Is It Possible to Blind a Trial for Community-Acquired Pneumonia?

Helen W. Boucher
Division of Infectious Diseases, Tufts University Medical School and Tufts Medical Center, Boston, Massachusetts

Blinding a randomized, controlled clinical trial provides benefits on several levels but often is not perfectly executed or well described. Most recent registration trials of therapy for community-acquired pneumonia were designed and conducted as blinded trials, although the descriptions of blinding were frequently incomplete. Issues related to definitions, conduct, testing success, and reporting of blinding are addressed in this article. The benefits of blinding clinical trial participants, study drug assignment, microbiological data, and outcome assessments of both efficacy and safety are presented. Particular attention is paid to challenges inherent in the blinding of trials of therapy for pneumonia, especially in trials involving seriously ill patients who require intravenous therapy.

Blinding of patients, investigators, treating physicians, and assessors is known to decrease bias at many stages of a randomized, controlled clinical trial; therefore, investigators and pharmaceutical sponsors go to great lengths to blind clinical trials [1]. Most studies of new antibiotics for the treatment of community-acquired pneumonia (CAP) are reported to be “blinded,” so it seems that the question of whether it is possible to blind a CAP trial is answered. However, several reports demonstrate that, despite the fact that most studies are described as “blind,” “double-blind,” or “double-blind, placebo-controlled,” our ability to ascertain whether and how the trial was blinded—and whether that blinding was effective—is severely limited [2–4].

A PubMed search with the keywords “blind” and “CAP antibiotic” yielded 139 articles. In a search for published clinical CAP trials of antibiotics approved since 1998, 7 of the 9 studies were blinded (table 1) [5–7]. It was also found that several other clinical trial reports included the term “double-blind” in the title, abstract, study design section, and/or discussion section. These publications include registration trials of ertapenem, gemifloxacin, and gatifloxacin [8–10]. It is noteworthy that all trial descriptions lacked details of the blinding or the assessment of blinding, which are recommended by the Consolidated Standards of Reporting Trials (CONSORT) guidelines [11, 12]. As pointed out by several experts, the assessment of bias associated with inadequate blinding in randomized, controlled clinical trials is “often hampered by inadequate reporting” [2, p. 360], despite the explicit suggestions in the CONSORT statement [2, 11]. The reader is referred to the CONSORT Web site (http://www.consort-statement.org/?o=1028) for more information on how to report and assess blinding in a randomized trial.

An example of a randomized trial for CAP that adequately describes blinding is a 1994 study by Fink et al. [13] that compared imipenem-cilastatin with ciprofloxacin as therapy for CAP. This study had the explicit goal of achieving a better blind. The authors included specific descriptions of how the blind was achieved. “The study was conducted and analyzed under fully blind conditions” [13, p. 548], and the publication clearly states that “adjustment of the study medication dose” [13, p. 549] was performed by an unblinded study pharmacist. In terms of how the study was conducted, decisions regarding assessment of premature terminations were made before unblinding. In presenting the results, the authors provided details...
### Table 1. Antibacterial agents approved by the US Food and Drug Administration since 1998 and related community-acquired pneumonia (CAP) studies.

| Antibacterial agent | Year initially approved | Blinded CAP study performed |
|---------------------|-------------------------|----------------------------|
| Moxifloxacin        | 1999                    | No                         |
| Gatifloxacin        | 1999                    | Yes                        |
| Linezolid           | 2000                    | No                         |
| Cefditoren pivoxil   | 2001                    | Yes                        |
| Ertapenem           | 2001                    | Yes                        |
| Geminofloxacin      | 2003                    | Yes                        |
| Daptomycin          | 2003                    | Yes                        |
| Telithromycin       | 2004                    | Yes                        |
| Tigecycline         | 2005                    | Yes                        |

**NOTE.** Data from [5–7].

about the number of patients who received placebo and specified that “determinations of evaluability” [13, p. 550], assessments of cause of death, and analysis of predetermined end points were made before unblinding. These factors are all important aspects of blinding. The fact that the blinding was successful and was adequately described in the article serves to confirm the assay sensitivity in the study. One element lacking was an assessment of the blinding, which is identified as an important component of reporting randomized trials in the CONSORT statement and in several clinical trial textbooks [11, 14–16].

In light of these examples and considering that numerous antibiotics have been demonstrated, in blinded and open-label studies, to be effective in treating CAP, one wonders whether providing the details of blinding or assessing the success of blinding justifies expending precious words in an article or whether the frequently extraordinary measures needed to design and conduct a blinded trial are worthwhile or necessary. Several investigators have examined this question and have concluded that successful blinding adds value but that readers and reviewers may be overlooking significant limitations of “blinded” trials [2–4, 17]. A number of groups concluded that reporting of trials is inconsistent and that an assessment of blinding is frequently lacking [2–4, 17].

The cohort study by Haahr and Hrobjartsson [2], involving 200 randomized trials published in 2001 that were selected randomly from the Cochrane Central Register of Controlled Trials, makes this point. They examined the completeness of the reporting of blinding, whether trial participants were double blinded, and whether physicians could identify which “key trial persons” were blinded. Among the 200 randomly selected publications, 78% described “double-blind” trials, 56% did not describe the blinding status of any trial person, 26% reported no information beyond the statement that it was a “double-blind” trial, and only 2% explicitly described the blinding status of patients, health care providers, and data collectors. Survey responders provided 15 different operational meanings of the term “double-blind” and typically believed that their preferred definition was the most widely used [2]. Other groups similarly concluded that interpretations of the word “blind” differ significantly [17–19].

This article addresses several issues related to blinding in CAP trials, to provide a means of determining whether blinding is ultimately possible, feasible, or desirable. The benefits of blinding clinical trial participants, study drug assignment, microbiological data, and outcome assessments of both efficacy and safety are addressed, as are other related issues.

**DEFINITIONS**

Allocation concealment prevents those who admit patients into a trial from knowing the upcoming assignments and prevents selection bias. Additionally, concealment protects the allocation sequence (i.e., the list of who will get what drug) before and until assignment. Fortunately, allocation concealment can always be implemented in a randomized clinical trial [17]. “Blinding,” or “masking,” refers to the process by which knowledge of intervention and/or treatment assignments is hidden from participants, investigators, or outcome assessors in a trial. The purpose of blinding is to prevent ascertainment bias and to protect the randomization sequence after allocation. Unlike allocation concealment, blinding cannot always be implemented—often because of feasibility or ethical constraints [17, 20]. Although several older textbooks and journal articles describe “masking,” more recent publications have chosen the term “blinding,” and this article follows suit [1].

Literature reports often use confusing terminology to describe the level of blinding. In a single-blind study, the patient is blind to the therapy or intervention, whereas the physician or investigator knows the treatment or intervention assignment. In a double-blind study, the patient, physician or investigator, and assessor are all blind. Triple-blind studies are defined as those in which the patient, physician or investigator, treatment assessor or monitoring groups, and data analysts are all blind to the treatment or intervention assignment. Because this terminology is confusing, it is important to provide a clear description of what is done to blind a study [1, 14].

**BENEFITS OF BLINDING**

When performed correctly, blinding of a study provides benefits to patient participants, investigators, and outcome assessors [1]. Table 2 shows the benefits, as outlined by Schulz and Grimes [1]. Among the most important and perhaps least appreciated benefits of blinding is that both patient participants and physician investigators are less likely to seek additional adjunctive therapies, including additional antibiotic therapy for CAP, and...
are less likely to discontinue use of the study drug or study participation early. In trials for pneumonia, many of which are designed as noninferiority trials, loss to follow-up is particularly problematic and often has an impact on the interpretability of the results [21].

It is possible to blind some outcome assessors—namely, members of adjudication or data safety–monitoring committees—even in an open-label study [22–24]. This mechanism has been used successfully in a number of studies of anti-infectives, but certain limitations exist. Although members of adjudication committees are provided with treatment-blind data and use standard criteria to make their assessments, the data they are provided are subject to interpretation (bias) by physicians who were unblinded to the drug or intervention assigned. In addition, these committees often are provided with an incomplete data set; data regarding toxicity that might reveal the treatment assignment (e.g., creatine phosphokinase levels in patients given treatment with daptomycin, renal function in patients given treatment with amphotericin, and visual adverse events in patients given treatment with voriconazole) are not provided, in an effort to protect the blinding [25]. Thus, although the committee’s review is blinded, it is unlikely that all bias is mitigated. When these adjudicators make their assessment of evaluability or outcome, they “may reverse the investigator’s assessment of efficacy simply because there is insufficient documentation to support it,” and, when they remove case patients from the primary efficacy population, they reduce patient numbers, thereby decreasing the power of the study and, potentially, the ability to draw conclusions [25]. If large numbers of patients are removed from the primary efficacy population, then the analysis could show results that are not similar to those of the intention-to-treat analysis, because of some bias in the data-review committee’s exclusion process [25].

**CHALLENGES OF BLINDING**

*Feasibility issues—matching.* Despite the benefits of blinding in clinical trials, a number of challenges exist. The process of matching, or ensuring that the treatments or interventions look, feel, taste, and smell alike, requires careful attention and significant resources. It is vital that the tablets, capsules, vials, and intravenous administration bags for the study drug and comparator drug resemble one another. For oral therapies, this often requires encapsulating the test agent and placebo in one capsule (rather than using tablets) and the use of substances to mask the drug’s color, odor, or taste. Although this is often feasible, it frequently requires expensive formulation processes or large capsules that are not well tolerated or practical [14]. The double-dummy design is often useful when comparing 2 active drugs with different properties. This design provides an identical placebo for each active agent.

Matching in studies of intravenous medications is more complex. The volume load, frequency of administration, need for adequate intravenous access, and need for other vital medications all increase the challenge of successfully matching and blinding intravenous drugs. Many of our patients with CAP are critically ill and require vasopressor agents, parenteral nutrition, blood products, and so forth. Several antibiotics used to treat CAP (e.g., certain β-lactam agents) require frequent administration and come with a significant sodium load. In many cases, the use of double-dummy intravenous infusions is not feasible. The need for therapeutic drug monitoring with subsequent dose adjustment provides an additional challenge. When considering blinding a trial of such a drug, one must consider how to handle changes in the dose and the timing of dose—for example, vancomycin administration every 12–18 h. Could adjustment of dose but not dose interval serve as an acceptable option to protect the blinding?

An additional issue surrounds the need to keep the investigator and study team unaware of selected laboratory data, especially the results of therapeutic drug monitoring. Unblinded pharmacists have been called on to perform these types of adjustments, but they are unable to provide all the medical care needed to manage drug toxicities, such as drug-related renal failure. For all these reasons, when a multicenter, international study of intravenous therapy for serious CAP is being considered, it seems reasonable to consider whether employing an unblinded pharmacist is possible, practical, or ultimately necessary.

In addition to matching the drug substance and delivery apparatus, it is vital to ensure that containers are identical, with codes that protect the blinding. In active-control drug studies, assurance of the blinding is vital but not always possible. In

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**Table 2. Potential benefits of blinding of trials.**

| Individuals blinded, potential benefit |
|--------------------------------------|
| Participants                          |
| Less likely to have biased psychological or physical responses to intervention |
| More likely to comply with trial regimens |
| Less likely to seek additional adjunct interventions |
| Less likely to leave the trial without providing outcome data (i.e., less loss to follow-up) |
| Investigators                         |
| Less likely to transfer inclinations and/or attitudes to patients |
| Less likely to differentially administer cointerventions |
| Less likely to adjust dose |
| Less likely to differentially withdraw patients from the trial |
| Less likely to differentially encourage or discourage patients to continue the trial |
| Assessors                             |
| Less likely to have biases affect outcome assessments |

**NOTE.** Adapted from [1], with permission from Elsevier.
the reporting of trials, possible inadequate matching (e.g., labels falling off pill bottles and revealing the drug assignment) should be discussed.

**Geographical differences.** The worldwide epidemiology of CAP varies in such things as the identification of the organism causing CAP and its susceptibility patterns and other standard-of-care activities. For example, in many Western European countries, empirical therapy is not provided for infection with atypical pneumonia pathogens, whereas it is the standard of care in the United States [26]. When an international trial of a new therapy for CAP is being designed, does one need to include different comparators with different blinding techniques for the United States and Western Europe or other parts of the world? Such differences would have an impact on the trial results and might influence the generalizability of those results.

**Microbiology.** Microbiological data play an important role in diagnosis of CAP and are used in core analyses of efficacy in CAP trials. Knowledge of the pathogen that is likely causing the pneumonia in a patient should lead to certain decisions regarding his or her care. Although practice guidelines make recommendations about how to react to knowledge of the microbiological data, the question remains as to whether results of Gram staining, pathogen identification, or susceptibility profile analysis should be blinded in CAP studies [26]. Considerations include which types of respiratory cultures—routine or quantitative (e.g., minibranchioalveolar lavage fluid)—are being performed, whether blood cultures are positive, whether there is laboratory evidence of any other sites of infection, and whether knowledge of these data should influence the treating physician’s decision making.

The recently released draft of the US Food and Drug Administration (FDA) guidance on studies of sinusitis states that “when microbiological sampling is performed, investigators should be blinded to the microbiological data at entry” [27, p. 9]. This approach is used to eliminate possible bias in the evaluation of the relationship between in vitro resistance at baseline and clinical outcome. “In vitro resistance (or infecting pathogen) at entry should not be used to alter treatment assignment or study conduct…rescue therapy can be provided to all patients regardless of microbiological status at entry if the study criteria for clinical failure are met while on the originally assigned treatment” [27, p. 9]. Although such guidance is reasonable for trials of less severe illnesses, such as sinusitis, it may not be acceptable for a more severe disease, such as CAP.

There are circumstances in which the isolated organism and/or susceptibility pattern should immediately be made known to the treating physician. Because of the associated unacceptably high morbidity and mortality rates, treating physicians need to know whether blood cultures are positive for *Staphylococcus aureus* or *Streptococcus pneumoniae* [28–30]. In the current era of community-associated methicillin-resistant *S. aureus* and drug-resistant *S. pneumoniae*, knowledge of susceptibility is vital, to determine whether the patient should discontinue the study and to ensure prompt administration of the most effective agent. The use of so-called tentative, or proposed, susceptibility breakpoints for agents in development remains controversial and has not been addressed in FDA CAP-related guidance documents to date [31].

**Outcome assessments—efficacy and safety.** Blinding of outcome assessments is one of the most important goals of a well-conducted randomized trial. “Hard” endpoints, such as death, are subject to less bias than are subjective assessments, such as cause of death, self-reported symptom scores, and patient-reported outcomes. Assessors should be blinded even in open-label trials, because knowledge of treatment assignment is such a strong source of bias [17]. The impact of blinding on assessment of safety is less appreciated. Knowledge of expected adverse effects influences how assessors react. For example, fewer investigators reported events of nephrotoxicity with either β-lactam or vancomycin when each was combined with initial low-dose gentamicin in a study of daptomycin for treatment of bacteremia. This was despite the fact that there was significantly more laboratory evidence of renal dysfunction with the regimens that included gentamicin. This likely reflected the investigator’s belief that low-dose gentamicin is not nephrotoxic [23].

**Ethical issues.** In studies of serious CAP, any consideration of blinding should address the concerns of patients, investigators, and institutional review boards or ethics committees regarding the risks of blinding of therapy, microbiological data, and treatment outcomes in terms of both safety and efficacy. In this context, is delayed or “rescue therapy” an option for mild-to-moderate CAP or serious CAP in hospitalized patients?

**Unblinding.** Unblinding poses another challenge and can occur both intentionally and unintentionally. Unintentional unblinding may occur during a trial because of mislabeling of the study drug or because of laboratory errors (especially when some but not all laboratory data are reported back to the local study site). It is critical that care is taken in planning and executing the distribution of study medication and laboratory samples and results.

Intentional unblinding should be avoided, if at all possible, and, if done, should involve only those who “need to know.” Investigators should always try to stop study medication, rather than unblind, and attempt to prospectively define criteria for intentional unblinding if it is deemed absolutely necessary [1, 14].

Unanticipated safety issues do arise, and prospective plans should specify how to best handle them. As Talbot [32] points out, lack of efficacy is a safety issue. For example, the devel-
opment of breakthrough bacteremia while a patient is receiving therapy can signal both lack of efficacy and a serious safety concern. Although such an event is serious, it is likely best to outline criteria for unblinding the microbiological data, rather than the study drug assignment. As a logical follow-up question, does an investigator need to know the assigned treatment at the time of withdrawal of his or her patient, to determine the most appropriate rescue therapy?

Assessment of blinding. Estimation of the degree to which the blinding was maintained is the final step in reporting a blinded trial and in demonstrating that the blinding was successful [11]. Some experts suggest that the study sponsor should ask participants and investigators and/or assessors to guess to which of the 2 treatment groups the participant was assigned. These guesses should approximate 50%, to reflect chance and to suggest that the blinding was maintained. If >50% of the responses are correct, it is likely that some degree of unblinding existed. On the other hand, if <50% of responses are correct, it is possible that some participants knew the treatment assignment but were not willing to admit it [14, 17].

When blinding is not possible. When blinding is not deemed possible, the protocol explanation must explicitly describe the reason for this and indicate the measures taken to minimize bias by other means. In this situation, allocation concealment plays a more important role, and investigators should consider the use of a central randomization system, when feasible (this tool already is used in most pharmaceutical phase 3 trials for CAP). Clinical assessments should be made by medical staff who are not involved in providing treatment to patients and who remain blinded to treatment assignment. When an open-label design is used, care should be taken to select primary outcomes that are as objective as possible. As in blinded trials, “hard” end points such as death (all-cause mortality), as well as perhaps certain microbiological end points (e.g., clearance of bacteremia), are desirable [1, 20].

CONCLUSIONS

Despite the fact that most registration trials of antibiotics for treatment of CAP are blinded, most reports fail to describe the steps taken to blind the trial or to assess the success of the blinding. Blinding in studies of CAP is possible, although at a cost. Matching of oral and, especially, intravenous therapy is resource intensive and may not always be feasible or in the patients’ best interests. Successfully designing, conducting, and reporting a blinded study is more challenging in studies of severe CAP. These studies often test intravenous antibiotics among hospitalized patients with multiple comorbidities. If a blinded design is selected, it is crucial to explicitly state what steps were taken to keep the various investigators, patients, and assessors blinded and then to document the success of the blinding.

Unanswered questions include how best to address the need for different comparators in different geographical areas and whether the blinding of any microbiological data is wise in a study of a new therapy for CAP. Regardless of the decision about whether to blind the study drug, other clinical trial design issues, especially allocation concealment, are important. CAP studies merit meticulous care in design, conduct, and reporting.

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