Unfortunately, the available data from the RCTs included in the meta-analysis were not enough to allow a stratification of the results of treatment success according to risk factors for poor outcome.

The findings of our study must be viewed in the context of its potential limitations. The major limitation of our meta-analysis is that results on treatment success in CE and ME patients were not stratified according to risk factors for poor outcome or for infection with an antibiotic-resistant pathogen. The available data from the included in the meta-analysis RCTs were not enough to evaluate the suggestion by experts that quinolones

should be considered for the initial treatment of the subgroups of patients with ABECB with the aforementioned risk factors. However, we performed a sensitivity analysis by including only RCTs (24, 28, 31) in which the majority of the enrolled patients had at baseline an impaired FEV1; quinolones were not found to be associated with better effectiveness in this subset of patients either.

Another limitation of our analysis is that the findings may not be fully applicable in areas where there is advanced problem of antimicrobial resistance among pathogens causing ABECB. It should be emphasized that antimicrobial resistance is a moving target and only data from local surveillance studies on this major clinical and public health problem provide information that help the clinician to the process of decision making regarding the choice of the appropriate antibiotic for a given patient with ABECB.

Also, the characteristics of the individual RCTs included in the present study contribute to others limitations of our meta-analysis. First, 2 (29, 30) out of the 19 RCTs included in our analysis also enrolled patients with a type III Anthonisen ABECB (not only patients with a type I or II Anthonisen ABECB). These patients (i.e. with a type III Anthonisen ABECB) do not need antibiotic therapy according to the recommendations of the international guidelines (14, 43, 44). However, we performed a subgroup analysis after exclusion of RCTs that included patients with a type III Anthonisen ABECB. Second, in 2 (26, 28) out of 19 RCTs the clinical endpoints were determined at 3 weeks or later after the onset of treatment. Anthonisen et al (2), in a large placebo-controlled trial, revealed that in 55% of patients with ABECB spontaneous resolution of the infection happens at 3 weeks after the onset of the infection. This spontaneous resolution, which is due to the immune-inflammatory response to infection, could mitigate differences between compared antimicrobial agents. However, we performed a subgroup analysis by including only trials in which the evaluation of the treatment success was performed up to 3 weeks from the onset of the ABECB. Third, 14 (24, 28-32, 34, 36, 38-42) out of 19 RCTs did not provide data on concurrent interventions for the management of ABECB, such as administration of systemic steroids, which could confound the results (48). Fourth, the majority of the RCTs included in this meta-analysis [18 (24, 26, 27, 29-42) out of 19] were not designed to follow-up enrolled

patients beyond 4-6 weeks; thus, time to next exacerbation, which is an very important outcome, was not adequately assessed.

In addition, we omitted studies written in languages other than English, French, German, and Italian, we did not seek for abstracts presented in scientific conferences, and we did not evaluate aspects related to cost-effectiveness issues of the compared antibiotics. Also, we did not perform comparisons of individual antibiotics (except A/C) in our study because they were not enough available data to perform such analyses. Instead, we examined the comparative effectiveness of broad-spectrum antibiotics belonging to classes of antimicrobial agents that are commonly used for the treatment of patients with ABECB, namely macrolides and quinolones.

Finally, one should bear into mind, when appreciating results on effectiveness and adverse effects, that the analyzed RCTs used not only different agents of the same antimicrobial class but also different dosages of the same antibiotic (as depicted in Table 1). In addition, the extremely wide confidence intervals of several of our results, namely those referring to treatment success between A/C- and macrolides- recipients as well as those pertaining to eradication rates, probably suggest that there is still insufficient evidence on these issues. All the above-mentioned points may be considered as limitations of our meta-analysis.

In conclusion, despite the above limitations, the findings of this meta-analysis suggest that there is no difference between macrolides, quinolones, and A/C for the treatment of patients with ABECB regarding effectiveness. However, there is enough evidence that quinolones are associated with better microbiological success than macrolides and very limited evidence that quinolones are associated with better long-term outcomes than comparators. As the available evidence is not enough to stratify outcomes according the risk factors for poor outcome or for infection with an antibiotic-resistant pathogen, we suggest that further research should be performed in the field of ABECB by focusing in this subgroup of patients (i.e. those with risk factors for poor outcome or for infection with an antibiotic-resistant pathogen).

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Table 1. Main characteristics of randomized controlled trials included in the meta-analysis.

First author (ref)	Year of publication	Study design	Population	Regimen 1*	Rgimen 2	Additional antibiotics allowed	Use of systemic corticosteroid before ABECB	Number of enrolled patients	Number of intention to treat patients (ITT)	Study quality score**
Macrolides versus quinolones :										
Martinez (24)	2005	MC, DB, RCT	Patients aged≥ 18 years with chronic bronchitis and an Anthonisen type I or II ABECB	Azithromycin 500mg q24h on day 1 and 250mg q24h for days 2-5	Levofloxacin 750mg q24h for 3 days	None	15/151 (10) vs 16/143 (11)	394	202 vs 192	4
Lode (25)	2004	MC, DB, RCT	Patients aged>35 years with chronic bronchitis and an Anthonisen type I or II ABECB	Clarithromycin 250 mg q12h for 10 days	Levofloxacin 500mg q24h for 7 days	None	NA¶	511	254 vs 250	4
Amsden (26)	2003	MC, DB, RCT	Patients aged 35-75 years with chronic bronchitis and an Anthonisen type I or II ABECB***	Azithromycin 500mg q24h on day 1 and 250mg q24h for days 2-5	Levofloxacin 500mg q24h for 7 days	None	NA	235	118 vs 117	3
Weiss (27)	2002	MC, RCT	Patients aged≥ 18 years with chronic bronchitis and an Anthonisen type I or II ABECB	Clarithromycin 500mg q12h for 10 days	Levofloxacin 500mg q24h for 10 days	None	NA	191	97 vs 94	1
Wilson (28)	2002	MC, DB, RCT	Patients aged> 40years with chronic bronchitis and an Antonisen type I ABECB	Clarithromycin 500mg q12h for 7 days	Gemifloxacin 320mg q24h for 5 days	None	76/358 (21) vs 74/351 (21) ¶	712	358 vs 351	3
Chodosh (29)	2000	MC, DB, RCT	Patients aged≥ 18years with chronic bronchitis or COPD with an Anthonisen type I,II or III ABECB	Clarithromycin 500mg q12h for 10 days	Moxifloxacin 400mg q24h for 5 or 10 days	None	74/312 (24) vs 134/614 (22)	936	312 vs 614	5
DeAbate (30)	2000	MC, DB, RCT	Patients aged≥ 18years with chronic bronhitis or COPD with an Anthonisen type I, II or III ABECB	Azithromycin 500mg q24h on day 1 followed by 250mg q24h for 4 days	Moxifloxacin 400mg q24h for 5 days	None	NA	567	284 vs 283	5

Wilson (31)	1999	MC, DB, RCT	Patients aged≥ 18 years with chronic bronchitis and an Antonisen type I or II ABECB	Clarithromycin 500mg q12h for 7 days	Moxifloxacin 400mg q24h for 5 days	None	128/327 (39) vs 160/322 (50) ¥	750	371 vs 374	4
Amoxicillin /clavulanic versus quinolones:										
Martinez (24)	2005	MC, RCT	Patients aged≥18 years with chronic bronchitis and an Anthonisen type I or II ABECB	Amoxicillin/clavulanic acid 875/125 mg q12h for 10 days	Levofloxacin 750 mg q24h for 5 days	None	17/126 (14) vs 20/120 (17)	369	182 vs 187	2
Starakis (32)	2003	RCT	Patients aged≥ 18 years with chronic bronchitis and an Anthonisen type II ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 7 days	Moxifloxacin 400 mg q24h for 5 days	None	32/74 (43) vs 38/79 (48)	162	79 vs 83	2
Schaberg (33)	2001	MC, RCT	Patients aged≥ 18 years with chronic bronchitis and an Anthonisen type I or II ABECB	Amoxicillin/clavulanic acid 500/125 mg q12h for 7 days	Moxifloxacin 400 mg q24h for 5 days	None	NA	577	283 vs 292	1
File (34)	2000	MC, DB, RCT	Patients aged≥ 40 years with chronic bronchitis and an Anthonisen type I ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 7 days	Gemifloxacin 320 mg q24h for 5 days	None	0/296 (0) vs 0/304 (0) †	600	296 vs 304	4
Amoxicillin/ clavulanic versus macrolides:										
Anzueto (35)	2001	MC, investigator blinded, RCT	Patients aged≥ 40 years with COPD (FEV1≤70% of predicted) and an Anthonisen type I ABECB	Amoxicillin/clavulanic acid 875/125 mg q12h for 10 days	Clarithromycin 1000 mg q24h for 7 days	None	Treatment groups comparable with respect to use of steroids§	287	143 vs 140	4
Martinot (36)	2001	MC, investigator blinded, RCT	Patients aged≥ 35 years with chronic bronchitis and Anthonisen type I or II ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 7 days	Clarithromycin 500 mg q24h for 7 days	None	0/123 (0) vs 0/127 (0) †	250	123 vs 127	4
Hoepelman (37)	1997	MC, DB, RCT	Patients aged≥ 18 years with chronic bronchitis and Anthonisen type I ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 10 days	Azithromycin 500 mg q24h for 3 days	None	NA	123	61 vs 62	4
Van Royen (38)	1997	MC, RCT	Patients aged≥ 18 years with chronic bronchitis and Anthonisen type I or II ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 7 or 10 days	Dirithromycin 500 mg q24h for 5 days	None	NA	334	165 vs169	3

Biebuyck (39)	1996	MC, RCT	Patients aged≥ 18 years with chronic bronchitis and Anthonisen type I ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 5 or 10 days	Azithromycin 250 mg q12h for 3 days	None	NA	139	45 vs 94	2
Gris (40)	1996	MC, DB, RCT	Patients aged≥ 18 years with chronic bronchitis and Anthonisen type I or II ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 10 days	Azithromycin 500 mg q24h for 3 days	none	NA	61	28 vs 33	4
Beghi (41)	1994	MC, RCT	Patients aged≥ 18 years with chronic bronchitis and Anthonisen type I or II ABECB∉	Amoxicillin/clavulanic acid 875/125 mg q12h for 8 days	Azithromycin 500 mg q24h for 3 days	none	allowed, daily dose not higher than 25 mg§	142	73 vs 69	2
Dautzenberg (42)	1992	MC, RCT	Patients aged≥ 18 years with chronic bronchitis and Anthonisen type II ABECB	Amoxicillin/clavulanic acid 500/125 mg q8h for 14 days	Roxithromycin 150mg q12h for 14 days	none	NA	65	33 vs 32	1

Abbreviations: MC: multicenter, DB: double-blind, ABECB: acute bacterial exacerbation of chronic bronchitis, COPD: chronic obstructive pulmonary disease, vs: versus

* All antibiotics were administered *per os*

**According to a modified Jadad score

*** Patients with types of COPD other than chronic bronchitis were excluded from this RCT

¶ Use of systemic corticosteroids at a dose of >10 mg prednisone or the equivalent was an exclusion criterion

¥ Refers to clinically evaluable patients who received inhaled, oral or intravenous corticosteroids

† Use of systemic corticosteroids at any dose was an exclusion criterion

§ According to the authors

∉ Both hospitalized patients and outpatients were included in this RCT

In the RCT by Martinez et al (24) a quinolone (levofloxacin) was compared with both a macrolide (azithromycin) and amoxicillin/clavulanate.

Table 2. Outcome data from the selected randomized controlled trials for the meta-analysis (macrolides versus quinolones, amoxicillin/clavulanic acid vs quinolones, and amoxicillin/clavulanic acid vs macrolides).

First author (ref)	Treatment success, n/N (%)				Adverse effects, n/N (%)			All-cause mortality n/N (%)
	ITT at TOCV	CE at TOCV	Need for hospitalization	Patients without recurrence	Total	Withdrawn patients from RCTs	Diarrhea	
Macrolides versus quinolones :								
Martinez (24)	NA	136/151 (90) vs 133/143 (93)	2/151 (1) vs 0/143 (0) [a]	NA	16/199 (8) vs 12/190 (6)	1/199 (0.5) vs 4/190 (2)	10/199 (5) vs 3/190 (2)	0/199 (0) vs 0/190 (0)
Lode (25)	(80) vs (83)	(85) vs (86)	NA	122/254 (48) vs 109/250 (44)[d]	25/258 (10) vs 24/252 (10)	12/258 (5) vs 14/252 (6)	NA	NA
Amsden (26)	NA	86/105 (82) vs 83/97 (86) *	NA	NA	21/118 (18) vs 23/117 (20)	NA	10/118 (9) vs 5/117 (4)	NA
Weiss (27)	NA	80/91 (88) vs 76/87 (87)	0/91 (0) vs 3/87 (3)	NA	NA	NA	NA	NA
Wilson (28)	280/358 (78) vs 279/351 (79)	190/224 (85) vs 183/214 (86) *	14/224 (6) vs 5/214 (2)[b]	100/171 (58) vs 120/169 (71)[e]	90/358 (25) vs 66/351 (19)	15/358 (4) vs 9/351 (3)	25/358 (7) vs 18/351 (5)	NA
Chodosh (29)	268/286 (94) vs 540/569 (95)	121/127 (95) vs 263/279 (94)	16/312 (5) vs 21/614 (3)	NA	103/312 (33) vs 172/614 (28)	NA	15/312 (5) vs 33/614 (5)	1/312 (0.3) vs 1/614 (0.2)
DeAbate (30)	239/261 (92) vs 228/252 (90)	208/227 (92) vs 192/212 (91)	NA	NA	49/284 (17) vs 61/283 (22)	0/284 (0) vs 5/283 (2)	19/284 (75) vs 13/283 (5)	1/284 (0.4) vs 0/283 (0)
Wilson (31)	308/371 (83) vs 302/374 (81)	289/327 (88) vs 287/322 (89)	23/371 (6) vs 25/374 (7)	NA	82/371 (22) vs 80/374 (21)	14/371 (4) vs 23/374 (6)	15/371 (4) vs 11/374 (3)	2/371 (0.5) vs 1/374 (0.3)

Pooled ORs	*OR=1.01* *95% CI 0.81-1.27*	*OR=0.94* *95% CI 0.73-1.21*	*OR=1.37* *95% CI 0.75-2.50*		*OR=1.11* *95% CI 0.94-1.32*	*OR=0.75* *95% CI 0.39-1.41*	*OR=1.37* *95% CI 0.99-1.87*	*OR=1.96* *95% CI 0.45-8.51*
Amoxicillin/clavulanic versus quinolones :								
Martinez (24)	NA	103/126 (82) vs 95/120 (79)	3/126 (2) vs 0/120 (0)	NA	16/179 (9) vs 16/183 (9)	1/179 (0.5) vs 5/183(3)	5/179 (3) vs 4/183 (2)	0/179 (0) vs 0/183 (0)
Starakis (32)	NA	66/74 (89) vs 70/79 (89)	1/79 (1) vs 0/83 (0)	NA	11/79 (14) vs 8/83 (10)	NA	4/79 (5) vs 1/83 (1)	NA
Schaberg (33)	241/283 (85) vs 270/292 (93)	230/251 (92) vs 251/261 (96)	NA	NA	55/283 (19) vs 52/292 (18)	NA	21/283 (7) vs 9/292 (3)	NA
File (34)	NA	248/266 (93) vs 247/264 (94)	NA	NA	57/296 (19) vs 34/304 (11)	NA	31/296 (11) vs 7/304 (2)	0/296 (0) vs 3/304 (1)
Pooled ORs	*NA*	*OR=0.86* *95% CI 0.55-1.34*	*NA*	*NA*	*OR=1.36* *95% CI 1.01-1.85*	*NA*	*OR=3.02* *95% CI 1.75-5.21*	*NA*
Amoxicillin/clavulanic versus macrolides:								
Anzueto (35)	116/143 (81) vs 117/140 (84)	116/133 (87) vs 117/137 (85)	3/145 (2) vs 5/142 (4)	NA	35/145 (24) vs 28/142 (20)	8/145 (6) vs 2/142 (1)	18/145 (12) vs 12/142 (8)	NA
Martinot (36)	108/119 (90.7) vs 113/124 (91)	96/106 (91) vs 105/113 (93)	NA	NA	27/123 (22) vs 17/127 (13)	NA	12/123 (10) vs 3/127 (2)	NA
Hoepelman (37)	NA	54/58 (89) vs 59/62 (95)	NA	NA	NA	NA	NA	NA
Van Royen (38)	NA	148/149 (93) vs 153/162 (94)	NA	NA	NA	NA	NA	NA

Biebuyck (39)	33/44 (75) vs 84/93 (90)	NA	NA	NA	NA	NA	NA	NA
Gris (40)	NA	24/26 (92) vs 24/28 (86)	NA	NA	NA	NA	NA	NA
Beghi (41)	71/73 (97.2) vs 46/68 (67.6)	71/73 (97) vs 46/68 (68)	NA	NA	NA	NA	NA	NA
Dautzenberg (42)	28/33 (85) vs 29/32 (91)	28/33 (85) vs 29/32 (91)	NA	NA	NA	NA	NA	NA
Pooled ORs	*OR=1.09 95% CI 0.41-2.95*	*OR=1.70 95% CI 0.72-4.03*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*

Abbreviations: NA: not available/applicable, ABECB: acute bacterial exacerbation of chronic bronchitis, ITT: intention-to-treat, TOCV: test-of-cure visit, 6-21 days from the onset of ABECB, CE: clinically evaluable patients, OR: odds ratio, CI: confidence interval, vs: versus

[a] 9-months assessment

[b] 26-week assessment

[c] 12-month period after therapy

[d] 26-week period after therapy

* In these two RCTs treatment success in CE patients was evaluated at 24 days from the onset of ABECB

In the RCT by Martinez et al (24) a quinolone (levofloxacin) was compared with both a macrolide (azithromycin) and amoxicillin/clavulanate.

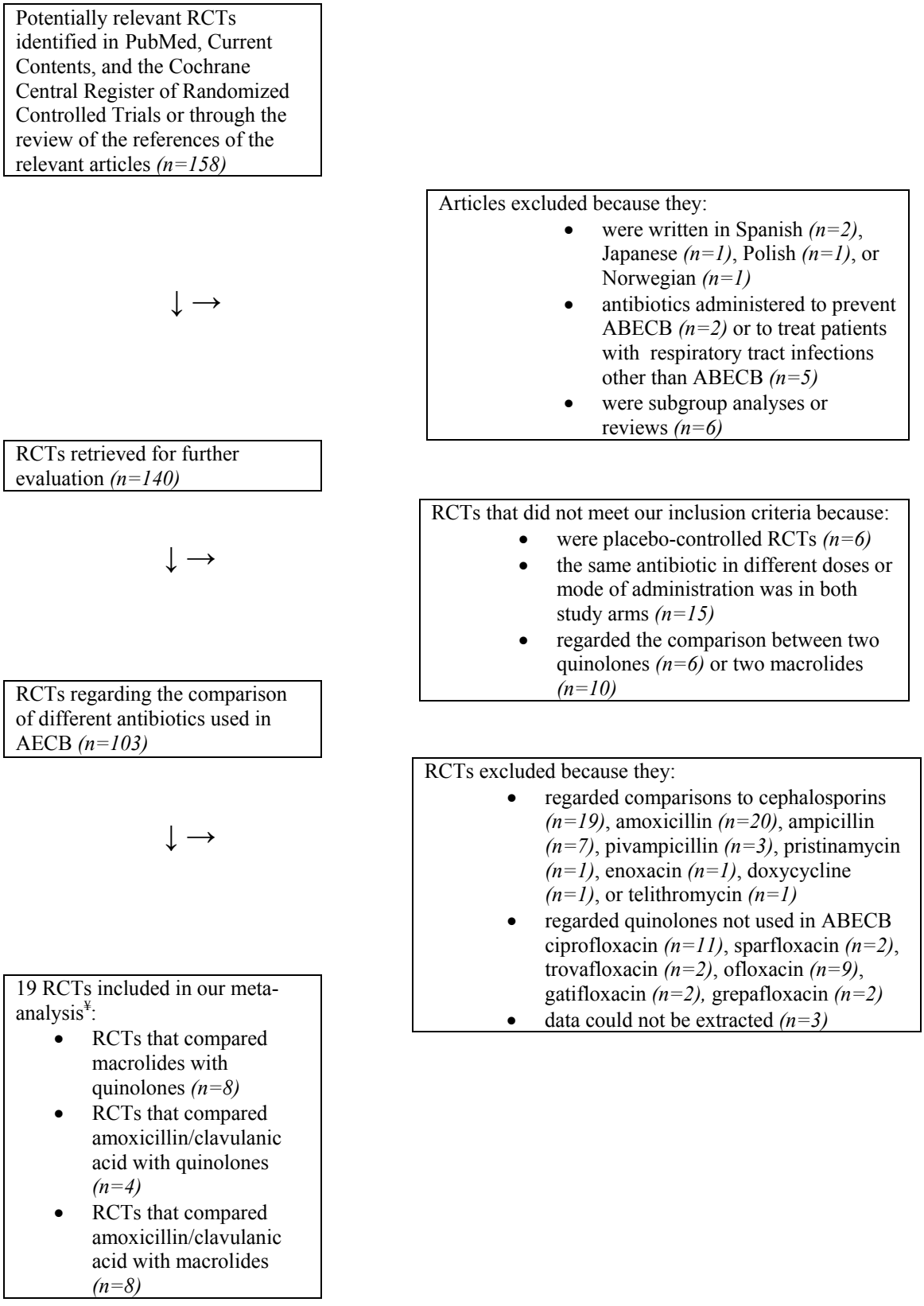
Table 3. Microbiological outcomes from the selected randomized controlled trials for the meta-analysis (macrolides versus quinolones, amoxicillin/clavulanic acid vs quinolones, and amoxicillin/clavulanate vs macrolides).

First author (ref)	Treatment success (microbiological evaluation)	Pathogen eradication, n/N (%)		
		Haemophilus influenzae	***Moraxella catarrhalis***	***Streptococcus pneumoniae***
Macrolides versus quinolones :				
Martinez (24)	72/87 (83) vs 75/80 (94)	21/24 (88) vs 26/27 (96)	18/20 (90) vs 14/14 (100)	10/11 (91) vs 11/12 (92)
Lode (25)	55/66 (83) vs 62/64 (97)	NA	NA	NA
Amsden (26)	22/23 (96) vs 17/20 (85)	14/15 (93) vs 5/6 (83)	7/7 (100) vs 9/10 (90)	1/1 (100) vs 2/2 (100)
Weiss (27)	NA	NA	NA	NA
Wilson (28)	44/54 (81) vs 44/47 (94)	NA	NA	NA
Chodosh (29)	115/127 (91) vs 265/280 (95)	33/40 (83) vs 69/69 (100)	24/24 (100) vs 57/58 (98)	21/23 (91) vs 36/36 (100)
DeAbate (30)	108/115 (94) vs 111/116 (96)	33/36 (92) vs 34/34 (100)	20/20 (100) vs 29/29 (100)	19/19 (100) vs 17/17 (100)
Wilson (31)	71/114 (62) vs 89/115 (77)	23/43 (53) vs 40/44 (91)	23/24 (96) vs 14/16 (88)	35/36 (97) vs 32/38 (84)
Pooled ORs	*OR=0.47 95% CI 0.31-O.69*	*OR=0.18 95% CI 0.06-0.55*	*OR=1.28 95% CI 0.32-5.19*	*OR=1.19 95% CI 0.27-5.24*
Amoxicillin/clavulanic versus quinolones :				
Martinez (24)	71/89 (80) vs 70/86 (81)	20/20 (100) vs 25/30 (83)	16/19 (84) vs 10/12 (83)	10/13 (77) vs 16/18 (88)
Starakis (32)	18/20 (89) vs 20/22 (91)	NA	NA	NA
Schaberg (33)	60/67 (90) vs 64/73 (88)	NA	NA	NA
File (34)	35/44 (80) vs 40/44 (91)	NA	NA	NA
Pooled ORs	*OR=0.84 95% CI 0.49-1.42*	*NA*	*NA*	*NA*
Amoxicillin/clavulanic versus macrolides:				
Anzueto (35)	55/62 (89) vs 54/59 (92)	18/19 (95) vs 17/20 (85)	12/14 (86) vs 18/20 (90)	11/14 (79) vs 11/15 (73)
Martinot (36)	41/55 (74) vs 55/69 (80)	8/15 (53) vs 15/29 (52)	3/4 (75) vs 5/6 (83)	9/12 (75) vs 12/16 (75)
Hoepelman (37)	26/59 (44) vs 26/60 (43)	16/20 (80) vs 15/21 (71)	11/11 (100) vs 11/11 (100)	6/6 (100) vs 9/9 (100)

Van Royen (38)	NA	NA	NA	NA
Biebuyck (39)	NA	NA	NA	NA
Gris (40)	NA	NA	NA	NA
Beghi (41)	70/71 (99) vs 45/67 (67)	15/15 (100) vs 13/26 (50)	9/9 (100) vs 5/5 (100)	34/34 (100) vs 19/27 (70)
Dautzenberg (42)	NA	NA	NA	NA
Pooled ORs	*OR=1.49 95% CI 0.51-4.39*	*OR=2.21 95% CI 0.72-6.72*	*OR=0.78 95% CI 0.18-3.45*	*OR=1.96 95% CI 0.49-7.89*

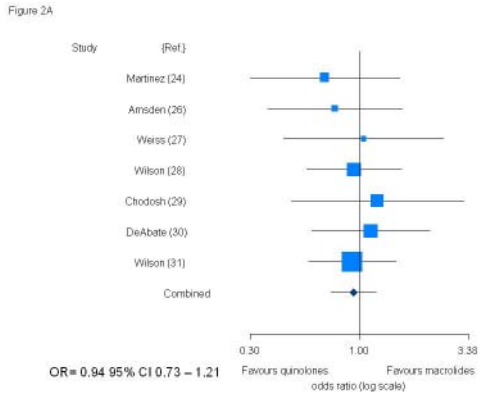
Abbreviations: NA: not available/applicable, OR: odds ratio, CI: confidence interval, vs: versus

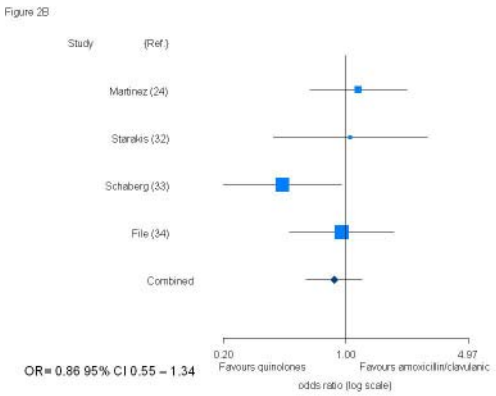
Figure 1. Flow diagram of reviewed articles



¥ In one RCT a quinolone (levofloxacin) was compared with both a macrolide (azithromycin) and amoxicillin/clavulanate.

Figure 2. Treatment success in clinically evaluable patients with acute bacterial exacerbations of chronic bronchitis (ABECB) in randomized controlled trials (RCTs) comparing: (A) macrolides vs quinolones, (B) amoxicillin/clavulanate vs quinolones, (C) amoxicillin/clavulanate vs macrolides, (D) macrolides vs quinolones, in RCTs that enrolled only patients with Anthonisen I or II ABECB. Vertical line= "no difference" point between the two regimens. Squared= odds ratio; the size of each squared denotes the proportion of information given by each trial. Diamond= pooled odds ratio for all RCTs. Horizontal lines= 95% CI.





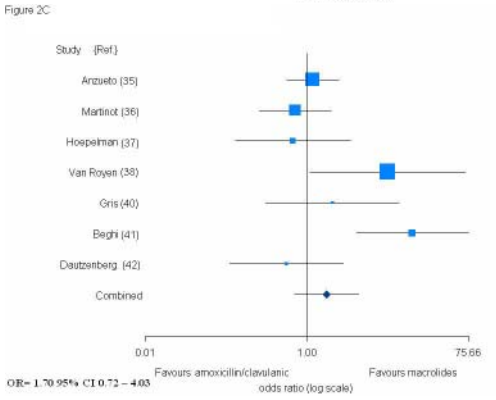
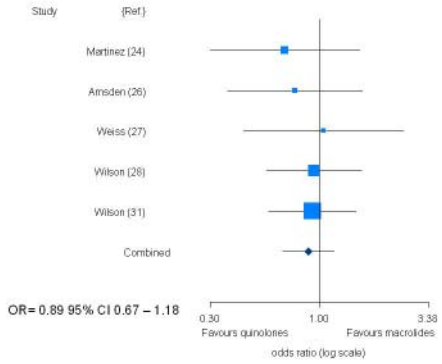


Figure 2D


Study
(Ref.)
Martinez (24)
Amsden (26)
Weiss (27)
Wilson (28)
Wilson (31)
Combined
OR= 0.89 95% CI 0.67 – 1.18
0.30
1.00
3.38
Favours quinolones
Favours macrolides
odds ratio (log scale)