Chapter 3

Blood transfusions: good or bad?

Confounding by indication, an underestimated problem in clinical transfusion research

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Introduction

Confounding by indication is a serious potential problem in clinical observational research and can easily lead to unjustified conclusions, as has also been described previously.\(^1\) In transfusion medicine such a conclusion could be “blood transfusions kill”, since patients receiving more transfusions are almost invariably more likely to die. Even though most would agree that blood transfusions save lives, this erroneous conclusion did find its way into the literature. Though this example might seem overly obvious, confounding by indication can be indirect and much more subtle and hard to detect. It is therefore of the utmost importance to thoroughly understand the nature of confounding by indication, to be able to recognize it and avoid unjustified conclusions. We introduce the problem of confounding by indication with examples from clinical transfusion research and provide a general explanation to help identify this form of bias in the literature and in the every day clinical research settings (for guidelines on detection and handling, see Table 1).

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<th>Table 1: Guidelines on detection and handling of confounding by indication</th>
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* Note: correction for confounding by indication is notoriously difficult, since patients get treated based on the risks perceived by the clinician and it is virtually impossible to capture all of the clinician’s considerations in a statistical model. Furthermore, multiple transfusions can also give other types of bias, which can not always be corrected by conventional methods.\(^4\)
Confounding by indication

Confounding by indication is a bias in clinical observational research that disturbs the association between a treatment and an outcome.\textsuperscript{1-3} This bias occurs when studying the effect of a treatment, while the indication for the treatment causes the outcome. Patients with the indication are more likely both to receive the treatment and to experience the outcome, even if the treatment is not actually causing the outcome. This form of bias is called confounding by indication, since the association between the treatment and the outcome is confounded by the indication for the treatment. Sometimes this is also referred to as selection bias because the bias is caused by patients being selected for treatment. However, since the term selection bias is also commonly used to denote a multitude of other sources of bias, we prefer to call this type of bias confounding by indication.

Confounding by indication can be avoided by performing a randomized clinical trial (RCT).\textsuperscript{2} In an RCT the allocation of treatment is independent of factors capable of causing the outcome (i.e. independent of indication). Many questions, however, can not be studied in an RCT, since this would be unethical or practically impossible. Therefore, much clinical research is observational and subject to the bias of confounding by indication. Unless adequately corrected for in the analyses, this bias prohibits any association between treatment and outcome from being interpreted as representing a causal relationship. Therefore, it is of the utmost importance to recognize and prevent or correct for confounding by indication.

Confounding by indication in transfusion medicine

In transfusion medicine the most common form of confounding by indication involves the number of transfusions received by a patient. Clearly, the sicker a patient is, the more transfusions will be indicated. Also, the sicker a patient is, the higher the risk that patient will have a poor outcome. Figure 1 illustrates how this causes a spurious association between receiving a high number of transfusions and experiencing a poor outcome, an association which should obviously not be interpreted as causal.

Indirect confounding by indication

A less easily recognized problem is “indirect confounding by indication”. In this case the indication still causes the outcome, but the relation with the treatment is indirect. If we again consider the example of a sicker patient receiving more transfusions, we can see that any other difference in treatment secondary to this higher number of transfusions will also become associated with poor outcome. For example we can imagine that patients receiving more transfusions are less likely to receive all transfusions from male donors (figure 2 A). Thus, comparing male-only to mixed-sex plasma transfusions will show a benefit for male-
only plasma where none exists. Importantly, the comparison of female-only to mixed-sex plasma transfusions should show a similar spurious association. An analogous situation with opposite bias arises for an analysis of the oldest unit transfused, which will on average be older in patients receiving more transfusions. A similar effect can be shown in the data by investigating the youngest unit transfused, which should be younger in patients with a poor outcome.

Figure 1: Cartoon of direct confounding by indication. Arrows indicate causal relationships and the dashed line denotes a spurious association. A more seriously ill patient is likely to receive more transfusions and experience a poor outcome. Therefore, a spurious association between receiving many transfusions and experiencing a poor outcome is created. This association is spurious because it is confounded by the indication for more transfusions (i.e. being more seriously ill). If in this example we were interested in the relation between the number of transfusions and a poor outcome (e.g. mortality) it would seem like transfusions are causing mortality, while this association is actually not causal.

Figure 2: Cartoons of indirect confounding by indication. Arrows indicate causal relationships and the dashed lines denote spurious associations. A: If transfusions are allocated independent of donor sex, receiving more transfusions will reduce the probability of receiving all transfusions from male donors. Since the number of transfusions was (spuriously) positively associated with poor outcome (see figure 1), receiving all transfusions from male donors will become (spuriously) negatively associated with poor outcome. If in this example we were interested in the relation between donor sex and a negative outcome (e.g. TRALI) it would seem like receiving transfusions only from male donors is protecting against TRALI (and therefore like female donors are causing TRALI), while this association is actually not causal. B: If clinicians believe younger blood to be safer and therefore specifically reserve or order younger blood for more vulnerable patients with poorer prognosis, a (spurious) negative association between high product age and poor outcome will be created. If in this example we were interested in the relation between storage time and a negative outcome (e.g. mortality) it would seem like receiving younger blood causes mortality, while this association is actually not causal but created by the clinician.
Correction for confounding by indication

The association between receiving all transfusions from male or female donors and the number of transfusions is based on probability distributions, as is the association of the age of the oldest or youngest unit and the number of transfusions. Therefore, the strength of this association can be predicted based on the number of transfusions and a correction can then be applied. It should be noted however that a simple correction for the number of transfusions does not usually suffice. Although the adequate correction is therefore not always straightforward to apply in practice, it does result in an unbiased estimate of the causal effect of donor sex or product age.

When no correction is possible

A problem that is generally beyond any hope of repair arises in the case where clinicians specifically ask for younger blood for their most vulnerable patients (figure 2 B). Young blood will then become spuriously associated with poor outcome and the strength of this spurious association can not be determined in any way. A similar problem, resulting in an association in the opposite direction, arises when blood banks specifically issue their oldest units for expected heavy bleeders. The blood bank only aims to reduce the chance of old units being returned to the blood bank near their expiration date, but it also ascertains that heavy bleeders who presumably have a poor prognosis get older blood. In both these examples the strength of the spurious association is not readily determined and correction is therefore not possible.

Implications

For an overview of a few simple steps that will help identify and deal with confounding by indication, see Table 1. Obviously, real causal relationships can be present alongside confounding by indication. However, these can not be quantified, or even qualitatively proven, and might in fact be completely obscured or even reversed, unless the bias of spurious associations is adequately corrected. It is therefore important to always realize which patient characteristics can both influence prognosis and are associated (directly or indirectly) with the treatment, or the secondary characteristics of treatment. Not all confounding by indication can be completely corrected for and adequate correction might require additional information. Therefore, it is vital to consider all these issues in the design phase of any study, when patient selection and data collection can still be adapted to avoid confounding by indication or allow for correction.
Confounding by indication

References
