CHEST

Original Research

CRITICAL CARE

Short- vs Long-Duration Antibiotic Regimens for Ventilator-Associated Pneumonia

A Systematic Review and Meta-analysis

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Background: **We performed a systematic review and meta-analysis of short- vs long-duration antibiotic regimens for ventilator-associated pneumonia (VAP).**

Methods: **We searched PubMed and Cochrane Central Registry of Controlled Trials. Four randomized controlled trials (RCTs) comparing short (7-8 days) with long (10-15 days) regimens were identified. Primary outcomes included mortality, antibiotic-free days, and clinical and microbiologic relapses. Secondary outcomes included mechanical ventilation-free days, duration of mechanical ventilation, and length of ICU stay.**

Results: **All RCTs included mortality data, whereas data on relapse and antibiotic-free days were provided in three and two out of four RCTs, respectively. No difference in mortality was found between the compared arms (fixed effect model [FEM]: OR = 1.20; 95% CI, 0.84-1.72; *P* = .32). There was an increase in antibiotic-free days in favor of the short-course treatment with a pooled weighted mean difference of 3.40 days (random effects model: 95% CI, 1.43-5.37; *P* < .001). There was no difference in relapses between the compared arms, although a strong trend to lower relapses in the long-course treatment was observed (FEM: OR = 1.67; 95% CI, 0.99-2.83; *P* = .06). No difference was found between the two arms regarding the remaining outcomes. Sensitivity analyses yielded similar results.**

Conclusions: **Short-course treatment of VAP was associated with more antibiotic-free days. No difference was found regarding mortality and relapses; however, a strong trend for fewer relapses was observed in favor of the long-course treatment, being mostly driven by one study in which the observed relapses were probably more microbiologic than clinical. Additional research is required to elucidate the issue.** ***CHEST 2013; 144(6):1759–1767***

Abbreviations: FEM = fixed effect model; RCT = randomized controlled trial; REM = random effects model; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; VAP = ventilator-associated pneumonia; WMD = weighted mean difference

Ventilator-associated pneumonia (VAP) is one of the major causes of morbidity and mortality in the ICU, accounting for 25% of the total infections occurring in this setting and for 50% of antibiotic prescriptions in patients who are mechanically ventilated.[1] Its incidence depends on the type of the institution, the preventive measures and therapeutic approaches that are used, and even on the type of surveillance systems by which incidence is estimated. There are reports of incidence across different settings varying from 1.4 up to 42.8 episodes of VAP/1,000 ventilation-days. However, it should be noted that when national data are reported, these rates are usually < 10 episodes of VAP/1,000 ventilation-days.[2-6]

For editorial comment see page 1745

Using shorter regimens may help in decreasing antimicrobial resistance and reduce drug-related adverse events.[7] Short-course treatments were found to be as effective as longer-course antibiotic treatment of other

types of respiratory infections, including exacerbations of chronic bronchitis and community-acquired pneumonia.[8,9]

Patients with VAP have significantly longer ICU and hospital lengths of stay compared with similar patients without VAP.[10,11] Consequently, the economic burden of VAP is considerable, leading to significant draining of resources. Even after adjusting for underlying severity of illness, the attributable cost of VAP amounts to several thousands of US dollars per patient.[12-14] An approach that may contribute to the reduction of this cost is the shortening of therapeutic regimens that are used for the treatment of VAP. We sought the available evidence to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) so as to determine whether a similar approach could be applied to the treatment of patients with VAP in the critical care setting.

Materials and Methods

Data Sources

Two independent reviewers performed the literature search in PubMed until November 15, 2012 and the Cochrane Central Register of Controlled Trials. Also, the bibliographies of evaluable studies were hand searched. The search terms used were "VAP," "ventilator-associated pneumonia," "short," "long," "duration," "course," "treatment," and "therapy." The same two reviewers performed the evaluation of papers that were potentially eligible for inclusion as well as the extraction of data. Any disagreements regarding the findings of the two reviewers were resolved in meetings including the majority of authors.

Study Selection Criteria

For an identified trial to be included in the meta-analysis, it had to (1) be a randomized controlled trial; (2) involve patients with VAP, diagnosed on the basis of cultures with or without the aid of complementary imaging, laboratory, or microbiologic criteria; (3) compare treatment administered for a different duration of time (short- and long-course); (4) have a short-course regimen with a duration up to 8 days and a long-course regimen with a duration of at least 10 days; and (5) report data regarding any of the following outcomes: mortality, antibiotic-free days, relapse of VAP, mechanical ventilation-free days, duration of mechanical ventilation, and length of ICU stay. Studies including patients with both early- and late-onset VAP were considered evaluable. No language restrictions were applied. Conference abstracts were excluded.

Quality Assessment

The methodological quality of the included RCTs was evaluated by criteria assessing the existence and appropriateness of randomization procedures, the existence and appropriateness of blinding procedures, and the reporting of information on study withdrawals, if present. One point was awarded for the existence of randomization and blinding procedures as well as for withdrawal information. The values of −1 (inappropriate), 0 (no specific data), and +1 (appropriate) were awarded for the appropriateness of randomization and blinding procedures, respectively. The maximum score was 5 points. Trials with >2 points were considered as being of adequately good quality.[15,16]

Data Extraction

Data extracted from each eligible RCT included author name and year of publication, country and setting, size of the total patient population, size per treatment arm, compared regimens, Simplified Acute Physiology score (SAPS) II or Sequential Organ Failure Assessment (SOFA) score. Data extracted regarding outcomes included mortality, antibiotic-free days, relapses, mechanical ventilation-free days, duration of mechanical ventilation, and length of ICU stay. All extracted data were used as defined by the authors.

Definitions—Outcomes

The primary outcomes of the meta-analysis were mortality, antibiotic-free days, and relapses. Regarding mortality, timing of the outcome assessment was 28 days. If no such data were reported, then available mortality data of at least 21 and up to 30 days were used. Antibiotic-free days were used as defined by the authors of each RCT. Relapses were defined as repetitive clinically and microbiologically documented pneumonias due to the same pathogen. The secondary outcomes were mechanical ventilation-free days, duration of mechanical ventilation, and length of ICU stay. They were used as defined by the authors of each RCT. Analyses were performed only when data from at least two RCTs were available. Sensitivity analyses were performed including trials reporting data for 28-day mortality only, trials reporting data on patients with nonfermenting gram-negative bacteria, trials including patients with late-onset VAP only, trials administering a short-course regimen of 8 days and a long course of 15 days, and trials using the same antibiotic in both treatment arms.

Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration). Statistical heterogeneity between studies was assessed by χ^2 test and I^2 test; values of the I^2 index of 25%, 50%, and 75% indicated the presence of low, moderate, and high between-trial heterogeneity, respectively, whereas a P value $<.10$ was considered to denote statistical significance of heterogeneity.[17] Continuous variables were analyzed using weighted mean differences (WMDs) and 95% CIs. Pooled ORs and 95% CIs were calculated for dichotomous variables. For all analyses performed, if no significant heterogeneity was noted, fixed effect model (FEM) analysis using the Mantel-Haenszel method[18] was presented; otherwise, results of the random effects model (REM) analysis using

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the DerSimonian-Laird method[19] were presented. The small number of the included RCTs did not allow the estimation of potential publication bias with the funnel plot method for any of the outcomes, either primary or secondary.

Results

Study Selection Process

A flow diagram of the screening and selection of articles to be included in the meta-analysis is presented in Figure 1. We identified 843 and 85 potentially evaluable trials from PubMed and Cochrane Central Register of Controlled Trials, respectively. Of those, four RCTs were eventually included in the meta-analysis.[20-23]

Study Characteristics

The main characteristics of the included RCTs are presented in Table 1. Three of four of the included RCTs were multicenter,[20,23] and the remaining RCT was single-center.[21] Two of four of the included RCTs were open.[21,23] Two of four of the included RCTs were performed in France,[20,23] one was performed in Tunisia,[21] and the remaining one was international.[22] The French trials had a duration of 8 days for the short-course treatment and 15 days for the long-course treatment, and the remaining trials had a duration of 7 and 10 days for the respective courses. One RCT included patients with early-onset VAP,[23] two included patients with late-onset VAP,[20,22] and the remaining RCT included patients with mixed types of VAP.[21] The administered antibiotic regimens varied between RCTs but were consistent in each of the compared arms except the international RCT,[22] in which the short-course regimen included doripenem and the long-course regimen included imipenem-cilastatin. Although the administered antibiotics were not the same, they belong to the same class, with similar administration pattern and pharmacokinetics. Three RCTs reported SAPS II data,[20,21,23] and two RCTs reported SOFA data.[20,22] The predicted mortality of both treatment arms in all of the included RCTs was < 35%, irrespective of the score used.

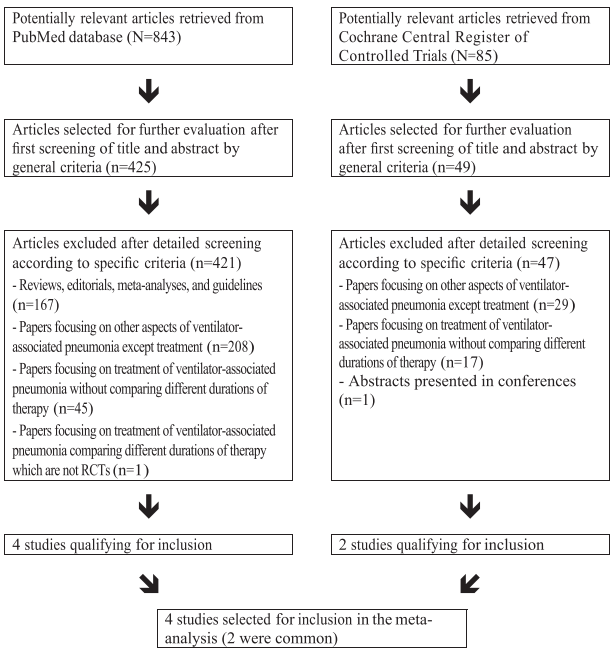

Figure 1. Flow diagram of the article selection process for this meta-analysis. RCT = randomized controlled trial.

Primary Outcomes

The extracted data regarding the primary and secondary outcomes are presented in Table 2.

Mortality: Data on mortality were provided in all RCTs included. There was no difference in mortality between the compared courses ($P = .86$; $I^2 = 0\%$; FEM: OR = 1.20; 95% CI, 0.84-1.72; $P = .32$) (Fig 2).

Sensitivity analysis limited to trials reporting data on 28-day mortality[20-22] showed no difference between the compared courses ($P = .71$; $I^2 = 0\%$; FEM: OR = 1.23; 95% CI, 0.83-1.81; $P = .30$). Sensitivity analysis limited to trials reporting data on 28-day mortality in patients with nonfermenting gram-negative bacteria[20,22] showed no difference between the compared courses ($P = .06$; $I^2 = 72\%$; REM: OR = 1.33; 95% CI, 0.33-5.26; $P = .69$) (Fig 3). Sensitivity analysis limited to trials reporting data of patients with late-onset VAP[20,22] showed no difference between the compared courses ($P = .47$; $I^2 = 0\%$; FEM: OR = 1.25; 95% CI, 0.84-1.88; $P = .27$). Sensitivity analysis limited to trials administering a short-course regimen of 8 days and a long course of 15 days[20,23] showed no difference between the compared courses ($P = .91$; $I^2 = 0\%$; FEM: OR = 1.10; 95% CI, 0.70-1.72; $P = .68$). Sensitivity analysis limited to using the same antibiotic in both treatment arms[20,21,23] showed no difference between the compared courses ($P = .97$; $I^2 = 0\%$; FEM: OR = 1.08; 95% CI, 0.71-1.67; $P = .71$).

Antibiotic-Free Days: Data on antibiotic-free days were provided in two of four of the included RCTs.[20,21] Antibiotic-free days were increased in the short-course treatment arm with a pooled WMD of 3.40 days ($P = .03$; $I^2 = 79\%$; REM: 95% CI, 1.43-5.37; $P < .001$) (Fig 4).

Relapses: Data on clinical and microbiologic relapses were provided in three of four of the included RCTs.[20,21,23] There was no difference in relapses between the compared arms, although a strong trend to lower relapses in the long-course treatment was observed ($P = .71$; $I^2 = 0\%$; FEM: OR = 1.67; 95% CI, 0.99-2.83; $P = .06$) (Fig 5). Similarly, sensitivity analysis limited to trials

Table 1—*Main Characteristics of the Included Trials*

Study/Year	Study Design	Short-Course Regimen (Type, Duration)	Long-Course Regimen (Type, Duration)	Population (Short, Long)	Timing of Outcome Assessment	SAPS II, SOFA (Short, Long)	Jadad Score
Capellier et al[23]/2012	Early-onset VAP Open, multicenter, France	β-Lactams combined with an aminoglycoside for the first 5 d 8 d	β-Lactams combined with an aminoglycoside for the first 5 d 15 d	225 (116, 109)	21 d	39.2 ± 13.4, 39.7 ± 12.5 NR	3
Kollef et al[22]/2012	Late-onset VAP Double-blind, multicenter, international	Doripenem 1 g q8h as a 4-h infusion 7 d	Imipenem-cilastatin 1 g q8h as a 1-h infusion 10 d	227 (115, 112)	28 d	NR 6 ± 2.7, 5.5 ± 2.39	4
Fekih Hassen et al[21]/2009	Mixed VAP Open, single-center, Tunisia	Empirical treatment based on nosocomial flora, type of VAP onset, and other risk factors and subsequent adaptation to antibiograms 7 d	Empirical treatment based on nosocomial flora, type of VAP onset, and other risk factors and subsequent adaptation to antibiograms 10 d	30 (14, 16)	28 d	46.3 ± 4.2, 39.2 ± 3.6 NR	3
Chastre et al[20]/2003	Late-onset VAP Double-blind, multicenter, France	Combination of at least an aminoglycoside or a fluoroquinolone and a broad-spectrum β-lactam 8 d	Combination of at least an aminoglycoside or a fluoroquinolone and a broad-spectrum β-lactam 15 d	401 (197, 204)	28 d	45 ± 15, 45 ± 15 7.3 ± 4, 7.4 ± 4	3

SAPS and SOFA were reported as mean ± SD. NR = not reported; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; VAP = ventilator-associated pneumonia.

Table 2—*Primary and Secondary Outcomes of the Included Trials*

Study/Year	Mortality, n of N (%)		Abx-Free Days (Mean ± SD)		Relapses, n of N (%)		MV-Free Days (Mean ± SD)		Duration of MV (Mean ± SD)		LOS in ICU (Mean ± SD)	
	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long
Capellier et al[23]/2012	10 of 116[a] (8.6)	9 of 109[a] (8.3)	NR	NR	6 of 116 (5.2)	2 of 109 (1.8)	NR	NR	13.6 ± 5.3	13.4 ± 5.9	15.9 ± 5.1	15.7 ± 5
Kollef et al[22]/2012	26 of 115[b] (22.6)	18 of 112[b] (16.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fekih Hassen et al[21]/2009	5 of 14 (35.7)	6 of 16 (37.5)	4.1 ± 1.9	1.8 ± 1.6	1 of 16 (6.3)	1 of 14 (7.1)	3.4 ± 1.9	2.1 ± 1.8	18.9 ± 3.3	18.9 ± 3.8	26.1 ± 3.8	27.7 ± 4.6
Chastre et al[20]/2003	37 of 197[c] (18.8)	35 of 204[c] (17.2)	13.1 ± 7.4	8.7 ± 5.2	33 of 197 (16.8)	23 of 204 (11.3)	8.7 ± 9.1	9.1 ± 9.4	NR	NR	30 ± 20	27.5 ± 17.5

Abx = antibiotic; LOS = length of stay; MV = mechanical ventilation. See Table 1 legend for expansion of other abbreviation.

[a]Refers to 21-d mortality.

[b]Mortality for nonfermenting gram-negative bacteria was 12 of 47 (25.5) and 4 of 38 (10.5) for short- and long-course therapy, respectively.

[c]Mortality for nonfermenting gram-negative bacteria was 15 of 64 (23.4) and 19 of 63 (30.2) for short- and long-course therapy, respectively.

administering a short-course regimen of 8 days and a long course of 15 days[20,23] showed no difference between the compared courses but a marginally nonsignificant trend to lower relapses in the long-course treatment ($P = .49$; $I^2 = 0\%$; FEM: OR = 1.71; 95% CI, 1.00-2.92; $P = .05$).

Secondary Outcomes

Mechanical Ventilation-Free Days: Data on mechanical ventilation-free days were provided in two of four of the included RCTs.[20,21] There was no difference in mechanical ventilation-free days between the compared arms ($P = .12$; $I^2 = 58\%$; FEM: WMD = 0.75 days; 95% CI, −0.32 to 1.82; $P = .17$).

Duration of Mechanical Ventilation: Data on duration of mechanical ventilation were provided in two of four of the included RCTs.[21,23] There was no difference in duration of mechanical ventilation between the compared arms ($P = .89$; $I^2 = 0\%$; FEM: WMD = 0.15 days; 95% CI, −1.12 to 1.42; $P = .82$).

Length of ICU Stay: Data on length of ICU stay were provided in three of four of the included RCTs.[20,21,23] There was no difference in length of ICU stay between the compared arms ($P = .23$; $I^2 = 31\%$; FEM: WMD = 0.16 days; 95% CI, −0.99 to 1.31; $P = .79$). Sensitivity analysis limited to trials administering a short-course regimen of 8 days and a long course of 15 days[20,23] showed no difference between the compared courses ($P = .25$; $I^2 = 25\%$; FEM: WMD = 0.46 days; 95% CI, −0.78 to 1.70; $P = .47$).

Discussion

The main finding of our meta-analysis was that short-course (7-8 days) treatment of VAP had no difference in terms of mortality compared with long-course (10-15 days) treatment. Short-course treatment was associated with increased antibiotic-free days compared with long-course treatment. No difference was found regarding relapses between the compared arms, although a marginally nonsignificant trend to lower relapses in the long-course treatment was observed.

Although data regarding the first two primary outcomes are consistent, relapses merit further consideration. The relapse data of the large French trial[20] have the greatest weight and seem to strongly drive the comparison with lower relapses in the long-course treatment. However, it should be noted that the bulk of patients with relapses in this study were those with VAP due to nonfermentative gram-negative bacilli, for which relapses and persistence are frequently reported.[24,25] Contrary to that, no difference in relapses was found between the compared courses in patients

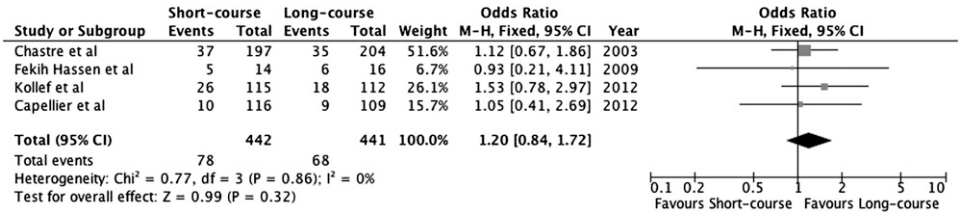

FIGURE 2. ORs of mortality. Vertical line is the "no difference" point in mortality between the two arms. Horizontal lines are 95% CI. ■ = OR; the size of each square denotes the proportion of information provided by each trial. ◆ = pooled OR for all trials. df = degrees of freedom; M-H = Mantel-Haenszel.

with VAP due to other pathogens. The role of nonfermenters in relapses of VAP, especially of *Pseudomonas aeruginosa*, has also been confirmed by other studies.[24,25] Failure to eradicate this pathogen in such patients may be associated with mechanisms that facilitate the evasion of the host immune response.[26] Furthermore, persistence of nonfermenters in low bacterial counts may represent colonization rather than infection, which might impact estimation of "relapse rates," depending on the objectivity of the criteria used for the definition of relapse. Actually, there is a fair chance that many of the "relapses" in the large French trial[20] may have been instances of persistent colonization rather than clinical failure, because relapses were primarily defined on the basis of microbiologic rather than clinical criteria. The stipulated clinical triggers for microbiologic reevaluation were broad and nonspecific for pneumonia. The lack of difference in concrete clinical outcomes supports the possibility that this trial detected higher microbiologic persistence rather than clinically impactful failures. On the other hand, long courses of antibiotic therapy essentially lead to fewer antibiotic-free days, consequently exerting increased selection pressure and predisposing to emergence of multidrug-resistant strains.[27]

A retrospective comparative study[28] assessing different durations of antibiotic therapy for VAP caused by nonfermentative gram-negative bacilli triggers further uncertainty regarding recurrences. It not only does not find any difference in the recurrences between the compared arms but also reports a trend in favor of the short-course treatments.

According to our findings, short-course therapies seem to be clinically equivalent for the treatment of patients with VAP, with a possible exception of nonfermenters being the causative pathogens. A solution that could help in evading this obstacle may be the administration of short-course regimens in conjunction with monitoring of biomarker serum levels. Such a biomarker that may be monitored is procalcitonin, the levels of which were found to be good predictors of relapses.[29] Procalcitonin-guided algorithms may also help in reducing the duration of antimicrobial administration without having a negative impact on survival.[30,31]

One relevant meta-analysis has been published.[31] Although it focuses on hospital-acquired pneumonia, it includes as a subset trials studying VAP. Analyses of this subset yield similar results to ours regarding mortality and antibiotic-free days. Additionally, in this meta-analysis short-course treatment was associated with fewer recurrences due to multiresistant pathogens but more recurrences due to nonfermenting gram-negative bacilli. Similar results with the aforementioned papers were also yielded by a review that examines trials that indirectly provide useful information on the issue.[32]

In our meta-analysis, we chose to focus on relapses and not on recurrences, which essentially include superinfections and constitute a composite outcome. Although we would like to assess the impact of nonfermenting gram-negative bacilli on the relapses, there is, to our knowledge, only one trial[20] that provided detailed data regarding nonfermenting gram-negative bacilli. A Uruguayan study,[33] which provided relevant data and was included in the previous meta-analysis, was excluded from ours as it was an abstract, which was never published as an article.

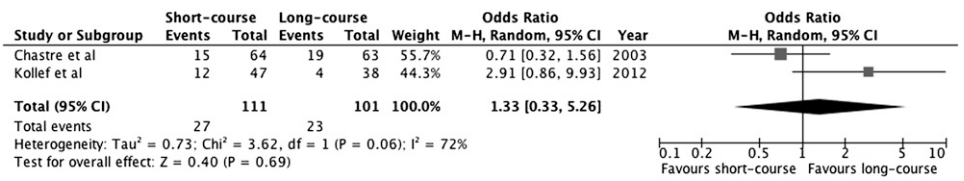

FIGURE 3. ORs of mortality in patients with nonfermentative gram-negative bacteria. Vertical line is the "no difference" point in mortality between the two arms. Horizontal lines are 95% CI. See Figure 2 legend for explanation of symbols and expansion of abbreviations.

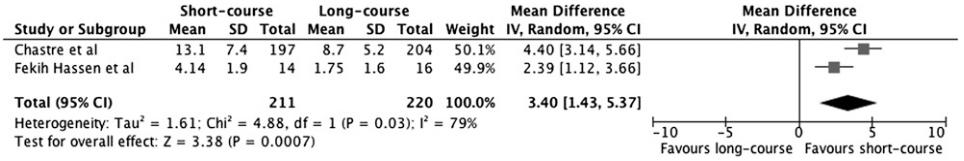

FIGURE 4. Weighted mean difference of antibiotic-free days. Vertical line is the "no difference" point in antibiotic-free days between the two arms. Horizontal lines are 95% CI. See Figure 2 legend for explanation of symbols and expansion of abbreviations.

One may argue that pooling data from trials including patients with both early- and late-onset VAP does not make clinical sense. The reason for that is the cause of early-onset VAP, which comprises mostly "community" pathogens, whereas late-onset VAP is caused by more resistant "nosocomial" strains.[34,35] Also, late-onset VAP is associated with worse outcomes compared with early-onset VAP.[36,37] Actually, in the small French study,[23] which includes only patients with early-onset VAP, most patients were infected by "community-acquired pathogens," such as *Streptococcus pneumoniae* and methicillin-sensitive *Staphylococcus aureus*, but very few "nosocomial" pathogens, such as methicillin-resistant *S aureus*, *P aeruginosa*, and *Acinetobacter baumannii*. Moreover, the antibiotic regimens assessed in the study, with the exception of aminoglycosides, include drugs usually used for severe community-acquired pneumonia (amoxicillin-clavulanic acid, ceftriaxone, or cefotaxime). Since most infections in this study resemble severe community-acquired pneumonia more than VAP, it would theoretically favor the absence of difference between treatments, because short therapy has been shown to be suitable for the former condition.[8] On the other hand, VAP is increasingly associated with multidrug-resistant pathogens regardless of early or late onset. Prior antibiotic use and previous hospitalization may have a role in this shift.[38-40] Furthermore, given that the comparisons include similar therapeutic schemes for different duration for similar pathogens in each of the compared arms may safely allow the performance of meaningful pooled analyses regardless of VAP onset and type of pathogen resistance. Thus, the extrapolation and applicability of our observations to the total of patients in the ICU with VAP may be facilitated and clinically valid. Additionally, the sensitivity analyses of trials including patients with only late-onset VAP, which we performed to further study the issue under this perspective, yielded similar results. Thus, despite the existing pooling of early-onset with late-onset VAP in the currently available literature, which may be debatable in general, we deemed that some common characteristics between the two types of VAP and the special design of the included trials comparing same regimens with different duration ensured the methodologic validity of our interpretations.

The timing of outcome assessment, $\leq$28 days, especially when it comes to hard clinical outcomes such as mortality, may be an insufficient length of time to capture all severe illness-related consequences in the hospital. It should be noted that the timing of outcome assessment of 28 days barely exceeds the mean length of stay in the ICU in the included trials. A longer timespan may be more appropriate to correctly measure outcomes, especially the ones serving as primary comparators.

There are some additional limitations of our meta-analysis that need to be further considered. First, the number of studies was small, including 883 patients. However, the number of included patients for the two out of three primary outcomes, namely mortality and relapses, as well as for most of the remaining outcomes, was large enough to allow for the detection of statistical significance, if any. Specifically, 590 patients (295 in each arm) are required to be 80% sure that a 95% two-sided CI will exclude a difference in favor of the long course of $>$10%, considering that the mortality of the long-course recipients with VAP is 25%. Even so, it should be noted that the large French trial is the major "driver" of the results in most of the

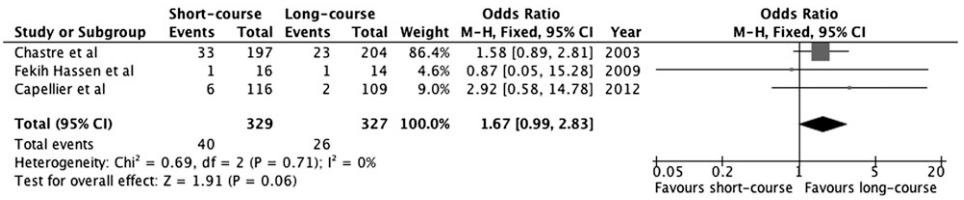

FIGURE 5. ORs of relapses. Vertical line is the "no difference" point in relapses between the two arms. Horizontal lines are 95% CI. See Figure 2 legend for explanation of symbols and expansion of abbreviations.

analyses. Overall, this does not impair the validity of the study but suggests the thoughtful interpretation of the findings and conclusions. Regarding the heterogeneity, which was found in two of the analyses, namely the antibiotic-free days and the 28-day mortality in patients with nonfermenting gram-negative bacteria, there should be no skepticism in the interpretation of the results. In the former case, more homogeneous data would further strengthen the already significant finding, whereas in the latter case the small sample size would not allow the detection of statistical significance even in the presence of homogenous data.

The overall quality was good, since all of the included trials yielded a Jadad score of ≥ 3. However, one-half of the included studies were open in design, which may inherently cause some bias. Second, all but one of the included RCTs were conducted in just two countries, with the bulk of the patients coming from France. The timing of outcome assessment was not the same in all of the included trials, being 28 days in three of four RCTs[20-22] and 21 days in the remaining one.[23] Furthermore, the duration of the short and long course varied, with one-half of the included trials using a short course of 8 days and a long course of 15 days, whereas the remainder used 7 and 10 days, respectively. Also, in one of the trials, the two regimens had different antibiotics, although of the same class. To overcome these limitations, we performed sensitivity analyses, which did not demonstrate any significant difference.

Conclusions

Conclusively, short-course antibiotic treatment had no difference in terms of mortality compared with long-course regimens for the treatment of patients with VAP. It was associated with increased antibiotic-free days and had no difference in terms of relapses, although there was a trend in favor of long-course treatment, which is attributed to nonfermentative gram-negative bacilli as causative pathogens of VAP. Further trials are warranted to shed light on the issue of optimizing duration of VAP treatment. Until more definitive data become available, treatment duration should be properly tailored with the use of other auxiliary methods to effectively balance the cons and take advantage of the pros of both short- and long-course antibiotic treatments. The optimal duration of treatment of VAP by nonfermenters merits further evaluation in targeted trials.

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Dr Dimopoulos: contributed to conceiving and designing the meta-analysis, revised the article critically for important intellectual content, and provided final approval of the version to be published.
Dr Poulakou: contributed to acquiring, analyzing, and interpreting the data; revised the article critically for important intellectual content; and provided final approval of the version to be published.
Dr Pneumatikos: contributed to interpreting the data, revised the article critically for important intellectual content, and provided final approval of the version to be published.
Dr Armaganidis: contributed to interpreting the data, revised the article critically for important intellectual content, and provided final approval of the version to be published.
Dr Kollef: contributed to conceiving and designing the meta-analysis, revised the article critically for important intellectual content, and provided final approval of the version to be published.
Dr Matthaiou: contributed to acquiring, analyzing, and interpreting the data; drafted the submitted article; and provided final approval of the version to be published.
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