Comparison of mono- and combination antibiotic therapy for the treatment of *Pseudomonas aeruginosa* bacteraemia: A cumulative meta-analysis of cohort studies

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**Abstract.** It is currently unknown whether antibiotic monotherapy or combination therapy is a more effective treatment for patients with *Pseudomonas aeruginosa* bacteraemia. The present study consists of a systematic review and meta-analysis of cohort studies in associated studies. The treatment options of monotherapy and combination therapy have been compared, to determine which is more effective against *P. aeruginosa* bacteraemia. Several electronic bibliographic databases were systematically searched and clinical studies that compared combination therapy with monotherapy for *P. aeruginosa* bacteraemia were identified. Dersimonian and Laird’s random-effects models were used to generate summary estimates of the effects and to assess their association according to different patient characteristics and research quality standards. A total of 17 studies were selected, 3 of which were prospective while the remaining 14 were retrospective. The studies involved a total of 2,504 patients. Significant differences between combination therapy and monotherapy treatment were not found when the data were combined (odds ratio (OR)=0.81, 95% confidence interval (CI)=0.61-1.08; P=0.035). The results demonstrated strength in a number of stratification and sensitivity analyses. The variables used included study type, treatment quality score and survival rate of subgroup analysis. To conduct cumulative meta-analysis, the number of years and samples were calculated. The OR value and 95% CI were stable and demonstrated good change trend. According to the size of the sample order following accumulation, OR values and 95% CI (0.89, 0.76-1.04) exhibited a narrow range. Neither combination therapy or monotherapy exhibited significant effects on the mortality of patients with *P. aeruginosa* bacteraemia. Future research is required and should include large, well-designed prospective cohorts, and grouped clinical studies.

**Introduction**

*Pseudomonas aeruginosa* is a common clinical cause of gram-negative bacterial, nosocomial infections (1), and causes serious infections in neutropenic and immunocompromised patients (2). Within intensive care units, *P. aeruginosa* has become the most common gram-negative bacterial species associated with severe hospital-acquired infections (2,3). At present, the worldwide morbidity and mortality rates of *P. aeruginosa* are 18 and 61% respectively (1-3). The treatment of *P. aeruginosa* infections in a clinical setting remains a notable challenge. The capacity of patients to ingest the appropriate antibiotics in a timely manner positively affects prognosis of severe pseudomonas-infection (4). As such, this variable serves as an important controllable risk factor (4,5). Clinical infection with *P. aeruginosa* may be associated with an increase in 30-day mortality in patients. Treatment with appropriate antibiotics, such as β-lactam and fluoroquinolone, is associated with the prognosis (6). However, the use of appropriate antibiotic treatment does not consistently show satisfactory effects on patients (7,8). It has previously been suggested that the inappropriate use of antibiotics in the treatment of *P. aeruginosa* bacteraemia may be minimised by a combination antibiotic regimen, in which the sensitivity of results is determined following treatment (8). Inappropriate use of empirical antibiotic therapy has been identified as an independent contributor to the high hospital mortality rate of *P. aeruginosa* bacteraemia (8,9). Combination therapy has been shown to yield improved results compared with

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single treatment of *P. aeruginosa* bacteraemia (6,9), and combination empirical antimicrobial therapy directed against gram-negative bacteria may be a more appropriate treatment approach than monotherapy (10). Despite the merits of relevant studies on empirical combination therapy, it is still unclear whether the use of combination therapy is more effective than monotherapy in treating *P. aeruginosa* infection (10-18). In the present study a meta-analysis was conducted and the mortality of patients treated with either combination therapy or the appropriate monotherapy for *P. aeruginosa* bacteraemia was compared and evaluated.

**Materials and methods**

**Search terms.** Several electronic bibliographic databases were searched including the Chinese Biomedical Literature Database (Wanfang, China), China Academic Journals Full-text database, Cochrane Library, PubMed and Embase for the identification of relevant studies (as of April 2017). The included search terms were: *Pseudomonas aeruginosa*, bacteraemia, monotherapy, combination therapy, antibiotic, mortality and outcome. The databases were searched manually to identify potentially relevant studies. The reference lists of all retrieved articles were also searched to find research that could qualify for the study. Only articles written in Chinese or English were considered; articles written in German, French, Spanish, Italian and Greek were not evaluated. Ultimately, all included papers were written in English. The study inclusion criteria were as follows: i) The study compared the efficacy of monotherapy and combination therapy; ii) retrospective and prospective studies; iii) the treatments discussed in the study included at least one antibiotic agent, which was reported following sustained or initial antibacterial spectrum results (8); and iv) the study results included data on mortality.

**Study selection.** Two experienced independent reviewers (S-YT and S-WZ) subsequently read through the results and decided which studies were appropriate to be included in the meta-analysis (5,10-25). Any differences in opinion between the two reviewers were resolved by discussion until a consensus was reached. The following data was extracted from each qualified study: Name of first author, type of publication, type of study design, gender and age of patients, sample size, length of hospital stay, type of treatment, type and choice of drugs, mortality, outcomes, number of different populations, and odds ratio (OR) and 95% confidence interval (CI) results. The possible risk estimates were extracted and adjusted using hybrid variables.

**Quality assessment.** The selected studies were evaluated using a system based on the cohort study using the Newcastle-Ottawa scale (26), which provides a score for studies between 1-9 ‘stars’. Three aspects were used to assess the quality of studies: i) Choice of learning study, ii) organisational evaluation and iii) evaluation of comparison results. As there is dispute over the number of stars that must be used as an indicator of high-quality studies (27-33), the included studies were compared; studies that received ≥7 stars (7,8,9) were defined as high-quality studies, and those that scored ≤6 were not.

**Statistical methods.** Statistical analysis was conducted using Stata version 12.0 software (StataCorp LP, College Station, TX, USA). ORs with 95% CIs were extracted from studies to evaluate the outcomes of mortality. Cochrane's X2 Q and I^2 tests were employed to assess the differences in data from different studies. Stochastic models were applied to heterogeneity studies (P<0.1 or I^2≥50%) (34,35). The Mantel-Haenszel fixed-effect model was used to calculate pools or studies when P>0.10 and I^2≥50%; otherwise, the Dersimonian and Laird's random-effects model was used to combine results (36). A sensitivity analysis was also conducted to examine the effects of each study on mixed outcomes. To establish the effects of clinical heterogeneity on meta-analysis, a subgroup analysis was conducted based on study characteristics. Egger's precision-weighted linear regression tests and funnel charts were used to assess potential publication bias (37). When a study demonstrated potential publication bias, the nonparametric correction and filling method was applied. The filling method evaluates the possibility of ‘missing’ studies that may exist and recalculates the pool or merges them (34,35). The results of the meta-analysis were stratified by types of study and treatment. P<0.05 was considered to indicate a statistically significant difference, unless otherwise stated.

**Results**

**Search results.** Fig. 1 demonstrates the process of study selection and the number of studies excluded at each stage. In the initial search 115 studies were identified, and following a review of the titles, 31 studies were considered for inclusion. The summaries of those 31 studies were reviewed and all studies that were considered eligible were retrieved. Among these studies 14 were excluded for the following reasons: 3 studies did not compare monotherapy and combination therapy; 4 studies did not include mortality rate in the assessment of results; 2 were excluded because patient infection did not cause bacteraemia; and 5 were excluded as data could not be extracted. Therefore, following the screening process 17 studies qualified (5,10-25) and were included in the meta-analysis; they covered a total of 2,504 patients with cases of *P. aeruginosa* bacteraemia.

**Study characteristics.** Within the qualified studies, 14 were retrospective studies and 3 were prospective studies (Fig. 2). There were 5 studies that reported outcomes of empirical treatment and 12 studies that reported outcomes of definitive treatment (Fig. 3). There were 4 studies conducted in the United States, 7 in Europe, 6 in Asia and 1 was conducted in the United States and Singapore (Table 1). According to the Newcastle-Ottawa Scale, 16 of the included studies scored ≥6 and were rated as good or excellent quality (Table 1).

**Mortality.** There were 8 studies that used survival for 30 days, 1 that used survival for 14 days and 1 that used survival for 10 days as the desired outcome of the study. There were 7 studies that considered overall survival as the desired outcome. In terms of mortality, significant difference was observed between patients who received definitive treatment compared with those who received the appropriate empirical treatment (OR=0.81, 95% CI=0.61-1.08; Fig. 3).
Publication bias. Considering the observed heterogeneity (P=0.035; I²=42.1%) of the 17 included studies, a random-effects model was used for their analysis (Fig. 2). The following factors were considered: Source of patients, types of study design (OR=0.85, 95% CI=0.60-1.19, P=0.034), types of treatment (OR=0.72, 95% CI=0.42-1.23, P=0.019), study population (OR=0.74, 95% CI=0.41-1.33, P=0.036), literature quality score (OR=0.67, 95% CI=0.45-1.00, P=0.082), and mortality of subgroup stratification analysis (OR=1.17, 95% CI=0.75-1.85, P=0.117; Table II). Retrospective and prospective studies were significantly different in subgroup analysis. Visual inspection of the funnel plots revealed asymmetry among studies (Fig. 4). Consolidation effect was assessed to review the influence results for each study (Fig. 5). Beggerr's and Egger's tests were conducted to determine publication bias (Figs. 6 and 7) and L'Abbé analysis was performed to assess the heterogeneity of effect sizes, which revealed no marked heterogeneity (Fig. 8). The Z-value and P-value of Beggerr's test reached 0.21 and 0.805, respectively, and the t-value and P-value of Egger's test totalled -0.24 and 0.815 respectively. Both P-values of Egger's test and Beggerr's test were >0.05. Therefore, these results indicated that there was no compelling evidence to affirm that results obtained were free from published publication bias.

Subgroup and sensitivity analysis. Table II demonstrates the stratified analysis designed to focus OR of 0.85 (95% CI=0.60-1.19) for 14 retrospective cohorts and the 12 studies with specific definitive therapy OR of 0.88 (95% CI=0.62-1.24). A strong correlation was identified in studies conducted in Asian countries, and study quality and mortality did not significantly affect the results (Figs. 9-11).

The contribution of studies to overall prevalence and 95% CIs was evaluated. In sensitivity analyses, surveyed time strip was omitted and then results were combined with a single dataset on pooled ORs. Corresponding pooled ORs did not change significantly from 0.67 (95% CI=0.45-1.00) to 0.85 (95% CI=0.60-1.19). Therefore, the results obtained were considered statistically strong.

Cumulative meta-analysis. Heterogeneity inspection was conducted initially and the effects, combined effects and their corresponding CI were evaluated to obtain the Q statistic and its corresponding P-value. Heterogeneity=27.63 (degree of freedom=16), P=0.035 and P=42.1%. Given
Table I. Characteristics of the eligible studies included in the meta-analysis of monotherapy vs. combination therapy for *Pseudomonas aeruginosa* bacteremia.

| Author, year | Study design | Study period | Country | Treatment | Mortality outcome | Mortality (mortality cases/total) | Study quality |
|--------------|--------------|--------------|---------|-----------|------------------|----------------------------------|--------------|
| Bowers et al., 2013 | Retrospective | 2002-2011 | USA/Singapore | Appropriate empirical therapy | Combination | 3/82 | 82/286 |
| Park et al., 2012 | Retrospective | 1997-2011 | South Korea | Appropriate empirical therapy | Combination | 11/33 | 17/32 |
| Bhrtis et al., 2011 | Retrospective | 2001-2007 | Greece | Definitive treatment | Combination | 8/31 | 82/286 |
| Park et al., 2012 | Retrospective | 2002-2011 | South Korea | Appropriate empirical therapy | Combination | 10/33 | 17/32 |
| Bliziotis et al., 2011 | Retrospective | 2001-2007 | Greece | Definitive treatment | Combination | 8/19 | 82/286 |
| Micek et al., 2005 | Retrospective | 1997-2002 | USA | Definitive treatment | Combination | 10/46 | 10/46 |
| Chamot et al., 2003 | Retrospective | 1988-1998 | Switzerland | Definitive treatment | Combination | 10/46 | 10/46 |
| Siegman-Isruga et al., 1998 | Retrospective | 1990-1992 | Israel | Definitive treatment | Combination | 7/42 | 7/42 |
| Kuikka et al., 1992 | Retrospective | 1976-1982 | Finland | Definitive treatment | Combination | 7/42 | 7/42 |
| Leibovici et al., 1997 | Prospective | 1988-1995 | Israel | Definitive treatment | Combination | 4/15 | 4/15 |
| Hilf et al., 1989 | Prospective | 1982-1990 | USA | Definitive treatment | Combination | 7/42 | 7/42 |
| Krikka and Valiente, 1999 | Retrospective | 1997-1998 | Finland | Definitive treatment | Combination | 7/42 | 7/42 |
| Kerret et al., 1994 | Retrospective | 1993-1994 | France | Definitive treatment | Combination | 7/42 | 7/42 |
| Lefkovitz et al., 1997 | Prospective | 1982-1990 | Israel | Definitive treatment | Combination | 7/42 | 7/42 |
| TANG et al. | Pseudomonas aeruginosa BACTEREMIA | 2421 | | | | | |
Table I. Continued.

| Author, year, Study Design, Study Period | Country | Therapy type | Drugs | Mortality (mortality cases/total) | Independent risk factors |
|----------------------------------------|---------|--------------|-------|----------------------------------|--------------------------|
| Peña et al, 2013, Prospective 2010-2011, Spain | Definitive treatment | A β-lactam + aminoglycoside, fluoroquinolones or colistin | A β-lactam or aminoglycoside or fluoroquinolones or colistin | 30 days 13/71 70/339 9 | Hepatobiliary HIV/AIDS, diabetes mellitus, MODS (18) |
| Kim et al, 2014, Retrospective 2010-2012, South Korea | Definitive treatment | A β-lactam and aminoglycosides fluoroquinolones, colistin and fluoroquinolones or aminoglycosides | A β-lactam, fluoroquinolones, colistin or aminoglycosides | 14 days 642 32/141 9 | Diabetes mellitus, liver cirrhosis, malignancy, hypertension (16) |
| Samonis et al, 2014, Retrospective 2004-2010, Greece | Definitive treatment | A β-lactam + aminoglycoside/ fluoroquinolone, colistin or colistin + other | A β-Lactam or fluoroquinolone, colistin | Mortality 12/37 14/45 8 | Chronic lung disease, diabetes mellitus, chronic heart disease, chronic renal disease (17) |
| Tan SH et al, 2014, Retrospective 2007-2008, Singapore | Definitive treatment | A β-lactam + aminoglycosides or ciprofloxacin | A β-Lactam or aminoglycosides or ciprofloxacin | 30 days 2/14 17/77 9 | SAPS II score, HIV/AIDS, diabetes mellitus, cardiovascular dysfunction (25) |
| Deconinck et al, 2017, Retrospective 1994-2014, France | Appropriate empirical therapy | A β-Lactam + an aminoglycoside, aquinolone or colistin | A β-Lactam, aminoglycoside, fluoroquinolone or colistin | 30 days 32/85 7/15 9 | Shock, SAPS II, multiresistant strains (13) |
| Paulsson et al, 2017, Retrospective 2005-2010, Sweden | Appropriate empirical therapy | Carbapenem, cefotaxime + tobramycin or piperacillin | Cefotaxime, cefuroxime or piperacillin | 30 days 16/79 12/56 7 | COPD, neurological paresis, diabetes mellitus, heart disorder, AIDS (14) |
| Yoon et al, 2017, Retrospective 2012-2015, South Korea | Appropriate empirical therapy | A β-Lactam and an aminoglycoside or a quinolone | A β-lactam or | 30 days 25/85 84/179 9 | Septic shock, neutropenia, Pitt bacteraemia score (24) |

*Study quality was evaluated according to the Newcastle-Ottawa scale (26). AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SAPS II, simplified acute physiology score; COPD, chronic obstructive pulmonary disease; APR-DRG, all patient refined-diagnosis related group; MODS, multiple organ dysfunction syndrome.*
that no clear heterogeneity was observed among studies, cumulative analysis was performed using a random-effects model. Fixed number of years and sample size were considered for cumulative meta-analysis. Organised in chronological order, OR value and 95% CI were stable and demonstrated good change trend, aside from the study by

Table II. Stratified analyses of pooled ORs.

| Factor                  | Level          | No. of studies | Pooled OR (95% CI) | Heterogeneity test |
|-------------------------|----------------|----------------|-------------------|--------------------|
| All studies             | -              | 17             | 0.81 (0.61-1.08)  | P-value 0.035      |
| Study population        | Asian          | 6              | 0.74 (0.41, 1.33) | 0.036 58.0         |
|                         | Non-Asian      | 11             | 0.88 (0.65, 1.20) | 0.196 26.0         |
| Study design            | Prospective cohort | 3 | 0.71 (0.42, 1.18) | 0.193 39.2         |
|                         | Retrospective cohort | 14 | 0.85 (0.60, 1.19) | 0.034 45.1         |
| Therapy type            | Definitive therapy | 12 | 0.88 (0.62, 1.24) | 0.173 27.7         |
|                         | Appropriate empirical therapy | 5 | 0.72 (0.42, 1.23) | 0.019 65.9         |
| Study quality           | 9 stars        | 8              | 0.67 (0.45, 1.00) | 0.082 44.5         |
|                         | 8 stars        | 3              | 1.15 (0.68, 1.95) | 0.515             |
|                         | 7 stars        | 5              | 1.03 (0.53, 1.99) | 0.029 63.0         |
|                         | 6 stars*       | 1              | 0.45 (0.08, 2.60) | -                 |
| Outcome                 | Overall mortality | 7 | 1.17 (0.75, 1.85) | 0.117 41.1         |
|                         | 30-day mortality | 8 | 0.67 (0.49, 0.90) | 0.611 0           |
|                         | 14-day mortality | 1 | 0.57 (0.22, 1.47) | -                 |
|                         | 10-day mortality | 1 | 0.42 (0.21, 0.84) | -                 |

*The fixed-effect model was used to calculate the pooled OR if P>0.10 and I²≤50%; otherwise, the random-effect model was used to merge the results. *Pooled ORs were not provided when stratified analysis only included one or two studies. CI, confidence interval; OR, odds ratio.

Figure 2. Forest plot of comparison of monotherapy and combination therapy for Pseudomonas aeruginosa bacteraemia by study design. OR, odds ratio; CI, confidence interval.

Figure 3. Forest plot of comparison of monotherapy and combination therapy for Pseudomonas aeruginosa bacteraemia by type of treatment. OR, odds ratio; CI, confidence interval.
Bliziotis et al (11) (Fig. 12). Based on sample size order following accumulation, when a large sample was included, the range of OR values and 95% CI (0.89; 0.76-1.04) was decreased (Fig. 13).
Discussion

The present study consisted of a meta-analysis that compared the effects of using either a combination of antibiotics or a single antibiotic for the treatment of *P. aeruginosa* bacteraemia. A total of 17 studies were systematically reviewed and compared. The antibiotic and appropriate empirical treatments used were determined by extracting data from the studies, and the patients’ all-cause mortality associated with *P. aeruginosa* bacteraemia was analysed. No significant differences were identified between monotherapy and combination therapy in regards to mortality. Therefore, definite combination therapy and appropriate combination of therapies failed to independently provide additional benefits for patient treatment. However, in the subgroup analysis process significant differences were observed in types of study design and types of treatment. In particular, the use of β-lactam and cephalosporin antibiotics as an empirical treatment were able to significantly reduce the mortality rate of patients.

In clinical treatment, patient mortality associated with *P. aeruginosa* bacteraemia remains high (61%) despite the progress of antibiotic therapy; thus, an improved treatment approach is required (38). Bliziotis *et al* (11) reported that combination therapy was superior to monotherapy in treating patients with *P. aeruginosa* bacteraemia; however, 81% of patients (25/31) who received monotherapy only received...
β-lactam, which cannot be considered the optimum monotherapy owing to the increased mortality rate associated with this drug compared with other monotherapies (20,21,39). Micek et al (5) observed that compared with single antibiotics, combination therapy yielded improved effects. However, given the open clinical design of the study, patients in a single-treatment group may be more likely to receive additional antibiotics and were therefore considered treatment failures in these studies. The number of patients included in meta-analysed subgroups were assessed in each randomised controlled study. As such, the baseline comparable P. aeruginosa bacteraemia infection between monotherapy and combination therapy groups was not established. Confounding factors in the remaining studies may be attributed to lack of randomisation, thus leading to incorrect conclusions (39). Another previous meta-analysis also performed a similar comparison by using β-lactam monotherapy and a combination of β-lactam and aminoglycosides on immunoreactive sepsis patients (6); the results revealed that association of combination therapy with single treatments was not advantageous in all-cause mortality or other treatment failure in patient subgroups with P. aeruginosa bacteraemia infection. By contrast, another study focused on analysis of patients with gram-negative bacteraemia. Following subgroup analysis of the results it was identified that combination antibiotic treatment led to a reduction in the mortality rates of P. aeruginosa bacteraemia compared with monotherapy, however these results were not
representative of all gram-negative bacteremia studied (6,40). As previously revealed, inferior quality and heterogeneity of studies considered in these meta-analyses resulted in unreliable clinical data. Differences among patients were also notable and results often differed (39). A recent meta-analysis studied the effects of carbapenem-resistant P. aeruginosa bacteremia on mortality (41). Another meta-analysis study on the benefits of clinical treatment was conducted through the use of an empirical combination therapy using β-lactam combined with an aminoglycoside or fluoroquinolones and β-lactam monotherapy for P. aeruginosa infection (42). In a subgroup analysis (5 studies) of P. aeruginosa bacteremia, the results of the clinical treatment demonstrated no significant difference in mortality between patients treated with monotherapy and combination therapy. According to the above variances, a meta-analysis was conducted in the present study; to the best of our knowledge P. aeruginosa bacteremia, although common in patients with bacteremia, is not very common in clinical settings. Thus, the sample size was limited. The present review also indicated limited clinical reviews and prospective study design. Owing to these limitations, baseline comparison of P. aeruginosa bacteremia infection between monotherapy and combination therapy was not established. Therefore, difficulty arose from completing large randomised prospective clinical trials. Patient complications also differed; multidrug-resistant (MDR) P. aeruginosa strains became increasingly common and varied in terms of selection of drug types. Therefore, studies were not analysed according to specific antibiotics, as the present meta-analysis was performed with different antimicrobial therapies. In several studies (13,14,16,18,24), comparisons between selected empirical antibiotic therapy and definitive treatment were retrospectively analysed. Other studies rated the Chronic Health Evaluation score of in-patients (12,16,23,25). Appropriate treatment involves antibiotic isolation therapy for certain in-vitro-sensitive agents, especially for aminoglycoside antibiotic-sensitive patients (19,35). The use of monotherapy for treatment of P. aeruginosa bacteremia was considered inappropriate in previous studies comparing single and combination therapies (10,15). Some meta-analyses conducted from the perspective of treatment and mortality compared effectiveness of combination antibiotics and monotherapy in clinical treatment of P. aeruginosa (43). The present meta-analysis did not focus on survival rate and quality evaluation. A limitation of the present study was the lack of scope in comparing study type and treatment selection. For patients with MDR bacterial infection and P. aeruginosa, providing combination antibiotic therapy may improve results as this method increases possibility of appropriate treatment (42). In addition to the appropriate choice of empirical treatment, the severity of complications is another risk factor that may also affect mortality rate of patients during bacterial infections including P. aeruginosa (42). Combination therapy with P. aeruginosa also presents potential risks, particularly drug toxicities, including aminoglycoside antibiotics associated with human renal toxicity (6). Likelihood of repeated infection in clinical patients and the increased cost must also be considered in comparing combination therapy with monotherapy. Limitations of meta-analysis conducted in the present study were recognised. The quality of included studies may be questioned due to incomplete or inaccurate data collection. The research on adjustment of these confusing factors is limited and therefore cannot be studied for potential co-founder influence, including severity of disease and potential for concurrent conditions. The funnel plot and Egger's test indicated a possibility of publication bias, however trim-and-fill analysis revealed that results did not change. Only sensitivity analysis and evaluation, patient source, study types, treatment options and mortality were analysed. Finally, only studies published in English were included. This may introduce language bias, possibly resulting in incomplete study and thus reducing accuracy of analysis of the treatment results.

In conclusion, the results demonstrated no significant difference in mortality between patients administered with combined antibiotic or monotherapy treatment against P. aeruginosa bacteremia. Combination therapy may be associated with clinical treatment of monotherapy, particularly when used in empirical therapy. These results were mainly obtained from retrospective and secondary studies. Thus, no definite conclusions may be drawn regarding combination of effectiveness and single therapy in patients and groups. Relevant evidence obtained was also limited. Therefore, large-scale and well-designed studies must be developed and conducted on credibility of treatment mechanisms to determine whether a causal association exists.

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