Transfusion-related acute lung injury not a two-hit, but a multicausal model

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BACKGROUND: The etiology of transfusion-related acute lung injury (TRALI) is often referred to as a “two-hit model,” the first hit being patient predisposition and the second being a transfusion. This model lumps all patient-related risk factors together and thereby may hamper identification of individual, potentially preventable or modifiable risk factors.

STUDY DESIGN AND METHODS: Like any disease, TRALI is multicausal in nature. To be able to effectively scrutinize all contributing causes, we need to clearly describe this multicausality as completely as possible. Several models are already commonly used to describe the multicausality of other diseases, including threshold models and the sufficient cause model.

RESULTS: Here we describe the application of two different multicausal models to TRALI. These models can readily describe any potential scenario for the etiology of TRALI. First we will introduce the intuitively appealing threshold model, which shows some similarities with the Bux and Sachs threshold model for TRALI. Second we discuss the more abstract sufficient cause model.

CONCLUSIONS: Both models have their strengths and limitations. Both are, however, better equipped than the two-hit model to describe the multicausal nature of TRALI. Further identification of all involved risk factors and the complex interplay between them is facilitated by these models.

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THRESHOLD MODELS

One characteristic all threshold models have in common is the fact they have to define one final common pathway for the disease of interest. There must be a single identifiable system with a modifiable level of activity for which it can be assumed that if the activity of this system passes a certain threshold level disease will ensue. In the case of TRALI, this system is the combination of pulmonary neutrophils and endothelium.

A threshold model for TRALI has previously been suggested by Bux and Sachs. This model indeed used passing a threshold in the activation level of pulmonary neutrophils and endothelium as the criterion for disease onset. This model actually used two distinct thresholds, one for mild and one for severe TRALI. We could even imagine that beyond a certain threshold, where physiologic passes into pathologic, there is a continuous scale of ever-increasing severity of pathology. The severity and therefore also the actual level of activation could be clinically relevant and should therefore not be ignored. Although this could therefore be a highly valuable extension of the threshold model it is not relevant for the conceptual understanding of the model. For the current discussion we will therefore ignore these subtleties and assume that there is only a single relevant threshold below which there is no disease and above which there is only a single level of severity of disease.

The Bux-Sachs threshold model is based on the two-hit model. Therefore, it precludes further distinction between individual patient-related or individual transfusion-related risk factors. Instead it puts the total activating effect of all patient-related risk factors on the top horizontal axis, while it puts the total activating effect of all transfusion-related risk factors (in reverse direction) on the bottom horizontal axis. In this way the model provides a beautiful graphical representation of the fact that the transfusion must give a stronger activation of the pulmonary neutrophils and endothelium if the patient-related activation (i.e., predisposition) is weaker (Fig. 1). However, it also limits the flexibility to represent many different risk factors each making a small contribution to the onset of TRALI.

A more general threshold model has previously been used by Rosendaal to illustrate the multicausality of venous thrombosis. The Rosendaal threshold model, like any threshold model, must put the activation status of the disease-causing system on the vertical axis. The horizontal axis represents time, allowing every risk factor to be represented as the temporary increase in activation status it causes. Some risk factors cause a higher level of activation than others and some will cause longer-lasting activation than others, but no distinction is made between patient- or transfusion-related risk factors. All risk factors are represented individually, allowing each risk factor to be judged individually for

Fig. 1. Bux-Sachs threshold model. TRALI occurs when activation of neutrophils and endothelium crosses the threshold. From left to right the contribution of patient-related risk factors (gray area) increases. Since the total amount of neutrophil and endothelial activation needed to cross the threshold is always the same, this automatically means the (minimal required) contribution of transfusion-related risk factors (white area) must decrease. Therefore, healthy individuals (far left) need extremely strong neutrophil and endothelial activation potential from the transfusion, while heavily predisposed patients (far right) need only a very mildly stimulating transfusion to develop a case of TRALI. Reproduced from Middelburg and van der Bom with permission from Nova Science Publishers, Inc.
the potential effect of preventive measures directed against it.

**Threshold model of TRALI**

The Rosendaal threshold model has previously been applied to venous thrombosis. However, it is not specific to this disease and can be applied equally well to any other disease, including TRALI. Figure 2 illustrates four possible scenarios in which a patient is at risk to develop TRALI. The patient always experiences three different predisposing events and always receives two transfusions, but the relative timing of both the events and the transfusions is different every time. The predisposing events are:

1. Severe pneumonia, requiring intensive care unit admission and prolonged mechanical ventilation.
2. Cardiac surgery, requiring cardiopulmonary bypass, but otherwise uncomplicated.
3. Hematologic malignancy, requiring intensive chemotherapy inducing extensive endothelial damage.

This event will raise the activation status of the pulmonary neutrophils and endothelium strongly and for a long time.

Fig. 2. Rosendaal threshold model of multicausality, applied to TRALI. The level and duration of activation of pulmonary neutrophils and endothelium by different events is indicated by solid lined blocks. Dashed lines (long dashes) indicate two events coinciding (i.e., one passing “behind” the other). The cumulative activation is determined by stacking these boxes on top of each other. The resulting cumulative level is indicated by the finely dashed lines. If the cumulative level passes the TRALI threshold (dashed horizontal line), TRALI ensues. See text for a detailed description of all depicted scenarios. Reproduced from Middelburg and van der Bom with permission from Nova Science Publishers, Inc.
and endothelium. Activation by Transfusion Y is twice as strong as activation by Transfusion X and both transfusions result in only very short activation. Other transfusions could have been given, but since these did not raise the activation of the pulmonary neutrophils and endothelium these are not depicted. Likewise, other diseases could occur and be the reason for receiving a transfusion outside of one of the depicted periods of disease. These other diseases are also not shown, since they did not raise the activation status of the pulmonary neutrophils and endothelium.

The four panels of Fig. 2 show different relative timing of predisposing events and transfusions.

A. There is no overlap in the effects of the different predisposing events. Each effect wears off before the next event occurs. Transfusion X is given during the period of hematologic malignancy. Both give only mild activation of the pulmonary neutrophils and endothelium. The combined activation (finely dashed line) therefore does not reach the threshold level and there is no TRALI. Transfusion Y is given in the absence of any predisposition and is by itself not capable of reaching the threshold level. Therefore, there is no TRALI.

B. Transfusions X and Y are switched relative to the situation in Fig. 2A. Transfusion Y gives twice as strong an activation as Transfusion X. The combined activation level of Transfusion Y and hematologic malignancy (finely dashed line) therefore crossed the threshold level and TRALI occurs.

C. Transfusion X is given during the period of severe pneumonia. Severe pneumonia gives a very strong predisposition. Therefore, the relatively mild activation caused by Transfusion X is sufficient for the combined activation level (finely dashed line) to cross the threshold level and TRALI occurs.

D. Transfusion X is given during cardiac surgery, which is performed during the period of hematologic malignancy. The combination of all three mildly activating factors is enough to raise the combined activation status of the pulmonary neutrophils and endothelium (finely dashed line) above the threshold and TRALI occurs.

Figure 2D clearly illustrates the main limitation of the two-hit model. Any combination of two of these three risk factors would not have caused TRALI. Lumping two risk factors together into “patient predisposition” causes a loss of information on causes of this predisposition. Only a truly multicausal model, like this threshold model, can show us that for preventing TRALI we have a choice between postponing cardiac surgery or providing a very-low-risk blood transfusion. Based on clinical considerations and availability of extremely-low-risk blood products either approach could be preferable. We can, however, only make an informed decision if we are first informed about all the relevant considerations. The two-hit model could not have informed us sufficiently, while the threshold model does.

**SUFFICIENT CAUSE MODEL**

A more abstract way of representing the multicausality of disease is the sufficient cause model. In this model individual contributing factors are called component causes and any possible combination of component causes that suffices to cause disease is called a sufficient cause. Component causes that are present in all possible sufficient causes are referred to as necessary causes. A person can have any number of partially completed sufficient causes, but only the first sufficient cause to be completed is considered to have caused disease. All component causes in the first completed sufficient cause are considered equally causal, since removal of any of them would prevent completion of this particular sufficient cause. It is unlikely that all minor contributing factors to a given sufficient cause are ever completely known. Therefore, it is standard practice to always include a component cause “U” (i.e., for unknown) in every sufficient cause, to represent all unknown component causes. The main objective of all research is to split these unknown components into an ever-increasing number of known component causes.

In the example of TRALI, transfusion is a necessary cause, since it must by definition be a component cause in every sufficient cause. The sufficient cause model can be graphically represented as pieces of a pie (i.e., component causes) accumulating to fill the entire pie (i.e., a sufficient cause; Fig. 3). The model is therefore also popularly referred to as the “causal pie model” and any person can be thought of as “walking around with a large number of uncompleted pies.”

It is important to note that even a completely healthy person, sitting behind his desk, reading a copy of TRANSFUSION, has the same number of incomplete “pies” as a person being mechanically ventilated in an intensive care unit after having extensive burns and a severe pneumonia. The latter person will only have more pieces of pie filled in for some of those pies. Any sufficient cause containing mechanical ventilation, burns, pneumonia, or any combination of these will be completed for those component causes. This could include a large number of different possible sufficient causes.

**Sufficient cause model of TRALI**

The sufficient cause model is a very general model of multicausality. It is not even specific to diseases and could be used to describe causes of the onset of any event or process which is considered multicausal. It can,
however, also readily be applied to TRALI. Figure 3 illustrates the application of the sufficient cause model to TRALI. In Fig. 3 we use the same scenarios we used in Fig. 2, to illustrate the threshold model.

As can be seen from Fig. 2A the combination of hematologic malignancy and Transfusion X is not enough to cause TRALI. This is reflected by the absence of any sufficient cause consisting only of hematologic malignancy and Transfusion X. As all other panels in Fig. 2 did lead to TRALI, those scenarios should all be represented as potential sufficient causes in Fig. 3.

In Fig. 2B hematologic malignancy and Transfusion Y contributed, which is represented in Fig. 3A. From the level of activation caused by different risk factors in Fig. 2 it can be seen that Transfusion Y could also have caused TRALI if given in combination with cardiac surgery (Fig. 3B), severe pneumonia (Fig. 3C), the combination of cardiac surgery and hematologic malignancy (Fig. 3D), or even in combination with Transfusion X (Fig. 3G).
As shown in Figs. 2C and 2D, Transfusion X can cause TRALI in combination with severe pneumonia (Fig. 3E) or together with the combination of cardiac surgery and hematologic malignancy (Fig. 3F).

**Timing in the sufficient cause model**

There are at least three peculiarities that should be noted about the sufficient cause model. These are all related to the timing of different events and are all illustrated by the examples already given.

1. Several sufficient causes can be completed simultaneously. The sufficient cause represented in Fig. 3D is only relevant if those in Figs. 3A and 3B have not yet been completed. In other words, cardiac surgery and hematologic malignancy must have occurred both before Transfusion Y is given. If Transfusion Y is given after either cardiac surgery alone or after hematologic malignancy alone, sufficient causes 3A or 3B would already have caused TRALI, rendering any subsequently completed sufficient cause (i.e., 3D) irrelevant. However, even if both cardiac surgery and hematologic malignancy were already present, it could still be argued Transfusion Y would then be capable of completing both sufficient causes 3A and 3B simultaneously, making 3D redundant and uninformative. The main reason sufficient cause 3D exists is to prevent two sufficient causes (3A and 3B) from being completed simultaneously. This simultaneous completion must be made impossible, to allow identification of the first completed sufficient cause. However, it could just as easily be reasoned that now, instead of only two, we have three sufficient causes completed simultaneously and we therefore still do not know who is the “guilty sufficient cause.” Therefore, unless “U” is very different in 3D (compared to 3A and 3B), 3D seems to be redundant. Even if “U” is indeed very different, until “U” is further specified, 3D will effectively still be redundant.

2. Component causes can disappear before completion of the sufficient cause. Transfusions X and Y together could cause TRALI. This can also be seen from Fig. 2. What is clear from Fig. 2 is that the two transfusions should be given very shortly after each other, since the effect of transfusion on the activation status of the pulmonary neutrophils and endothelium is short-lived. From Fig. 3G it is impossible to tell the importance of the timing of the two transfusions. In fact all of the sufficient causes in Fig. 3 require some temporal proximity of the component causes, since all component causes have only temporary effects on the activation status of the pulmonary neutrophils and endothelium. There is no way of representing this in the sufficient cause model. When considering individual patients with “pies filling up” we can maybe imagine “pieces of pie disappearing” after some time. However, for the more general description of all possible ways of causing TRALI there is no way to represent the timing of different risk factors relative to one another.

3. Absence of other disease could be a component cause in all sufficient causes. From Fig. 2 it can be seen that severe pneumonia and cardiac surgery are sufficient to cause acute lung injury. Since this would not include a transfusion, it can by definition not be TRALI and this sufficient cause of acute lung injury is therefore not represented in Fig. 3. However, sufficient causes 3B, 3C, 3D, 3E, and 3F would all be partially completed and could all be further completed by hematologic malignancy (3D and 3F), Transfusion X (3E and 3F), or Transfusion Y (3B, 3C, and 3D). All these sufficient causes would be irrelevant after the onset of normal (i.e., not transfusion-related) acute lung injury. This illustrates the importance of the chronologic order in which component causes accumulate, which cannot be adequately represented in the sufficient cause model. To fix this problem we could make absence of prior acute lung injury a necessary cause of TRALI (i.e., a component cause present in all possible sufficient causes). However, this is only a cosmetic patch, which does not tell us much about the timing of transfusion relative to the addition of “the second clinical risk factor” (i.e., either severe pneumonia or cardiac surgery, whichever wasn’t the first).

In conclusion, the relative timing of different component causes might be better considered using the threshold model, or as further demonstrated in the discussion, by combining both models.

**DISCUSSION**

We have discussed the threshold model and the sufficient cause model of multicausality and their application to TRALI. We have illustrated the parallels between these two models, based on the example of a number of possible scenarios for the etiology of TRALI.

Both models are better adapted than the currently popular two-hit model, to represent the complex multicausal nature of TRALI. We have, however, also discussed a few limitations, mainly of the sufficient cause model. All these limitations of the sufficient cause model are related to the timing of risk factors. The threshold model is very well suited to depict timing and is intuitively more appealing than the sufficient cause model.

Why then would we bother with the sufficient cause model at all? One reason is the representation of “interaction” or “effect modification.” If two component causes are in the same sufficient cause they are said to interact of
modify each other’s effect. For example, cardiac surgery and hematologic malignancy interact to make Transfusion X a potential cause of TRALI (Fig. 3F). In other words the effect of cardiac surgery (i.e., no effect in combination with Transfusion X alone) is modified by the presence of hematologic malignancy (i.e., now it does cause TRALI). This is the simplest possible form of effect modification and can also easily be illustrated using the threshold model (Fig. 2D). However, if we consider the combination of Transfusion X and Transfusion Y, we may find the threshold model more limited.

For all scenarios depicted in Fig. 2 we always assumed the level of activation of the pulmonary neutrophils and endothelium caused by different risk factors simply adds up. In other words, the presence of one risk factor does not influence the size of the effect of another risk factor. Now, assume first that both Transfusion X and Transfusion Y contain biologically active lipids: Transfusion Y in twice as high a concentration as Transfusion X. Adding them together would most likely result in an approximately additive effect on the activation status of the pulmonary neutrophils and endothelium. Conversely, if we assume both Transfusion X and Transfusion Y contain neutrophil-activating antibodies of similarly high affinity and against two closely adjacent epitopes, adding Transfusion X to Transfusion Y, by competition for binding and steric hindrance, would likely reduce rather than increase the total activation of the pulmonary neutrophils and endothelium. This cannot readily be represented in the threshold model. In the sufficient cause model on the other hand, this is solved quite easily by deleting sufficient cause 3G.

Another reason to use the sufficient cause model is the option to include unknown component causes “U,” which can be different for different sufficient causes. For example, for a patient having his endothelium damaged by intensive chemotherapy a gene variant influencing the sensitivity of the endothelium to the chemotherapeutic agent in question could be a relevant component cause. For another patient, undergoing cardiac surgery, this gene variant would be completely irrelevant. This cannot be easily represented in the threshold model. One option would be to, like in the sufficient cause model, introduce a factor “U” with its associated level of activation. However, even if the level of activation of an unknown factor could be estimated at all, since the “U” can be different in different sufficient causes, so can the level of activation. Therefore, one “U” would be valid only during one identified potential cause and another only during another. The sufficient cause model leaves us much more flexibility to leave “U” and its biologic effect completely undefined.

A last limitation of the threshold model is that it does not need to be specific for the disease under investigation. In our case it describes the causation of acute lung injury in general, rather than specifically of TRALI. As can be seen from Fig. 2, the combination of cardiac surgery and severe pneumonia would be sufficient to cause acute lung injury. Since no transfusions would be involved, this could by definition never be TRALI. The threshold model describes the level of activation of a final common pathway for a given disease. If this final common pathway is shared with another disease, we cannot distinguish the two. However, the observed symptoms will almost certainly also be shared and it could be argued the two diseases are really one and the same. Nevertheless a clinically relevant distinction can sometimes be defined, as in the case of “normal” acute lung injury and TRALI. The threshold model has no real solution for this, except for simply checking whether at least one of the risk factors was a transfusion. The sufficient cause model solves this problem by simply making transfusion a necessary component cause (i.e., a component cause present in all possible sufficient causes).

Both models have their merits and limitations, but both provide new insights that the two-hit model could not provide. One example is a slight variation to the scenario represented in Fig. 2D. In this scenario cardiac surgery during hematologic malignancy raises the activation status of the pulmonary neutrophils and endothelium to such a level that a subsequent Transfusion X can complete sufficient cause 3F: If, however, Transfusion X would have been given shortly (i.e., a day) before cardiac surgery, it would have been the surgery that would have completed sufficient cause 3F. In this case the onset of acute lung injury would biologically speaking be transfusion related, but it is unlikely it would even be considered TRALI. It will be a matter of debate whether this scenario should lead to a revision of the definition of TRALI. In the interest of prevention of acute lung injury, in which a transfusion is involved, this would definitely seem to be a debate worth having. A previous suggestion to introduce a definition of “delayed TRALI,” with symptoms occurring up to 72 hours after transfusion, has not considered the possibility that additional clinical risk factors might be acquired during those 72 hours after the transfusion. This does, however, seem a biologically plausible mechanism. TRALI is said to typically resolve spontaneously after 48 to 96 hours. It is likely the raised activation status of pulmonary neutrophils and endothelium lasts a similar period. This is probably even the case if there is no diagnosable TRALI, because the activation level did not initially reach the threshold level. Any additional risk factor acquired during that period could then further raise the activation level and cause an acute lung injury. This acute lung injury should then arguably be considered transfusion related.

If this is in fact (delayed) TRALI, we should not only consider much more instances of acute lung injury to be TRALI. We should also consider risk factors acquired after transfusion as potentially causal for that case of
TRALI. It is unlikely this option would ever have been considered at all if not for the application of truly multicausal models like the threshold model and the sufficient cause model.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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