Université de Montréal

La surcharge volémique liée à la transfusion

Définition et épidémiologie aux soins intensifs pédiatriques

par

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présenté par

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Résumé

Les transfusions de culots globulaires sont une pratique fréquente aux soins intensifs; elles sont associées à de nombreuses complications. Ce travail s'intéresse à l'une d'entre elles, celle qui occasionne le plus de décès, la surcharge volémique liée à la transfusion (Transfusion-Associated Circulatory Overload - TACO).

Dans une première étude, nous avons tenté de déterminer l'impact des critères diagnostiques pris en compte dans la définition adulte du TACO dans une population de soins intensifs pédiatriques. Cette définition a été appliquée à 136 patients de soins intensifs pédiatriques durant leur séjour. Nous avons obtenu des taux d'incidence du TACO très variables (entre 1,5 et 76%) selon la manière d'interpréter les critères diagnostiques proposés.

Notre seconde étude a consisté en une revue exploratoire de la littérature concernant le TACO aux soins intensifs adultes et pédiatriques, peu importe le type de produit sanguin labile transfusé. Neuf études ont rencontré nos critères d'inclusion, à savoir décrire au moins un des critères suivants : l'incidence, les facteurs de risque ou les conséquences du TACO. Huit études étaient observationnelles. Seules trois études étudiaient la population pédiatrique.

Les résultats montrent une incidence cumulée de TACO plus élevée aux soins intensifs (5,5%) que dans la population générale. Les principaux facteurs de risque chez l'adulte sont liés à la balance liquidienne préexistante, aux caractéristiques de la transfusion elle-même et aux comorbidités déjà présentes chez le patient. En outre, le TACO adulte est associé à une augmentation de la durée de séjour à l'hôpital.

Les études pédiatriques incluses ne rapportaient aucune donnée sur les facteurs de risque et les conséquences du TACO dans cette population.

Ce travail a permis de montrer que la définition actuelle du TACO n'est pas applicable à la population des soins intensifs pédiatriques.

Le TACO aux soins intensifs est peu présent dans la littérature scientifique malgré sa fréquence et les risques qu'il présente; d'autres études sont indispensables pour en améliorer sa compréhension. Nous évoquerons certaines voies de recherche qui permettraient une meilleure connaissance de cette complication potentiellement mortelle des transfusions.

Mots-clés : surcharge volémique liée à la transfusion, réaction transfusionnelle, définition, surcharge volémique, pédiatrie, soins intensifs

Abstract

Red blood cell transfusions are common practice in intensive care and lead to many adverse reactions. This research project is focused on the most frequent fatal complication: transfusion-associated circulatory overload (TACO).

In our first study, we tried to determine the impact of the diagnostic criteria of the adult definition of TACO in a pediatric intensive care population. The definition was applied to 136 pediatric intensive care patients during their stay. We obtained highly variable incidence rates (from 1.5 to 76%) depending on the interpretation of the diagnostic criteria.

Our second study is a scoping review of the literature about TACO in intensive care, both adult and pediatric, regardless of the type of labile blood product transfused. Nine studies met our inclusion criteria, namely, to describe at least one of the following criteria: incidence, risk factors or outcomes of TACO. Eight studies were observational. Only three studies were conducted in pediatric population.

The results showed a pooled incidence of TACO which is higher (5.5%) in intensive care than in the general population. The main risk factors in the adult population were related to the positive pre-existing fluid balance, the characteristics of the transfusion itself and the patients' preexisting comorbidities. Furthermore, the results showed an association between TACO in adult intensive care and an increased length of stay.

None of the included pediatric study reported data on risk factors or outcomes.

This research demonstrates that the current TACO definition is not applicable for the pediatric intensive care population.

There is limited literature about TACO in intensive care despite its occurrence rate and the associated risks; other studies are therefore necessary to enhance its comprehension. We will touch on potential research pathways that would lead to a better understanding of this deadly transfusion complication.

Keywords : transfusion-associated circulatory overload, transfusion reaction, definition, fluid overload, pediatrics, critical care

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Liste des abréviations

BNP : *Brain Natriuretic Peptide*

FDA : *Food and Drug Administration*

HLA : *Human Leucocyte Antigen*

HNA : *Human Neutrophil Antigen*

ICU : *Intensive Care Unit*

ISBT : *International Society of Blood Transfusion*

NHSN : *National Healthcare Safety Network*

NT-proBNP : *N-terminal prohormone Brain Natriuretic Peptide*

PICU : *Pediatric Intensive Care Unit*

RBC : *Red Blood Cell*

SHOT : *Serious Hazards of Transfusion*

TACO : *Transfusion-Associated Circulatory Overload*

TRALI : *Transfusion Related Acute Lung Injury*

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1. Introduction

Des transfusions de culots globulaires sont très fréquemment pratiquées aux soins intensifs pédiatriques. Les données de la littérature indiquent que la moitié des enfants admis en reçoivent (1,2). Toutefois, ce taux d'incidence semble avoir diminué depuis les recommandations de pratiques transfusionnelles plus restrictives publiées en 2007 (3); il est actuellement de 17% dans notre unité (4). L'anémie est la raison principale de ce type de transfusion; elle concerne entre 55 et 75% des patients des soins intensifs pédiatriques durant leur séjour (1,5). Elle peut avoir différentes causes. Une hémorragie, de l'inflammation, un déficit en fer, ou encore des prélèvements sanguins répétés sont les motifs principaux de ce type de transfusion aux soins intensifs pédiatriques (6).

L'anémie entraine une diminution de la capacité de transport en oxygène par le sang, provoquant ainsi un déséquilibre entre l'apport et le besoin en oxygène des tissus (6). Il est parfois nécessaire de procéder à une transfusion pour rétablir la capacité de transport en oxygène requise par l'organisme. Toutefois, aucun seuil d'hémoglobine n'est universellement admis pour tous les patients; la décision de transfuser doit être basée sur l'état clinique du patient et sa tolérance à l'anémie, mais également sa pathologie sous-jacente et la cause de l'anémie (7).

Malheureusement, les transfusions sanguines ne sont pas sans risque et sont associées à de nombreuses complications que nous détaillerons ci-dessous.

Ce mémoire porte sur une de ces complications : la surcharge volémique liée à la transfusion (*Transfusion Associated Circulatory Overload – TACO*) aux soins intensifs pédiatriques. Une première partie présentera les principales complications liées aux transfusions, avant d'aborder deux études réalisées durant ma maitrise : la première porte sur le problème de la définition du TACO aux soins intensifs pédiatriques, et la deuxième s'intéresse à l'épidémiologie du TACO aux soins intensifs. Ces deux études ont été publiées et les articles correspondants seront présentés dans ce travail.

Enfin, la discussion permettra de réfléchir aux questions non-résolues liées au TACO et d'envisager différentes manières de l'étudier davantage.

1.1. Complications des transfusions

Les taux d'incidence des complications des transfusions ne sont pas toujours précis. En effet, la plupart des données épidémiologiques retrouvées dans la littérature sont issues de rapports d'hémovigilance. Ces derniers recueillent les événements indésirables rapportés de manière volontaire par les cliniciens.

Toutefois, il existe également certaines données issues d'études prospectives. Ces dernières rapportent des taux d'incidence souvent supérieurs aux rapports d'hémovigilance grâce à leur surveillance active des complications (8,9).

Le rapport d'hémovigilance québécois de 2017, publié en 2019, fait état d'une incidence d'environ 7 événements indésirables par 1000 transfusions de produit sanguin (10). Ce taux est légèrement inférieur, à celui rapporté par le système d'hémovigilance français de 2018, qui rapportait 3 évènements indésirables par 1000 transfusions (11).

Les complications des transfusions sanguines dépendent de la qualité du produit sanguin administré, de l'état clinique du patient transfusé et de ses caractéristiques génétiques, mais également de la qualité des procédures transfusionnelles (12). L'amélioration des techniques de préparation et de conservation des produits sanguins, le perfectionnement des tests de dépistage et la meilleure connaissance et donc évaluation de l'incidence des effets indésirables ont diminué la fréquence des complications dues aux procédures transfusionnelles (12,13). Les risques sont moins fréquents mais restent importants et nécessitent une évaluation réfléchie lors de chaque prescription de produits sanguins.

Les complications des transfusions sont de trois ordres (12,14,15) :

- immunologiques
- infectieuses
- liées à la surcharge volémique.

Complications	Incidence dans la population générale (nombre de cas par transfusion, tout produit sanguin labile confondu) (13,16)
Complications immunologiques	
- Anticorps irrégulier	1/13
- Réaction allergique (anaphylaxie)	1/100 (1/3.000)
- Réaction fébrile non hémolytique	1/300
- Lésion pulmonaire aigue post-transfusionnelle (TRALI)	1/10.000 (estimation)
- Incompatibilités immunologiques ABO	1/40.000
- Purpura post-transfusionnel	1/100.000
- Réaction du greffon contre l'hôte	Inconnue mais exceptionnel
Complications infectieuses	
- Infection bactérienne	1/250.000
- Infection virale	Moins de 1/1.400.000
- Infection parasitaire	1/4.000.000
Complications liées à la surcharge volémique	
- Surcharge volémique associée à la transfusion (TACO)	1/100

Les acronymes TRALI et TACO n'ont pas d'équivalents en langue française et sont reconnus dans la littérature scientifique; ils seront donc utilisés dans ce mémoire.

1.1.1. Les complications immunologiques

Les complications immunologiques sont variées et leur mécanisme lésionnel précis n'est pas entièrement compris dans tous les cas.

Anticorps irrégulier

L'apparition d'un anticorps irrégulier est la complication la plus fréquente de la transfusion avec une incidence de 1/13 transfusions (16). Les globules rouges du donneur

portent des antigènes inconnus du receveur; celui-ci peut donc produire des anticorps contre ces antigènes. La formation de ces anticorps dépend du type d'antigène rencontré mais également de la compétence du système immunitaire du receveur. En cas de réaction antigène-anticorps, une hémolyse se produit. La manifestation clinique la plus fréquente est un ictère d'importance variable. La mortalité est possible mais reste très rare; parfois, il n'y a même aucune conséquence clinique.

Réaction allergique

Les réactions allergiques représentent la deuxième complication la plus fréquente avec une incidence pouvant aller jusqu'à 1/100 transfusions (16). Ce sont surtout les transfusions de plaquettes qui entrainent ce type d'événement indésirable. La réaction d'hypersensibilité se produit quand le receveur est exposé à un allergène présent dans le plasma du donneur. S'en suit alors une stimulation des mastocytes qui libèrent une quantité massive d'histamine, responsable de la symptomatologie. Les signes cutanés tels qu'un érythème ou une urticaire restent les plus fréquents et le pronostic n'est engagé qu'en cas d'œdème de Quincke ou de choc anaphylactique (1/3000 transfusions).

Réaction fébrile non hémolytique

La réaction fébrile non hémolytique est un événement indésirable survenant rapidement après le début de la transfusion. Il s'agit d'une réaction immunologique se présentant par des frissons et une hyperthermie; s'y associent parfois des symptômes subjectifs de malaise, de gêne respiratoire, de douleur musculaire. Les symptômes disparaissent spontanément en quelques heures. Les études donnent des chiffres très variables concernant l'incidence des réactions fébriles non hémolytiques à cause de la sous-déclaration de ce processus mineur. Les données canadiennes rapportent une incidence de 1/300 transfusions; mais il semblerait que les chiffres soient plus élevés pour la population pédiatrique (17).

Lésion pulmonaire aigue post-transfusionnelle

La lésion pulmonaire aigue post-transfusionnelle (*Transfusion Related Acute Lung Injury – TRALI*) est un œdème pulmonaire lésionnel survenant dans les six heures suivant la transfusion et évoluant vers la détresse respiratoire aiguë. Le diagnostic de TRALI repose sur

des critères cliniques et radiologiques. Selon la nouvelle définition publiée en 2019 par Vlaar *et al.* (18), le TRALI associe une hypoxémie aigue, la présence d'infiltrats bilatéraux à la radiographie et l'absence de défaillance cardiaque gauche dans les six heures suivant la fin de la transfusion, et ceci en l'absence de lésion pulmonaire aigue préexistante,. La physiopathologie du TRALI est de mieux en mieux connue mais il reste encore des points à éclaircir. L'hypothèse la plus acceptée actuellement est que le TRALI survient suite à la présence de deux atteintes distinctes. La première consiste en une activation inflammatoire de l'endothélium pulmonaire; celle-ci est secondaire à différents facteurs dont les mieux connus sont la présence d'une infection sévère (via les lipopolysaccharides), une première transfusion et la ventilation mécanique. La deuxième atteinte correspond à la transfusion de produits sanguins contenant des anticorps anti-HLA (Human Leucocyte Antigen) ou anti-HNA (Human Neutrophil Antigen) dirigés contre les neutrophiles du receveur, et qui vont adhérer à l'endothélium pulmonaire préalablement activé. Ceci explique la physiopathologie du TRALI immun, le plus fréquent. Son incidence a toutefois diminué grâce à une meilleure sélection des donneurs, en particulier, l'exclusion des femmes ayant eu une grossesse pour les dons de plasma. Toutefois, la situation est différente aux soins intensifs où la plupart des cas de TRALI diagnostiqués sont non-immuns. Dans ce cas, il semblerait que la deuxième atteinte soit liée à la présence de modificateurs de la réponse biologique dans le produit transfusé, également capable d'activer les neutrophiles adhérents (18,19). L'incidence réelle du TRALI est difficile à préciser car il n'est pas toujours rapporté tel quel au système d'hémovigilance; mais il reste une des premières causes de décès attribuable aux transfusions sanguines.

Incompatibilités immunologiques de type ABO

Les incompatibilités immunologiques de type ABO résultent toujours d'une erreur humaine. L'administration de produit sanguin non compatible avec le receveur peut entrainer une hémolyse importante qui évolue jusqu'à un état de choc associé à une coagulation intravasculaire disséminée (12,16). L'amélioration des procédures transfusionnelles avec, par exemple, la nécessité de réaliser deux typages du groupe sanguin du receveur à deux moments différents et les nombreuses vérifications de compatibilité tout au long du processus ont permis de diminuer considérablement l'incidence de cette complication. Hélas, elle n'a toujours pas totalement disparu (12).

Purpura post-transfusionnel

Le purpura post-transfusionnel est une complication rare (environ 1/100.000 transfusions) qui se présente cliniquement par une thrombopénie importante dans les cinq à dix jours suivant la transfusion. Les signes cliniques retrouvés sont une épistaxis, un purpura ou encore une hémorragie interne, parfois intracrânienne. La mortalité liée à cette complication peut aller jusqu'à 10% (12,16).

Réaction du greffon contre l'hôte

La réaction du greffon contre l'hôte est létale dans 90% des cas mais se produit extrêmement rarement. Elle survient quand des lymphocytes T activés présents dans le produit sanguin transfusé reconnaissent le receveur comme étranger (12,16). Les manifestations cliniques sont majoritairement cutanées; la mortalité est principalement liée à l'hypoplasie médullaire et la pancytopénie induite met le receveur à très haut risque infectieux. Les receveurs les plus à risque sont les patients immunodéprimés (déficit immunitaire congénital, traitement immunosuppresseur ou greffe de cellules souches hématopoiétiques), les patients atteints d'un lymphome de Hodgkin, les fœtus et les nouveau-nés (16). Afin de protéger les patients à haut risque de réaction du greffon contre l'hôte, une irradiation du produit sanguin à transfuser peut être faite; elle permet d'inactiver les lymphocytes T résiduels.

Autres

L'hémolyse retardée post-transfusionnelle des anémies falciformes, l'immunosuppression post-transfusionnelle, et le microchimérisme associé à la transfusion sont des complications mal connues et parfois controversées (12).

1.1.2. Les complications infectieuses

Les complications infectieuses sont celles dont l'incidence a le plus diminué avec l'amélioration de tout le processus de transfusion, du prélèvement chez le donneur à l'administration du produit chez le receveur. Elles sont de plusieurs ordres : bactériennes, virales et parasitaires.

Infections bactériennes

Les produits sanguins peuvent être contaminés par une bactérie, soit au moment du prélèvement, soit lors de la manipulation du sang. Les produits les plus à risque sont les plaquettes car elles sont entreposées à température ambiante, ce qui favorise la croissance bactérienne. Les manifestations cliniques vont de l'hyperthermie avec frissons au choc septique. On constate une forte diminution de l'incidence des infections bactériennes transmises par les transfusions (1/250.000 transfusions) grâce à l'amélioration des procédures d'hygiène lors du prélèvement, le respect des règles de conservation des produits sanguins, le dépistage systématique de chaque don de plaquettes, mais également l'obligation pour les donneurs de remplir une questionnaire post-don (11,13,16). Malgré tout, la contamination bactérienne reste le principal risque infectieux.

Infections virales

Le risque de transmission virale est devenu très faible dans les pays développés grâce à une meilleure sélection des donneurs et à l'utilisation de tests sérologiques. Les principaux virus transmis dans le passé étaient les virus de l'hépatite B, de l'hépatite C, et de l'immunodéficience humaine (VIH). Depuis lors, le dépistage du génome viral dans le produit sanguin prélevé a été implémenté de manière systématique et obligatoire. Les risques actuels d'infection sont estimés à 1/12.900.000 pour le VIH, 1/27.100.000 pour l'hépatite C et 1/1.400.00 pour l'hépatite B (13). Actuellement, les transmissions virales rapportées concernent principalement le virus de l'hépatite E. Le virus du Nil occidental est dépisté au Canada durant la période à risque (du printemps à l'automne). Les très rares cas de transmissions virales sont expliqués par des dons de sang effectués durant la période de latence du virus, lorsqu'il n'est pas encore détectable par toutes les mesures mises en place actuellement.

Le cas du cytomégalovirus est particulier car il s'agit d'un organisme intracellulaire. La déleucocytation systématique des produits sanguins assure une prévention suffisante contre le cytomégalovirus, même pour les femmes enceintes ou les patients immunodéprimés. Les transfusions in utero, quant à elles, restent les situations où la déleucocytation n'est pas jugée suffisante; elles nécessitent des produits sanguins négatifs pour le cytomégalovirus (20).

Infections parasitaires

Les infections parasitaires sont extrêmement rares. Il s'agit principalement de la malaria et de la maladie de Chagas. La babesiose fait actuellement l'objet d'études au Canada afin d'évaluer la nécessité de mise en place de mesures de sécurité particulières; à l'heure actuelle, aucun cas transmis lors d'une transfusion n'a été rapporté au Canada, contrairement aux États-Unis (13). La prévention des infections parasitaires passe par l'exclusion des donneurs pendant plusieurs mois après un séjour dans une région endémique.

Autres pathogènes

Le virus de la Dengue, le virus Zika et le variant de la maladie de Creutzfeldt-Jacob sont des agents transmissibles émergents qui ne font pas l'objet d'un dépistage systématique. La prévention de ces infections rares passe également par l'exclusion des donneurs à risque.

1.1.3. Les complications liées à la surcharge volémique

La surcharge volémique associée à la transfusion (*Transfusion Associated Circulatory Overload – TACO*) est la complication mortelle la plus fréquente (12). Son incidence est variable selon les études mais avoisine 1% dans la population générale (8,21,22). Le TACO se définit actuellement par la survenue d'un œdème pulmonaire d'origine hémodynamique dans les six heures après une transfusion. Il associe quatre des symptômes suivants : tachycardie, hypertension, détresse respiratoire, œdème pulmonaire et bilan liquidien positif (23–25). Toutefois, cette définition est discutée; la première étude présentée dans ce travail porte sur ce point.

La problématique de la surcharge volémique liée à la transfusion apparait dans la littérature dès la première moitié du siècle dernier. En effet, en 1940, Marriott et Kekwick insistaient déjà sur les risques de défaillance cardiaque secondaire à l'administration rapide de globules rouges (26). Toutefois, 80 ans plus tard, la physiopathologie de cette complication potentiellement mortelle reste mal connue. La théorie la plus acceptée actuellement présente le TACO comme la conséquence de deux situations cliniques distinctes. D'une part, le patient serait incapable de gérer une surcharge de volume suite à une insuffisance rénale ou cardiaque

par exemple. Et d'autre part, l'apport rapide de liquide lié à une transfusion de produits sanguins entraine une surcharge volémique, qui aurait pour conséquence, un œdème pulmonaire par augmentation de pression dans les capillaires pulmonaires (27). Mais cette théorie est controversée car des cas de TACO sont décrits chez des patients ne présentant aucun facteur de risque. En outre, certains TACO surviennent après la transfusion de faibles volumes de produits sanguins. Dès lors, certains auteurs émettent la possibilité d'une composante inflammatoire au TACO, directement liée à la composition du produit transfusé (28–30).

1.2. Pourquoi nous intéresser au TACO?

Le TRALI et le TACO sont les complications respiratoires les plus sévères des transfusions et elles entrainent un taux de mortalité important (23,24). C'est en raison de sa fréquence, de sa sous-reconnaissance et de sa gravité que nous nous sommes intéressés au TACO aux soins intensifs pédiatriques.

Dès nos premières recherches, nous nous sommes rendu compte qu'il n'existe pas de définition pédiatrique du TACO. Comment le TACO est-il donc étudié en pédiatrie? Les cliniciens-chercheurs utilisent-ils la définition adulte?

Nous étions également surpris du petit nombre d'études réalisées aux soins intensifs. Pourtant, la défaillance d'organes que ces patients en état critique présentent nous laissait penser que cette population était plus à risque de TACO.

Nous nous sommes aussi demandé en quoi le TACO se différencie de toute autre surcharge volémique. En effet, beaucoup d'études démontrent les effets néfastes d'un bilan liquidien positif chez les patients hospitalisés aux soins intensifs (31–40). Le TACO est-il donc vraiment une entité à part entière avec ses caractéristiques propres qui le distingueraient de la surcharge volémique non liée à la transfusion? La composition du volume administré est-elle aussi déterminante ou est-ce seulement la quantité de volume?

Pour répondre à certaines de nos questions, nous avons tout d'abord étudié l'impact de différentes interprétations des critères diagnostiques d'une définition adulte du TACO sur son

incidence dans une population de soins intensifs pédiatriques. Par la suite, pour approfondir notre compréhension du TACO dans la population spécifique des soins intensifs, nous avons procédé à une revue exploratoire de la littérature sur l'incidence, les facteurs de risque et les conséquences du TACO dans cette population.

1.3. Quelle définition pédiatrique du TACO?

En l'absence de définition pédiatrique du TACO, nous avons appliqué les critères diagnostiques adultes de la définition de l'*International Society of Blood Transfusion* (ISBT) (25) à une population de soins intensifs pédiatriques recevant une transfusion de culot globulaire. L'ISBT définit le TACO par la présence de quatre des cinq critères suivants dans les six heures suivant une transfusion : détresse respiratoire aiguë, tachycardie, hypertension artérielle, œdème pulmonaire nouveau ou qui s'aggrave sur la radiographie du thorax, balance liquidienne positive.

Les critères eux-mêmes n'étant pas définis de manière précise, nous avons choisi différentes valeurs de référence :

- Tout d'abord, nous avons comparé les paramètres physiologiques des patients (fréquence respiratoire, fréquence cardiaque, hypertension artérielle) aux limites supérieures publiées dans le *Nelson Textbook of Pediatrics* (41).
- Nous avons ensuite comparé les paramètres d'un même patient après la transfusion et dans les six heures précédant celle-ci.

Afin d'élargir encore l'interprétation de la définition, nous avons étendu la période étudiée au-delà des six heures post-transfusion; nous avons donc observé les patients jusqu'à 24 heures après la transfusion.

Nous avons alors calculé le taux d'incidence du TACO dans notre population de 136 patients de soins intensifs pédiatriques en utilisant chacune de ces différentes façons d'interpréter des critères diagnostiques.

Les résultats obtenus nous ont amenés à réfléchir sur la pertinence de transposer la définition adulte à la population pédiatrique sans y apporter les adaptations nécessaires. Comment mieux définir chacun des critères diagnostiques afin de mieux correspondre à une population déjà

sévèrement malade au moment de la transfusion? Si cette définition n'est pas tout à fait adaptée à cette population, faudrait-il y ajouter d'autres critères pour la rendre cliniquement plus pertinente?

Ces travaux ont mené à un article publié dans *Transfusion* en avril 2018 présenté en format manuscrit dans le prochain chapitre. La version publiée est reproduite en annexe.

1.4. Qu'en est-il du TACO aux soins intensifs?

Afin de faire un état des lieux du TACO aux soins intensifs, nous avons entrepris une revue exploratoire de la littérature pour en étudier l'incidence, les facteurs de risque et les conséquences. Nous y avons inclus tous les articles étudiant le TACO aux soins intensifs adultes et/ou pédiatriques et rapportant au moins l'un des trois éléments cités.

Ces travaux ont mené à un article publié dans *Critical Care Medicine* en juin 2019 présenté en format manuscrit dans le troisième chapitre. La version publiée est reproduite en annexe.

2. Étude 1: Quelle définition pédiatrique du TACO?

« Transfusion-associated circulatory overload in a pediatric intensive care unit: different incidences with different diagnostic criteria. »

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Abstract

Background

The incidence of transfusion-associated circulatory overload (TACO) is not well known in children, especially in pediatric intensive care unit (PICU) patients.

Study design and methods

All consecutive patients admitted over one year to the PICU of CHU Sainte-Justine were included after they received their first red blood cell transfusion. TACO was diagnosed using the criteria of the International Society of Blood Transfusion, with two different ways of defining abnormal values: 1) using normal pediatric values published in the Nelson Textbook of Pediatrics 2007 and 2) by using the patient as its own control and comparing pre- and post-

transfusion values with either 10% and 20% difference threshold. We monitored for TACO up to 24 hours post-transfusion.

Results

136 patients were included. Using the “normal pediatric values" definition, we diagnosed 63, 88 and 104 patients with TACO at 6, 12 and 24 hours post-transfusion respectively. Using the “10% threshold” definition we detected 4, 15 and 27 TACO in the same periods respectively; using the “20% threshold” definition, the number of TACO was 2, 6 and 17 respectively. Chest radiograph was the most frequent missing item, especially at 6 and 12 hours post-transfusion. Overall, the incidence of TACO varied from 1.5% to 76% depending on the definition.

Conclusion

A more operational definition of TACO is needed in PICU patients. Using a threshold could be more optimal but more studies are needed to confirm the best threshold.

Key words:

Transfusion reaction; Intensive care units, Pediatric; Transfusion-associated circulatory overload; Diagnostic criteria.

Introduction

Transfusion-associated circulatory overload (TACO) is the most frequent serious transfusion adverse reaction in adult population [1] and was the second leading cause of transfusion-related fatalities reported by the FDA in 2015 [2]. It is associated with increased mortality and morbidity, and a longer length of stay in hospital [3].

TACO is underdiagnosed and underreported [3]. This is due to the lack of recognition of the diagnosis, the underestimation of its severity, the confusion between TACO and transfusion-related acute lung injury (TRALI) [4], and probably to the absence of an operational definition.

The best diagnostic criteria for TACO is still a matter of debate [5]. There are at least two lists of diagnostic criteria of TACO in adults, one advocated by the National Healthcare Safety Network (NHSN) of the Centers for Disease Control [6], the other one advocated by the British Hemovigilance Scheme and the International Society of Blood Transfusion (ISBT) [7]. Recently, the ISBT submitted another list of diagnostic criteria [8]. None of these diagnostic criteria are adapted to children as they do not define cutoffs for age-adapted vital sign values. Moreover these definitions ignore the effect of critical illness that can per se influence vital signs: for example, tachycardia is prevalent among PICU patients. The diagnosis of TACO is therefore challenging in critically ill children and a definition adapted to the PICU is highly needed as this population often receive transfusions and is prone to the adverse effects of circulatory overload [9].

The objectives of this study were 1) to compare different criteria or abnormal values for TACO in PICU and 2) to compare the incidence of TACO in PICU using those different criteria.

Material and methods

Study design

This retrospective observational study of consecutively transfused children is based on a previous prospective study, which aimed to describe the respiratory dysfunction associated

with red blood cell transfusions[10]. This study was undertaken in the PICU of CHU Sainte-Justine, a 24 beds unit of a quaternary university-affiliated pediatric hospital, from April 2009 to April 2010. All patients consecutively admitted to the PICU over one year were eligible if they received at least one RBC transfusion during their PICU stay. The exclusion criteria were gestational age < 40 weeks, age < 3 days or > 18 years, pregnancy, transfusion on extracorporeal membrane oxygenation, transfusion in operating room, admission to PICU just after labor and death within one hour of first RBC transfusion.

Any administration of RBC units in the PICU was considered a transfusion, regardless of the volume given. Only pre-storage leukocyte-reduced AS-3 RBC units were used. Time zero was defined as the time the first RBC transfusion was started in the PICU. Data was collected on the first RBC transfusion administered for each included patient.

This TACO study is a secondary study undertaken in 2013 using the database of the prior study mentioned above.

Data collection

Patient's data were recorded in a validated case report form (CRF) by research assistants. Data were collected from 6 hours before time 0 until 24 hours following time 0. Three periods were set: 6, 12 and 24 hours following time 0. In this article, the terms pre-transfusion and post-transfusion always refer to time zero (beginning of the transfusion).

The following data were collected: demographic data, diagnosis of cardiac disease, post-cardiac surgery, duration of transfusion, transfusion volume, use of vasopressive or inotropic agent, highest inspired fraction of oxygen (FiO_2), highest respiratory rate, highest positive end-expiratory pressure (PEEP) and peak inspiratory pressure (PIP), lowest arterial partial pressure of oxygen (PaO_2)/FiO_2 or oxygen saturation measured by pulse oximetry (SpO_2)/FiO_2, non-invasive or invasive ventilation required, mean and highest heart rate, mean and highest blood pressure (systolic and mean pressure), mean and highest central venous pressure, mean and highest left atrial pressure and fluid balance. The worst values of each parameter were recorded for each period.

For each ventilated patient, a chest radiograph is done every morning in the PICU; another chest radiograph can be ordered by the physician when judged necessary. For non-ventilated patients, chest radiograph is ordered when judged necessary by the physician. A pediatric radiologist (CJ) retrospectively and independently reviewed all chest radiographs to evaluate if any pulmonary edema was present, and if it had worsened after RBC transfusion compared to before transfusion. The radiologist was blinded to the time of administration of transfusion, the clinical condition of the patient and to the presence or not of other TACO criteria. The radiologist was also blind to the results of other previous reports by intensivists or radiologists who interpreted the radiographs during the stay of the patient.

TACO criteria

We used the criteria proposed by the International Society of Blood Transfusion [7] which diagnoses TACO when any 4 of the 5 following criteria are observed within 6 hours of completion of transfusion: 1) acute respiratory distress; 2) tachycardia; 3) increased blood pressure; 4) acute or worsening pulmonary edema on frontal chest radiograph; 5) evidence of positive fluid balance.

Since there is no clear definition to specify each criterion, we decided to compare two ways to define abnormal values for those criteria (as detailed in Table 1). The first way was to use the upper limit of the normal pediatric values according to age, as published in the Nelson Textbook of Pediatrics [11]; this was used for respiratory distress, tachycardia and high blood pressure. The two other criteria consisted of edema found on chest radiograph, according to the radiologist, and a positive fluid balance. For positive fluid balance, since there is no available normal value in the literature, we decided to use the absolute value of $\geq$ 1 ml as threshold. The second way was to use the patient's worst values post-transfusion compared with his baseline values (observed within 6 hours pre-transfusion), and look for a threshold of 10% and 20% deterioration; this was used for respiratory distress, tachycardia and high blood pressure. For example, a threshold of 10% deterioration is reported for a patient who shows an increased heart rate (between 10% and 20%) after transfusion compared to before transfusion (maximal heart rate of 140/min after transfusion compared to 120/min before

transfusion which gives a difference of 140-120/120 = 16%). A threshold of 20% is reported if the deterioration is more than 20%. The two other criteria consisted of: 1) edema on chest radiograph that had worsened post-transfusion compared to pre-transfusion according to the radiologist (there was no difference between 10% and 20% deterioration as it is impossible to specify such a specific deterioration on chest radiograph), and 2) a fluid balance that was increased post-transfusion compared to pre-transfusion (with a 10% or 20% deterioration).

Since other definitions suggest that TACO can appear later than 6 hours post-transfusions[8], we decided to evaluate all these criteria at 6, 12 and 24 hours post-transfusion even though it is not part of the ISBT definition.

Statistical analysis

Continuous variables are presented as mean with standard deviation (SD) or median with interquartile ranges (IQR) according to the distribution. Categorical variables are presented as number with proportion (%). The incidence of TACO was calculated separately for each group of patients and for each studied period (6, 12 or 24 hours post-transfusion) as followed: total number of TACO per total number of patients transfused.

Data were collected on Microsoft Excel 2010 and analyzed with SPSS Statistics version 24.

Ethical approval

This observational study was approved by the Institutional Review Board (IRB) who waived informed consent.

Results

As detailed in Figure 1, 916 consecutive patients were admitted to the PICU from April 2009 to April 2010, including 144 who received at least one RBC transfusion. Eight patients

were excluded while 136 (14.8%) were retained in the study. Demographic characteristics are detailed in Table 2. Most patients (62.5%) were younger than 3 years (median: 12 months). Mean duration of the first RBC transfusion was 126 minutes and half of our patients had more than one blood product transfused during the 24 hours after the first RBC transfusion.

The number of patients with TACO based on the 3 distinct periods is detailed in Tables 3, 4 and 5. At 6 hours post-transfusion, 63 patients (46%) had a TACO using the "normal pediatric values" criteria, while only 4 patients (3%) had a TACO using the "10% threshold" criteria, and 2 patients (1.5%) using the "20% threshold" criteria.

At 12 and 24 hours post-transfusion, TACO was observed in 88 (65%) and 104 patients (76%) respectively, using the "normal pediatric values" criteria, 15 (11%) and 27 patients (20%) using the "10% threshold" criteria, and 6 (4%) and 17 patients (12%) using the "20% threshold" criteria.

Missing data are described in Tables 3, 4 and 5. Chest radiograph was the most frequent missing item; no chest radiograph was done at 6 hours post-transfusion in most patients (86/136 = 63%). Pre-transfusion fluid balance was also frequently unavailable (15/136 = 11%). Those missing data made the diagnosis of TACO impossible in 11 patients at 6 hours post-transfusion, 8 patients at 12 hours post-transfusion and 6 patients at 24 hours post-transfusion. Overall, depending on the criteria used and the interval post-transfusion used, the incidence of TACO varies from 1.5% to 76%.

New cases of TACO per period, using the different criteria studied are shown in Figure 2.

No case of TACO diagnosed in this study was reported by the attending physician to the Quebec Hemovigilance System.

Discussion

In our study, the incidence of TACO differed significantly when using different values for diagnostic criteria and different post-transfusion intervals; using the "normal pediatric values" criteria, the incidence of TACO varied from 46% to 76% depending on the post-transfusion interval; using the "10% threshold" criteria, the incidence varied from 3% to 20%; and using the "20% threshold" criteria, it varied from 1.5% to 12%. Thus, this study about TACO in PICU raises many questions.

First, can we use the definition suggested by the different Scientific Societies to diagnose TACO in children? The results of our study suggest that it might not be appropriate, because this definition is too vague and not adapted to children. In our study, we used the adult definition with different criteria or abnormal values and found that the incidence of TACO varied widely.

Second, which criteria or abnormal values should be used to diagnose TACO in PICU patients? The incidence of TACO with the "normal pediatric values" definition was very high (46% to 76%). Is this high incidence due to over-diagnosis (unsuitable and too sensitive criteria) or is it due to the fact that PICU patients were more at risk of TACO because of previous overload and/or cardiac failure?

If we compare to the adult literature[12,13], the incidence we found using a comparison between pre- and post-transfusion values (threshold) seems to be more appropriate. This study does not allow determining the best threshold (10% or 20%) since there is no reference standard. However this approach is also supported by Lieberman et al [14] who showed significant differences in the values of vital signs before and after the diagnosis of TACO in adult population.

In the current study, the incidence rate of TACO ranges from 1.5% to 11% using the "10% threshold" and the "20% threshold" at 6 and 12 hours of transfusion, which is similar to the literature from critically ill adults [12,13]. This could suggest that a threshold of 10% to 20% could possibly be an appropriate choice. The optimal threshold comparing pre- and post-

transfusion values to diagnose TACO remains to be determined in prospective studies in this PICU population.

Third, what should be the best post-transfusion interval to define TACO: 6, 12 or 24 hours? Presently, definitions of TACO suggest that the diagnosis must be done during the first 6 hours following transfusion, but could be done beyond 12 hours [5]. The rationale supporting a shorter period of onset for TACO is that RBC transfusion associated fluid overload should occur within a few hours. However, longer interval could be expected due to the interaction between fluid status and cardiac function as fluid overload could lead to cardiac insufficiency that may progress more slowly. Furthermore, different patients with different comorbidities and fluid balances are expected to demonstrate the clinical effects of volume overload at different times suggesting that there isn't a single ideal time to define TACO. In our study, incidence of TACO varies widely according to post-transfusion period and it was impossible to choose the best post-transfusion interval. Nevertheless, it is interesting to note that many cases of TACO appeared at 12 and 24 hours post-transfusion. Again, further studies should determine the peak onset of vital sign disturbances in all patients. Moreover, these studies should ideally be done using invasive and echocardiographic hemodynamic criteria that could help differentiating cardiac overload from other etiology producing a similar clinical picture.

Fourth, how frequent is TACO in children? Some papers reported that TACO is more frequent in children younger than 3 years and in people older than 60 years [3,12,15,16]. On the other hand, literature reports very few TACO in children [17,18]. Moreover, in the present study, no case of TACO was reported to the Quebec Hemovigilance System. The most probable explanations are that TACO is underdiagnosed and underreported [4]. Other reasons may be due to a lower risk of TACO in children compared to adult, to the inadequacy of the current diagnostic criteria in pediatrics or the clinician's lack of awareness of this condition. Another reason is that the difference between respiratory transfusion reactions like TACO and TRALI is more difficult to establish in critically ill patients because of their pulmonary status. Furthermore, the differentiation between the diagnosis of TRALI and TACO is sometimes difficult [15,19–22].

Finally, the best clinical criteria to diagnose TACO are still a matter of debate. A review of the different definitions made by SHOT showed large variations in incidence of

TACO depending on the definition used [5]. They concluded that all the definitions presently used are unsatisfactory. In 2016, the International Society of Blood Transfusion (ISBT) proposed new criteria including increased blood level of natriuretic peptide (BNP or NT-pro BNP) levels [8]. A high BNP level is an additional clue to the diagnosis of TACO as it supports the diagnosis of fluid overload and cardiac dysfunction [23]. Nevertheless, BNP has so far rarely been measured in PICU patients since we don't have baseline values, it was developed for adult congestive heart failure and the test requires a large amount of blood for analysis in small children. The usefulness of BNP to diagnose TACO in PICU patient must be evaluated in prospective studies. Perhaps the use of a 50% or 100% increase in BNP/NT-pro-BNP at 6, 12 and 24 hours as the gold standard for the diagnosis of TACO could be studied.

Another problematic criterion is the chest radiograph. First, in our study, the chest radiograph, which is necessary to ascertain lung infiltrates and is of one of the 5 diagnostic criteria, was unavailable in most instances (86/136) at 6 hours post-transfusion. These missing data made the diagnosis of TACO impossible in many patients and may contribute to the variation in the incidence rate. Second, the x-ray must be read by a radiologist as it can sometimes be difficult to differentiate pulmonary edema from another type of infiltrate and to adequately determine worsening of preexisting pulmonary edema.

This study has some limitations. The TACO definition was meant for patients who develop acute frank respiratory distress as part of obvious transfusion reaction; thereafter the criteria are applied to help differentiate TACO from TRALI or another transfusion reaction. Since we used the database of a previous prospective study, it is impossible to assume that all patients developed respiratory distress as part of transfusion reaction, even though deterioration was post-transfusion.

Diagnostic criteria could not always be fulfilled due to missing criteria. However, this reflects the clinical practice since some tests or vital signs are not routinely performed during the time surrounding RBC transfusion.

There was only one radiologist to diagnose pulmonary edema; expert opinion and clinical judgment was used without specific criteria. This could introduce bias and weaken the

results of this criterion. Furthermore, the interpretation of chest radiograph was conducted a posteriori by an independent radiologist. Although the radiologist was blind to the clinical criteria, it is possible that fluid overload was more frequently diagnosed because of the study context.

For positive fluid balance, we used the absolute value of ≥ 1 ml as threshold. This threshold is probably too sensitive but there is no clear published definition and no optimal threshold has been validated in the literature [24–27]. The results of this study will serve as preliminary data to prepare further validation studies.

Our study was not designed to validate a new list of diagnostic criteria; its principal aim was to compare different criteria or abnormal values for diagnosis of TACO and it is only generating hypothesis. Indeed, our results provide some hints on which values could be considered to diagnose TACO in critically ill children and to elaborate more operational diagnostic criteria.

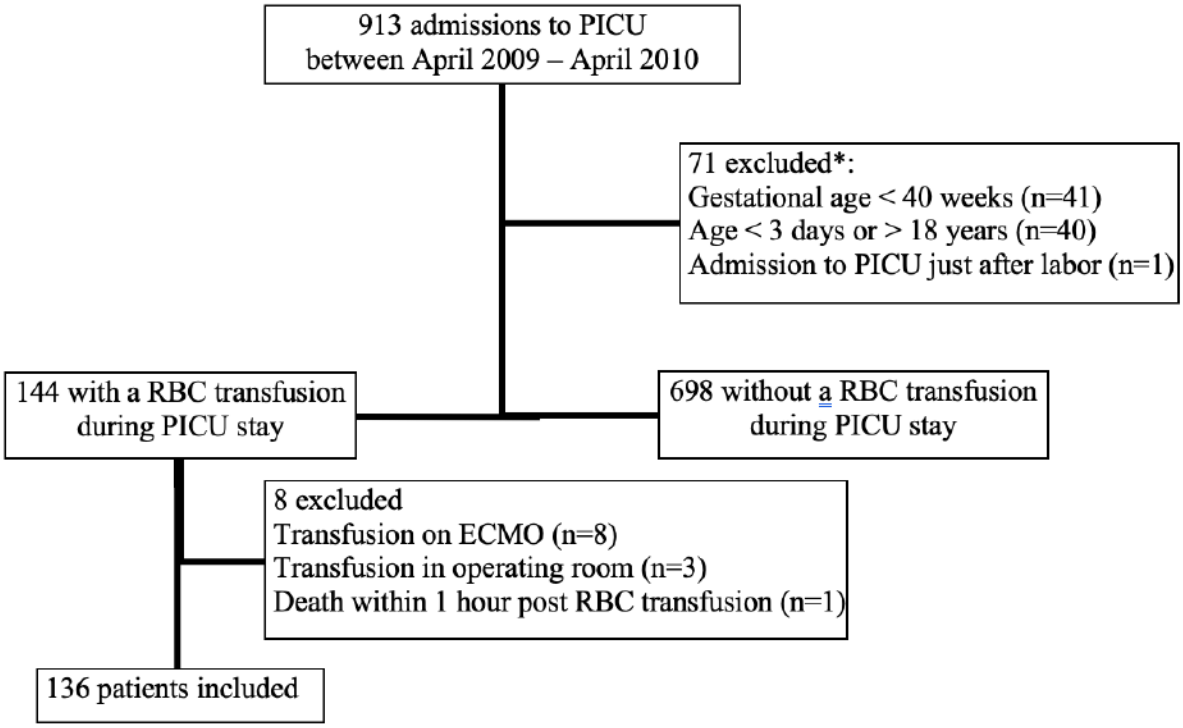
Finally, we do not have the data on other blood products and fluids that the patient received before their TACO was diagnosed; this could have been a useful guide as to when patients in the ICU become at risk of having a TACO. We also do not have data about TACO prevention strategies employed in any child (slow rate of transfusion, pre- or post-transfusion furosemide administered), as this would have been very helpful data.

Conclusion

The incidence of TACO in PICU differs widely depending on the diagnostic criteria used. The current definitions of TACO (SHOT, ISBT, NHSN) might not be adequate for PICU patients. Prospective multicenter studies are required to develop and validate a new list of diagnostic criteria for pediatric TACO, and to determine the real incidence and clinical impact of TACO in critically ill children.

Figures

Figure 1: Patients' flow chart.



PICU: pediatric intensive care unit; RBC: red blood cell; ECMO: extracorporeal membrane oxygenation.

*Some patients presented more than one exclusion criterion.

Figure 2: New cases of TACO per period.

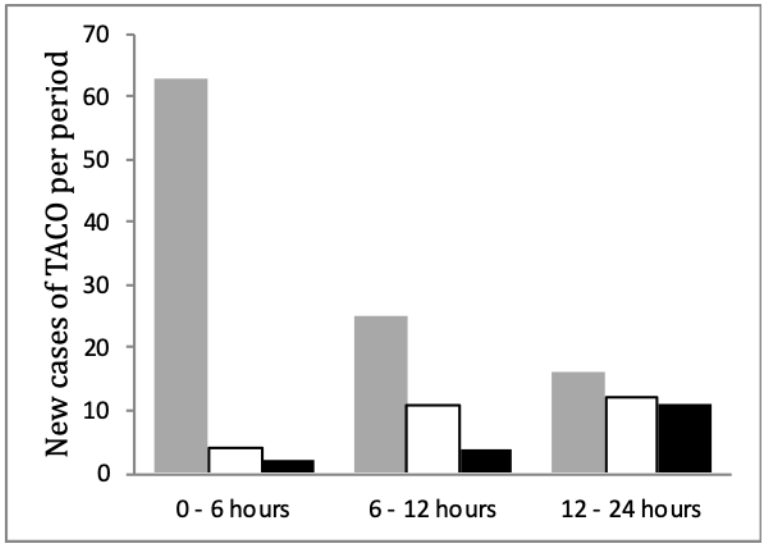


Figure 3 shows the new cases of transfusion-associated circulatory overload (TACO) diagnosed using the different criteria, during each period (at 6, 12 and 24 hours post-transfusion).

Grey boxes: using the “normal pediatric values" criteria.

White boxes: using the “10% threshold” criteria.

Black boxes: using the “20% threshold” criteria.

Tables

Table 1: Detailed parameters that we used to diagnose cases of TACO.

Criteria (TACO = 4/5 criteria)	**1) Normal pediatric values** (at least one positive value necessary to confirm criteria)	**2) Comparison of patient's values before and after transfusion, using a threshold of 10% or 20%** (at least one positive value necessary to confirm criteria)
Acute respiratory distress	Maximal respiratory rate according to age * $PaO_2/FiO_2 \leq 300$ or $SpO_2/FiO_2 \leq 315$	Values found in patient: Maximal FiO_2 Maximal respiratory rate Maximal PEEP † and PIP † Minimal PaO_2/FiO_2 or SpO_2/FiO_2
Tachycardia	Maximal heart rate according to age *	Maximal heart rate in patient
Increased blood pressure	Maximal systolic blood pressure according to age *	Maximal blood pressure in patient: Systolic and mean blood pressure Central venous pressure ‡
Edema on chest radiograph	Edema found on post-transfusion chest radiograph, according to radiologist	Edema found on post-transfusion chest radiograph and worsened compared to pre-transfusion chest radiograph, according to radiologist
Positive fluid balance	Positive fluid balance ($\geq$ 1 ml)	Patient's post-transfusion fluid balance – pre-transfusion fluid balance

* According to the Nelson Textbook of Pediatrics [10].

† If patient on mechanical ventilation.

‡ If central venous catheter in place.

TACO: transfusion-associated circulatory overload; PaO_2: arterial partial pressure of oxygen; FiO_2: inspired fraction of oxygen; SpO_2: oxygen saturation measured by pulse oximetry; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure.

Table 2: Demographic data.

All subjects	n = 136 *
Population	
Age (months)	12 (3-128)
Female	67 (49%)
Initial diagnosis of cardiac disease	48 (35%)
Post-cardiac surgery	35 (26%)
Description of first RBC transfusion	
Transfusion volume (mL/kg)	10.5 (7-15)
Duration of transfusion (min)	126 ± 61
Rapid transfusion (< 30 min)	7 (5%)
Slow transfusion (>180 min)	36 (26%)
Rate of transfusion (mL/kg/h)	5.4 (3.6-9.4)
Length of stay in PICU before transfusion (day)	1.3 ± 2.1
Any other blood product transfused †	69 (51%)
Total volume of all blood product transfused (mL/kg/patient) ‡	15 (10-27)

* Continuous data are presented as mean ± standard deviation or median (interquartile range); categorical data are presented as number (%).

† During the 24 hours following the first RBC transfusion.

‡ During the 24 hours following the first RBC transfusion and including this first transfusion.

PICU: pediatric intensive care unit; RBC: red blood cell.

Table 3: Number of patients with TACO at 6 hours post-transfusion according to different diagnostic criteria.

Total of transfused patients n = 136 *					
Diagnostic criteria for TACO	**Number of patients with positive criteria using normal pediatric values**		**Number of patients with positive criteria using comparison in patient's values (pre- and post-transfusion)**		
	Patients with positive criteria	**Patients with missing data**	**Patients with positive criteria (threshold set at 10%)**	**Patients with positive criteria (threshold set at 20%)**	**Patients with missing data**
Acute respiratory distress	**125 (92%)**	**0**	**78 (57%)**	**58 (43%)**	**0**
Tachycardia	**111 (82%)**	**0**	**19 (14%)**	**10 (7%)**	**2**
Increased blood pressure	**96 (71%)**	**0**	**66 (49%)**	**46 (34%)**	**3**
Edema on chest radiograph	**24 (18%)**	**86**	**7 (5%)**	**7 (5%)**	**86**
Positive fluid balance	**99 (73%)**	**0**	**70 (51%)**	**69 (51%)**	**15**
TACO (≥ 4/5 criteria)	**63 (46%)**	**0 †**	**4 (3%)**	**2 (1.5%)**	**11 †**

* Data are presented as number (%).

† Number of patients with ≥ 2 unavailable criteria which made the diagnosis of TACO impossible.

TACO: transfusion-associated circulatory overload.

Table 4: Number of patients with TACO at 12 hours post-transfusion according to different diagnostic criteria.

Total of transfused patients n = 136 *					
Diagnostic criteria for TACO	**Number of patients with positive criteria using normal pediatric values**		**Number of patients with positive criteria using comparison in patient's values (pre- and post-transfusion)**		
	Patients with positive criteria	**Patients with missing data**	**Patients with positive criteria (threshold set at 10%)**	**Patients with positive criteria (threshold set at 20%)**	**Patients with missing data**
Acute respiratory distress	**130 (96%)**	**0**	**104 (76%)**	**81 (60%)**	**0**
Tachycardia	**116 (85%)**	**0**	**33 (24%)**	**15 (11%)**	**2**
Increased blood pressure	**106 (78%)**	**0**	**87 (64%)**	**62 (46%)**	**3**
Edema on chest radiograph	**39 (29%)**	**57**	**14 (10%)**	**14 (10%)**	**57**
Positive fluid balance	**117 (86%)**	**0**	**78 (57%)**	**77 (57%)**	**15**
TACO (≥ 4/5 criteria)	**88 (65%)**	**0 †**	**15 (11%)**	**6 (4%)**	**8 †**

* Data are presented as number (%).

† Number of patients with ≥ 2 unavailable criteria which made the diagnosis of TACO impossible.

TACO: transfusion-associated circulatory overload.

Table 5: Number of patients with TACO at 24 hours post-transfusion according to different diagnostic criteria.

Total of transfused patients n = 136 *					
Diagnostic criteria for TACO	**Number of patients with positive criteria using normal pediatric values**		**Number of patients with positive criteria using comparison in patient's values (pre- and post-transfusion)**		
	Patients with positive criteria	**Patients with missing data**	**Patients with positive criteria (threshold set at 10%)**	**Patients with positive criteria (threshold set at 20%)**	**Patients with missing data**
Acute respiratory distress	**130 (96%)**	**0**	**112 (82%)**	**97 (71%)**	**0**
Tachycardia	**119 (88%)**	**0**	**37 (27%)**	**21 (15%)**	**2**
Increased blood pressure	**115 (85%)**	**0**	**102 (75%)**	**83 (61%)**	**3**
Edema on chest radiograph	**57 (42%)**	**15**	**27 (20%)**	**27 (20%)**	**15**
Positive fluid balance	**123 (90%)**	**0**	**87 (64%)**	**85 (62%)**	**15**
TACO (≥ 4/5 criteria)	**104 (76%)**	**0 †**	**27 (20%)**	**17 (12%)**	**6 †**

* Data are presented as number (%).

† Number of patients with ≥ 2 unavailable criteria which made the diagnosis of TACO impossible.

TACO: transfusion-associated circulatory overload.

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3. Étude 2 : Qu'en est-il du TACO aux soins intensifs?

« Transfusion-associated circulatory overload (TACO) in intensive care units: a scoping review of incidence, risk factors, and outcomes. »

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Abstract

Transfusion-associated circulatory overload (TACO) is the most frequent serious adverse transfusion reaction, with an incidence close to 1% of transfused patients in the general adult population. Patients in intensive care units (ICUs) are probably more at risk of TACO as they are more frequently transfused and associated with more comorbidities. However the epidemiology of TACO in ICU is not well characterized, leading to a risk of underdiagnosis.

Objectives

We conducted a scoping review to describe the incidence, risk factors and outcomes of TACO in pediatric and adult ICUs.

Data Sources

PubMed, Ovid Medline, Ovid All EBM Reviews, Ovid Embase, and EBSCO CINAHL COMPLETE.

Study Selection

Two reviewers independently screened each article for inclusion criteria. Studies were eligible if they reported data on incidence, risk factors, or outcomes of TACO in at least 10 ICU patients.

Data Synthesis

Among 5926 studies identified, nine were included. Five studies were prospective, and four were retrospective. The definition of TACO varied among studies.

The pooled incidence of TACO was of 5.5% (95% CI: 2.6%, 9.4%) in adult ICUs (4 studies, 2252 patients, high heterogeneity). In pediatric ICUs, 2 studies (345 patients) reported 0 cases, and a third study (136 patients) reported variable incidences between 1.5 and 76%, depending on diagnostic criteria.

Risk factors for TACO included positive fluid balance, the number and type of products transfused, rate of transfusion, cardiovascular and renal comorbidities.

TACO was associated with increased ICU and hospital lengths of stay, while the association with mortality was not consistent.

Conclusions

TACO is frequent in ICU patients and is associated with adverse outcomes. The lack of a pediatric-adjusted definition of TACO may lead to a risk of under-diagnosis of this condition in pediatric ICUs. Further research is warranted to improve the knowledge of TACO and the safety of transfusion in ICU patients.

Introduction

Transfusion-associated circulatory overload (TACO) is an important adverse transfusion reaction. It is defined as acute respiratory distress associated with signs of fluid overload, including tachycardia, hypertension, pulmonary edema, positive fluid balance, or elevated levels of brain natriuretic peptides (1). According to the Food and Drug Administration, it was reported in 2012 to be the second cause of death attributable to transfusion (2). In the general population, TACO has an incidence close to 1% of transfused patients (3–5). It is associated with increased mortality, a longer duration of post-operative mechanical ventilation, and a longer length of stay in hospital (6, 7). Risk factors associated with TACO include a positive fluid balance, the number of blood products transfused, transfusion of plasma, pre-existing cardiac or renal dysfunction and older age (6, 8–10).

The risk of TACO seems greater in patients in intensive care units (ICUs). Transfusion is very common during critical illness, with 25-45% of patients being transfused during their ICU stay (11–13). Additionally, ICU patients frequently have at-risk comorbidities, in particular a high prevalence of fluid overload, cardiac failure, and systemic inflammation. Nevertheless, TACO still seems to be an under-diagnosed complication from transfusion in ICUs (4, 14–16). This is probably due to the condition not being recognized, but also to diagnostic criteria which are not adapted to critically ill patients, and to the severity and clinical impact of this complication being underestimated.

We conducted a scoping review in order to highlight the importance of this complication in ICU patients. The primary objective was to describe the incidence, risk factors

and outcomes of TACO in pediatric and adult ICUs. The secondary objective was to identify knowledge gaps and potential future research directions.

Material and methods

Search Strategy

The search strategy was established by two intensivists (GE, LDC) in collaboration with a scientific librarian. Systematic searches of the databases PubMed, Ovid Medline, Ovid All EBM Reviews, Ovid Embase and EBSCO CINAHL COMPLETE were performed by a librarian of Centre Hospitalier Universitaire Sainte-Justine with special training and skills in medical literature searches in May 2018.

In 2018, all that was indexed in the MeSH and subheading 'Blood Transfusion/adverse effects' was re-indexed with the heading 'Transfusion Reaction'. Both terms were taken into account to avoid any bias in the methodology of the research

Study Inclusion and Exclusion Criteria

Studies were eligible if they reported data at least on incidence, risk factors, or outcomes of ICU patients with TACO. Both adult and pediatric ICU studies were eligible. The definition used for TACO was up to the discretion of the authors, with no specific inclusion criteria, although this information was collected. As TACO has not always been a common acronym, studies reporting cases of cardiogenic (non-inflammatory) pulmonary edema were included as TACO. Studies looking at any adverse transfusion reactions were reviewed, and eligible if TACO specific incidences were clearly identified. Similarly, studies conducted in a general population could be included if some data were provided for ICU patients. We did not restrict the study selection to the type of blood product (transfusion of red blood cells, plasma and/or platelets were eligible).

We included all published observational, interventional, retrospective and prospective studies (17). We excluded abstracts and posters as the information provided was insufficient to assess the incidence of TACO and also to rule out any risk of overlap with a published study. We also excluded studies including fewer than 10 transfused patients.

In case of doubt about the ICU subgroup or the incidence calculation, we contacted the authors of the study to obtain the original information.

Systematic and narrative reviews were not included in the scoping review, but were evaluated to look for other eligible references. Only articles in English or French were included.

Study Selection and Data Extraction

Two reviewers (LDC, NS) independently screened each title and abstract of the search results to determine whether the article should be fully read, based on pre-specified criteria. If there was insufficient information to warrant inclusion or exclusion, reviewers included the article for further analysis.

The full manuscripts of the remaining studies were fully read independently by the two reviewers, and inclusion/exclusion criteria were noted. Discrepancies regarding study eligibility were resolved by consensus, and with a third reviewer if needed (GE).

Data was then extracted from included articles using a standardized report form. Quality assessment of individual studies was not done, according to the methodological framework for scoping reviews provided by Arksey (17).

Statistical Analysis

The characteristics of the studies retained for the scoping review, including time and place where the study was conducted, study design, population assessed, type(s) of blood products evaluated, as well as the definition and strategy used to diagnose TACO was taken into account.

Incidence of TACO was reported as the percentage of cases in transfused ICU patients. A pooled incidence was calculated separately in pediatric and adult studies, and reported with a 95% confidence interval (CI), using random effects modeling. Heterogeneity in the study data was assessed with I^2 statistics. The analysis was conducted with MedCalc (MedCalc, Ostend, Belgium). Identified risk factors and outcome data were reported using descriptive statistics.

Results

Results of the Search

The initial literature extraction identified 5926 potentially eligible articles (Figure 1). Of those, 5892 were eliminated based on the review of the title and abstract. Thirty-four full manuscripts were read. The authors from seven articles with missing data were contacted; this permitted us to keep one additional study in the analysis (18). Of the 34 full texts read, 26 were excluded because of exclusion criteria or insufficient information, as detailed in Figure 1. One article that was not found in the initial literature search was identified from the references of another manuscript. Finally, nine studies met the inclusion criteria and were included in the scoping review (14, 18–25).

Study Characteristics

As detailed in Table 1, included studies were published between 1999 and 2018. Most studies were conducted in North America, one in The Netherlands. Six were conducted in adult ICUs, and three in pediatric ICUs. Five studies were prospective, four were retrospective including one retrospective study with prospective screening for TACO (20). Eight studies considered transfusion of any blood products, while one study considered only red blood cell transfusions.

Hébert *et al*. (19) conducted a randomized controlled study to compare the safety of two different transfusion thresholds; we only kept the liberal arm of transfused patients so we could determine an accurate incidence of TACO.

Many sets of criteria were used to diagnose TACO, as detailed in the Appendix. Two studies used the definition of the International Society of Blood Transfusion definition (1) or of the Centers for Disease Control definition (26) while the others used locally developed definitions.

Two studies screened for cases of TACO with an electronic surveillance system (20, 24); the other ones reviewed the clinical and paraclinical data collected in the medical files.

Incidence of TACO in ICU

Seven studies reported the incidence of TACO in ICUs (Table 1 and Figure 2) (14, 18–20, 22, 23, 25).

In adult ICUs, four studies including respectively 420, 901, 1351 and 1140 transfused patients reported 45, 51, 25 and 66 cases of TACO. The pooled incidence was 5.5% (95% CI: 2.6%,9.4%), with a significant heterogeneity (I^2 = 95.2%).

In pediatric ICUs, two studies that enrolled 40 and 305 transfused patients reported no cases of TACO (18, 23). A third pediatric study of 136 transfused patients reported between 2 and 104 cases of TACO according to the diagnostic criteria used (14). The pooled incidence was 0.56 % (95% CI: 0.0%,2.24 %), when retaining only two cases of TACO in the latter study, with non-significant heterogeneity (I^2: = 53.6 %). When we estimated the pooled incidence using the more liberal diagnostic strategy in De Cloedt *et al.* (104 cases of TACO) (14), heterogeneity was very high (I^2: 99.5%) and the pooled incidence was 14.4% (95% CI: 11.2%,82.2%).

To explore the variability in the incidence of pediatric TACO, we analyzed the methods for collecting data and the patient characteristics. The three pediatric studies diagnosed TACO using clinical and paraclinical data collected by bedside nurses (heart rate, blood pressure, respiratory rate, oxygen saturation, fluid balance). In the study of Gauvin *et al.*

(18), nurses prospectively collected data for every patient transfused up to four hours post-transfusion; transfusion reactions were reviewed by experts only if reported by the nurses. In the study by De Cloedt *et al*. (14), nurses prospectively collected data for every patient transfused but up to 24 hours post-transfusion, and the authors reviewed each case even if it was not reported as an adverse event. Agrawal *et al*. (23) conducted a retrospective chart review to compare slow and liberal transfusion groups in stable patients only (no acute blood loss or hemolysis).

Risk Factors for TACO in ICU

As detailed in Table 2, four studies (20, 22, 24, 25) described risk factors of TACO in ICU patients, including two prospective and two retrospective studies. None were in pediatric ICUs.

The reported risk factors reflect both the patients' poor tolerance to fluid administration and the characteristics of transfusion. Regarding patient tolerance to fluid, positive fluid balance was a risk factor in the four studies, and pre-existing cardiac or renal comorbidity was associated with TACO in three studies.

Regarding transfusion characteristics, the number, volume, and rate of transfusions were associated with TACO. Hemorrhagic shock was also found to be a risk associated with TACO. Two studies analyzed the type of blood products transfused (red blood cells, plasma, and platelets). Plasma (2 studies) and platelets (1 study) transfusions were associated with TACO.

Outcomes of TACO in ICU

As detailed in Table 3, four studies (20, 21, 24, 25) reported outcomes of TACO in adult ICUs. TACO was associated with an increased length of stay in ICUs and in hospital. One study reported that the impact on mortality was significant in TACO while two other studies reported no significant difference in mortality.

Discussion

There are more and more studies about TACO but very few studies address the problem of TACO in ICU.

In the literature, the incidence of TACO in the general population is close to 1% (3–5). In our studies, we found a pooled incidence of 5.5% in critically ill adults. This suggests that ICU patients be more at risk to developing TACO than the general population. This is probably due to the fact that ICU patients have more pre-existing comorbidities that increase the risk of TACO. Moreover, as ICU patients are often unstable, they are probably transfused more rapidly. However, it is possible that this increased frequency of TACO is attributable to a closer monitoring of ICU patients' complications post-transfusion (ascertainment bias). The studies included had significant heterogeneity and all of them reported a higher incidence of TACO in ICU patients compared to the 1% observed in the general population. The study by Hébert *et al*. (19) reported the highest incidence (10.7%). This could be partly explained by the fact that these patients were treated using the liberal transfusion strategy (every patient was transfused if the hemoglobin level fell under 9 g/dL). Moreover, as the study was a randomized controlled trial, patients were probably very closely monitored for any adverse reactions.

Contrastingly, two pediatric studies reported no cases of TACO (incidence of 0%). This absence of pediatric TACO cases could be explained by the fact that the definition is not adapted to pediatric patients (14) which makes the diagnosis much more difficult. This is supported by the study by De Cloedt *et al*. (14), which reported major differences in incidence rates (from 1.5% to 76%) depending on the diagnostic criteria used. This retrospective study confirms that TACO exists in pediatric ICUs and seems quite frequent, in stark contrast to what we found in the other studies. Moreover, the two pediatric studies reporting no cases of TACO included relatively few patients as compared to the adult studies (40 and 305 respectively) and did not use an electronic surveillance system; TACO cases could thus have been missed by bedside nurses or attending physicians. Furthermore, Agrawal *et al*. (23) included only stable patients with no acute blood loss; no patient presented with

cardiopulmonary dysfunction before transfusion and nearly half of them received diuretics close to the transfusion. This excludes an important part of at-risk population.

All studies included in this review detailed the TACO definition they used and we observed many variations. Only two of them (14, 24) used published definitions by the Centers for Disease Control and the International Society of Blood transfusion. The seven others used diagnostic criteria of TACO like circulatory overload and cardiac congestion. Such variation in TACO definitions is a limit of our study, but it can explain part of the spectrum of reported TACO incidences and TACO-related outcomes. A universally accepted definition of TACO in ICU patients is required to standardize future studies.

The ISBT definition (27) that is in the process of development seems to be the most adequate as it includes clinical, paraclinical parameters, and also biomarkers such as brain natriuretic peptide. More studies are required to validate this definition in pediatrics, in particular as no one has looked into brain natriuretic peptide in pediatric TACO. Nevertheless, operational criteria should be specified, in particular with specific thresholds to define clinical variables like tachycardia, hypertension, or positive fluid balance. As suggested by De Cloedt *et al* (14), the use of pre- and post-transfusion changes in the parameters instead of absolute values may improve the discrimination performance of the definition.

TACO and TRALI (transfusion-related acute lung injury) are both clinical syndromes that share several characteristics: acute respiratory distress following a transfusion and pulmonary edema. They, however, differ in other aspects. Fluid overload is one corner stone for TACO diagnosis, while it is an exclusion criterion for TRALI, in which the lung edema is inflammatory. Cardiovascular changes are part of TACO criteria but not of TRALI. The studies included in this review all distinguished TACO from TRALI. However, there is a potential overlap between both conditions, and we cannot exclude that some reported TACO were misdiagnosed. The development of a future definition for TACO should also take this aspect into account, and facilitate the distinction between both entities.

Only two studies used an electronic surveillance system to detect TACO. As ICU patients are extensively monitored, computerized screening based on electronic medical

records may help to detect cases more rapidly and efficiently. Further studies should explore this potential avenue for the identification of TACO in ICUs.

We found four studies describing the risk factors of TACO in ICU with relatively consistent results. Factors that are mostly associated with TACO were positive fluid balance, characteristics of the transfusion linked with fluid overload (volume and speed of transfusion), and comorbidities (cardiovascular and renal). As TACO is defined as pulmonary edema due to circulatory overload, the importance of pre-existing positive fluid balance and cardiovascular dysfunction is not surprising. Thus, it is reasonable to pay particular attention to the development of respiratory distress when transfusing patients with these conditions. The volumes transfused and the transfusion rates are also reported as risk factors of TACO. We may therefore speculate that ICU patients should be transfused less frequently and as slow as possible. It has been well established that lower transfusion thresholds in ICUs are safe in both adult and pediatric ICUs (28–31). Decreasing the amount of blood transfusions should be a priority and will limit the population at risk of transfusion-related complications, including TACO.

Furthermore, the type of blood product transfused is detailed in only two studies (20, 22). Transfusion of plasma is reported to be a risk factor for TACO in both studies. The existing data do not permit to ascertain if this association is related to specific properties of the plasma, or rather explained by a confounding association (e.g. the plasma being transfused in conditions at higher risk of TACO). In addition, transfusion of plasma may be different in terms of volume and rate (in addition to different indications). Future studies should further explore the respective importance of the different blood product characteristics regarding their association with TACO.

There are no studies reporting risk factors for TACO in pediatric ICUs. The risk factors reported in adults are also often present in pediatric ICU patients. We may speculate that in their presence, critically ill children might be at higher risk for TACO. However, pediatric and adult ICU patients have important pathophysiological differences. Further research is warranted to explore specific pediatric risk factors of TACO.

We observed that TACO was associated with adverse outcomes. Importantly, those outcomes are difficult to interpret, as ICU patients are already critically ill, and performing transfusions is correlated with the severity of the patient's underlying condition. The included studies reported associations but no causalities. However, the four studies describing outcomes of TACO reported consistently an increased length of ICU stay, and two reported an increased length of stay in hospital. Concerning mortality, results were not consistent, with one study reporting a significant increase in mortality rate (24) and two others reported no significant difference (21, 25).

Even if these are only associations, it remains that all studies included in this scoping review reported less favorable outcomes in patients with TACO, which justifies improving not only the prevention, but also the diagnosis and management of TACO.

Conclusion

We found only few studies describing incidence, risk factors and outcomes of TACO in ICU patients even if this population seems to be at higher risk. The pooled incidence of TACO in adult ICUs was particularly high, compared to the general population. TACO is associated with adverse outcomes. The identification of TACO in pediatric ICUs appears suboptimal.

We need more studies concerning TACO in ICU patients, more so in pediatric ICU patients. A more operational definition of TACO adapted to pediatric patients is crucially needed.

Acknowledgments

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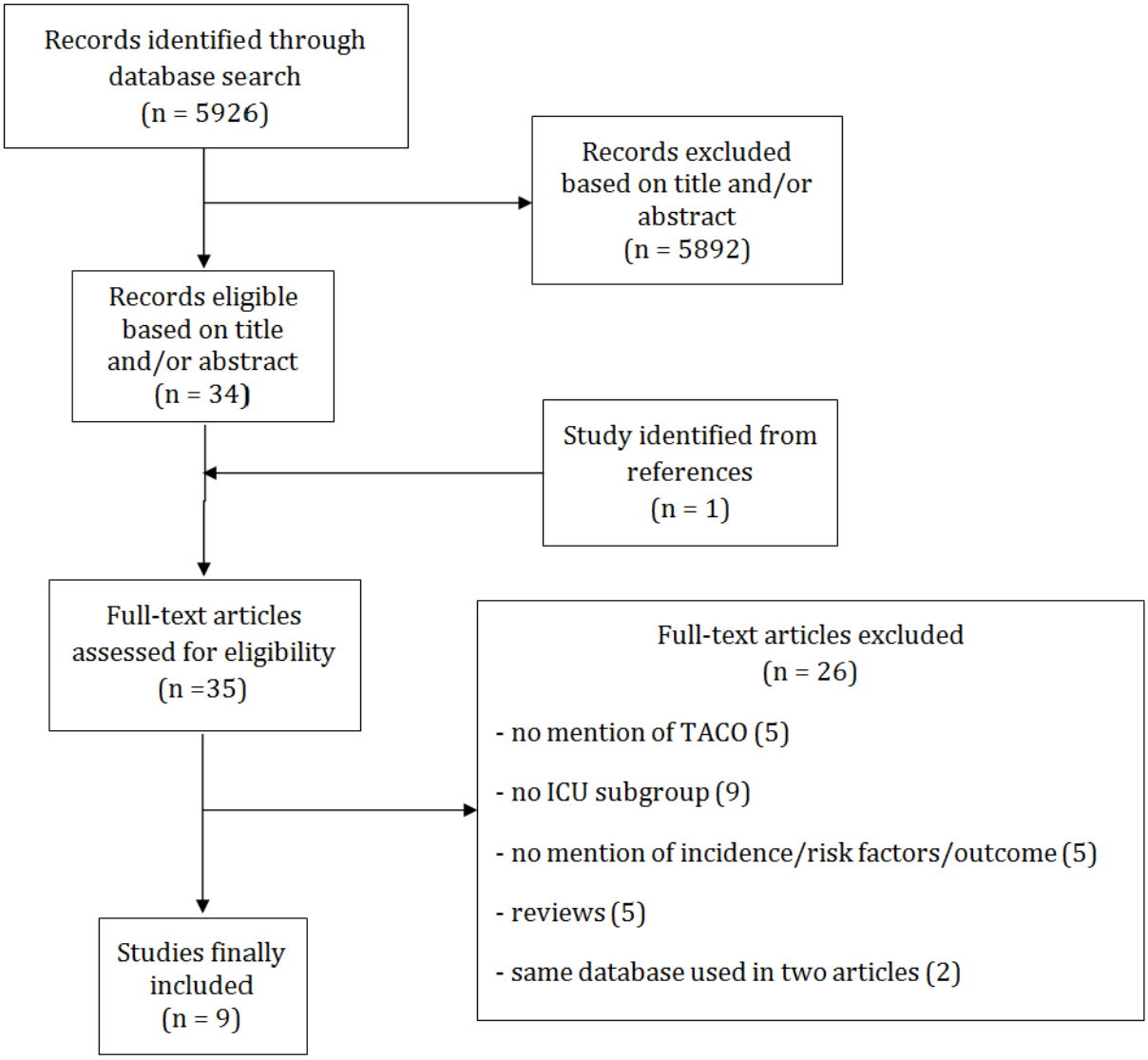
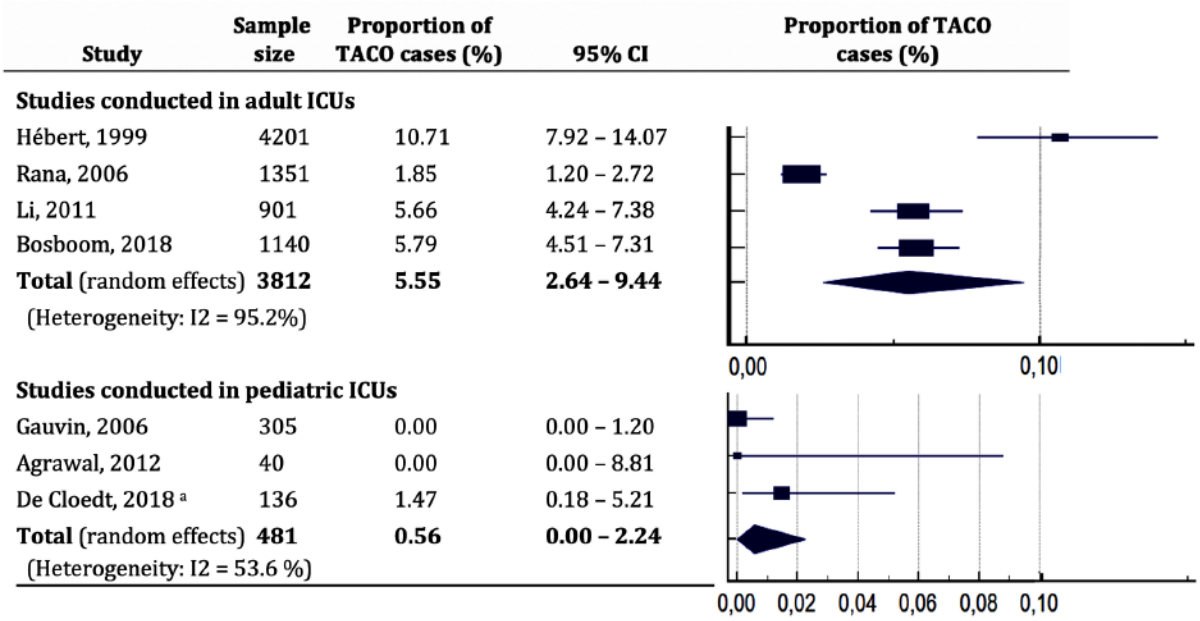
Figures

Figure 1: Study selection



TACO: transfusion-associated circulatory overload; ICU: intensive care unit.

Figure 2: Estimates of incidence of transfusion-associated circulatory overload in adult and pediatric intensive care units



[a] the conservative definition was used

TACO: transfusion-associated circulatory overload; CI: confidence interval; ICU: intensive care unit.

Tables

Table 1: Characteristics of included studies

Study	Design	Population	Country	Blood product transfused	Number of ICU patients transfused (Cases of TACO); Incidence
Hébert, 1999	Randomized controlled trial – liberal arm	Adult	Canada	All blood products	420 (45 TACO); 10.7%
Gauvin, 2006	Prospective, observational	Pediatric	Canada	All blood products	305 (0 TACO); 0%
Li, 2010	Prospective, observational	Adult	United States of America	All blood products	N/A (51 TACO)
Li, 2011	Prospective, observational	Adult	United States of America	All blood products	901 (51 TACO); 6%
Agrawal, 2012	Retrospective, observational	Pediatric	United States of America	Red blood cells	40 (0 TACO); 0%
Murphy, 2013	Prospective, observational	Adult	United States of America	All blood products	N/A (22 TACO)

Bosboom, 2018	Retrospective, observational	Adult	The Netherlands	All blood products	1140 (66 TACO); 5.8%
De Cloedt, 2018	Retrospective, observational	Pediatric	Canada	All blood products	136 (2 to 104 TACO (1.5-76%), depending on the diagnostic criteria used)

TACO: transfusion-associated circulatory overload; ICU: intensive care unit; N/A: not available.

Table 2: Risk factors of transfusion-associated circulatory overload in intensive care units.

Risk factor	Reference	Risk
Positive fluid balance	- Rana, 2006	- 5.9 L versus 2.0 L ($p < 0.01$) [a,b]
	- Li, 2011	- OR 1.38 (1.12-1.71) [a]
	- Murphy, 2013	- adjusted OR 9.4 (3.1-28.0) [c]
	- Bosboom, 2018	- adjusted OR 1.15 (1.07-1.24) [c]
Transfusion		
- Number of transfused products	- Rana, 2006	- 6 units versus 2 units ($p < 0.01$) [a,b]
	- Li, 2011	- OR 1.45 (1.12-1.88) [a]
	- Murphy, 2013	- adjusted OR 1.10 (1.01-1.22) [c]
- Transfusion rate	- Li, 2011	- OR 1.88 (1.06-3.33) [a]
- Transfusion of plasma	- Li, 2011	- OR 1.39 (1.07-1.80) [a]
	- Rana, 2006	- 40% versus 14% ($p < 0.01$) [a,b]
- Plasma transfused for anticoagulation reversal	- Li, 2011	- adjusted OR 4.31 (1.45-14.30) [c]
- Volume of plasma transfused	- Li, 2011	- OR 4.88 (1.55-15.36) [c]
	- Rana, 2006	- (female) 0.17 L versus 0.04 L ($p < 0.01$) [a,b]
		- (male) 0.33 L versus 0.07 L ($p < 0.01$) [a,b]
- Transfusion of platelets	- Rana, 2006	- 32% versus 7% ($p < 0.01$) [a,b]
Cardiovascular comorbidities		
- History of heart failure	- Murphy, 2013	- adjusted OR 6.6 (2.0-21.0) [c]
	- Bosboom, 2018	- adjusted OR 2.4 (1.2-4.6) [c]
- Pre-existing left ventricular dysfunction	- Li, 2011	- adjusted OR 8.23 (3.36-21.97) [c]
- Cardiology referral	- Bosboom, 2018	- adjusted OR 13.6 (5.1-35.7) [c]
- Cardiothoracic surgery referral	- Bosboom, 2018	- adjusted OR 8.8 (3.7-20.7) [c]

Renal comorbidities - Chronic renal failure - Continuous veno-venous hemofiltration before transfusion	 - Murphy, 2013 - Li, 2011 - Bosboom, 2018	 - adjusted OR 27 (5.2-143.0) [c] - OR 2.87 (0.89-11.08) [a] - adjusted OR 3.2 (1.2-8.9) [c]
Hemorrhagic shock	- Murphy, 2013	- adjusted OR 113 (14-903) [c]
Age	- Murphy, 2013 - Li, 2011	- adjusted OR 0.78 (0.62-0.99) [c] - OR 0.99 (0.96-1.02) [a]

TACO: transfusion-associated circulatory overload; ICU: intensive care unit; OR: odds ratio (95% confidence interval)

[a] Univariate analysis

[b] TACO versus controls

[c] Multivariate analysis

Table 3: Association between transfusion-associated circulatory overload and outcomes

Outcome	Reference	Risk
Increased ICU length of stay	- Rana, 2006	- 7.1 days versus 1.6 days ($p < 0.05$) [a,b]
	- Li, 2010	- 3.0 days versus 1.7 days ($p < 0.05$) [a,b]
	- Murphy, 2013	- HR for discharge 0.37 (0.26-0.53) [c]
	- Bosboom, 2018	- 7.2 days versus 4.3 days ($p < 0.01$) [a,b]
Increased ventilation time	- Bosboom, 2018	- 118 hours versus 61.5 hours ($p < 0.01$) [a,b]
Increased hospital length of stay	- Li, 2010	- 9.4 days versus 6.1 days ($p < 0.05$) [a,b]
	- Murphy, 2013	- HR for discharge 0.64 (0.48-0.86) [c]
	- Bosboom, 2018	- 15.9 days versus 14 days (p = n.s.) [a,b]
Mortality		
- In hospital mortality	- Li, 2010	- 7.8% versus 11.8% ($p = 0.73$) [a,b]
	- Murphy, 2013	- HR 3.20 (1.23-8.10) [c]
- Mortality at 28 days	- Bosboom, 2018	- 22.7% versus 18.8% (p = n.s.) [a,b]
- Mortality at 90 days	- Bosboom, 2018	- 27.3% versus 24.4% (p = n.s.) [a,b]
- 1 year mortality	- Li, 2010	- 38% versus 28% ($p = 0.37$) [a,b]
- 2 years mortality	- Li, 2010	- 44.9% versus 38.8% ($p = 0.51$) [a,b]

TACO: transfusion-associated circulatory overload; ICU: intensive care unit; HR: Hazard ratio (95% confidence interval); n.s.: not significant.

[a] Univariate analysis

[b] TACO versus controls

[c] Multivariate survival analysis

Annexes

Annexe 1: TACO definition used in included studies

Study	TACO definition used
Hébert, 1999	"Acute pulmonary edema"
Gauvin, 2006	"Respiratory distress due to circulatory overload causing congestive heart failure and acute pulmonary edema."
Rana, 2006	"Hypoxemia with a PaO_2/FiO_2 ratio of not greater than 300 mmHg or SpO2 less than 90 percent on room air, bilateral infiltrates on chest radiograph in the presence of clinically evident left atrial hypertension. No existing pulmonary edema before transfusion. During or within 6 hours of transfusion."
Li, 2010	"A combination of clinical signs, radiographic, electrocardiographic, laboratory, hemodynamic, and echocardiographic findings, and the prompt response to appropriate therapy—diuretic or vasodilator use, treatment of ischemia, and/or inotropic agents"
Li, 2011	Same as Li, 2010.
Agrawal, 2012	"Increasing tachycardia, tachypnea, hypoxia leading to ventilator support, worsening hypertension and positive fluid balance leading to diuretic usage."
Murphy, 2013	Center for Disease Control Biovigilance System definition (26)

Bosboom, 2018	"Acute decline in lung function measured as a drop in the PaO_2/FiO_2 ratio below 300 within 6 hours after transfusion in combination with a clinical diagnosis of circulatory overload (…)."
De Cloedt, 2018	International Society of Blood Transfusion definition (1)

TACO: transfusion-associated circulatory overload; PaO_2/FiO_2 ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Annexe 2: Search strategies for the systematic review

PubMed

1	TACO	Transfusion Reaction[MH] OR transfusion reaction*[TIAB] OR transfusion associated circulatory overload[TIAB] OR TACO[TIAB] OR transfusion reaction*[OT] OR transfusion associated circulatory overload[OT] OR TACO[OT]
2	Intensive care	Critical Care[MH] OR Critical Care Nursing[MH] OR Critical Care Outcomes[MH] OR Emergencies[MH] OR Evidence-Based Emergency Medicine[MH] OR Emergency Medicine[MH] OR Emergency Medical Services[MH] OR Emergency Nursing[MH] OR Emergency Treatment[MH] OR Intensive Care Units[MH] OR acute*[TIAB] OR critical*[TIAB] OR emergenc*[TIAB] OR intensive*[TIAB] OR ICU*[TIAB] OR NICU*[TIAB] OR PICU[TIAB] OR acute*[OT] OR critical*[OT] OR emergenc*[OT] OR intensive*[OT] OR ICU*[OT] OR NICU*[OT] OR PICU[OT]
3	Combination	(#1 AND #2) 753 results on November the 13th, 2017. 2765 results on May the 16th, 2018.

Medline (OVID) 2.3 All EBM Reviews

1	TACO	exp Transfusion Reaction/ OR (transfusion reaction* OR transfusion associated circulatory overload OR TACO).ti,ab,kf,kw
2	Intensive care	(acute* OR critical* OR emergenc* OR intensive* OR ICU* OR NICU* OR PICU).ti,ab,kf,kw,hw
3	Combinaison	(1 AND 2) Medline (OVID): 846 results on November the 13th, 2017. Medline (OVID): 2986 results on May the 16th, 2018. All EBM Reviews: 53 results on November the 13th, 2017. All EBM Reviews: 73 results on May the 16th, 2018.

Embase

1	TACO	exp blood transfusion reaction/ OR (transfusion reaction* OR transfusion associated circulatory overload OR TACO).ti,ab,kw
2	Intensive care	(acute* OR critical* OR emergenc* OR intensive* OR ICU* OR NICU* OR PICU).ti,ab,kw,hw
3	Combinaison	(1 AND 2) 3828 results on November the 13th, 2017. 3903 results on May the 16th, 2018.

CINAHL COMPLETE

1	TACO	Blood Transfusion Reaction/ OR TI(transfusion reaction* OR transfusion associated circulatory overload OR TACO) OR AB(transfusion reaction* OR transfusion associated circulatory overload OR TACO)
2	Intensive care	MV(acute* OR critical* OR emergenc* OR intensive* OR ICU* OR NICU* OR PICU) OR TI(acute* OR critical* OR emergenc* OR intensive* OR ICU* OR NICU* OR PICU) OR AB(acute* OR critical* OR emergenc* OR intensive* OR ICU* OR NICU* OR PICU)
4	Combinaison	S1 AND S2 201 results on November the 13th, 2017. 236 results on May the 16th, 2018.

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4. Discussion

4.1. Résumé des principaux résultats des deux études

La première étude nous démontre une très grande variabilité dans les taux d'incidence du TACO au sein de notre population de 136 patients de soins intensifs pédiatriques en fonction de la façon d'interpréter les critères diagnostiques de la définition adulte. Il est à noter que notre population comporte 35% de patients atteints de pathologies cardiaques (admis pour cause médicale ou en post-opératoire). La dysfonction cardiaque plus fréquente chez ces patients pourrait nous avoir fait surestimer l'incidence de TACO. Cette particularité de notre population impacte la validité externe de notre première étude.

En utilisant les limites supérieures des valeurs de référence pédiatriques, nous avons diagnostiqué 63, 88 et 104 patients présentant un TACO dans les, respectivement, 6, 12 et 24 heures suivant la transfusion.

En utilisant les variables pré-transfusionnelles comme valeurs de référence et en appliquant un seuil minimal de 10% d'augmentation, nous avons diagnostiqué respectivement 4, 15 et 27 TACO dans les mêmes intervalles de temps.

Enfin, en appliquant un seuil minimal de 20% d'augmentation, nous avons 2, 6 et 17 TACO en respectant les mêmes intervalles de temps. Tous groupes confondus, le taux d'incidence varie de 1,5% à 76%.

La deuxième étude nous montre le peu d'articles publiés sur le TACO aux soins intensifs. En effet, sur les 5926 références identifiées, seules neuf répondent à nos critères d'inclusion. L'incidence cumulée du TACO est de 5,5% dans la population adulte (quatre études). En pédiatrie, deux études ne rapportent aucun cas de TACO, tandis qu'une troisième, la nôtre, rapporte une incidence très variable.

Quatre articles ont étudié les facteurs de risque du TACO, uniquement chez l'adulte. Les résultats de ces quatre études sont similaires avec comme principaux facteurs de risque la balance liquidienne positive préexistante, la quantité et le type de produit sanguin transfusé, le débit de transfusion, ainsi que la présence de comorbidité cardiovasculaire ou rénale.

Quatre articles également rapportent les conséquences du TACO dans la population de soins intensifs adultes. Les résultats montrent une association avec une augmentation de la durée de séjour aux soins intensifs mais également à l'hôpital. L'association avec une augmentation de la mortalité n'est pas consistante dans les différentes études.

4.2. Quelle définition pédiatrique du TACO?

Les résultats de notre première étude nous montrent une grande disparité de l'incidence du TACO aux soins intensifs pédiatriques selon l'interprétation des critères diagnostiques de la définition adulte. Ceci permet donc d'affirmer que nous ne pouvons pas appliquer cette définition à la population pédiatrique sans y apporter de modifications. S'agit-il seulement de préciser chacun des critères existants ou faut-il aussi en ajouter de nouveaux?

Les différents éléments pris en compte dans la définition de l'ISBT ne sont pas détaillés. Dès lors, une possibilité pour rendre la définition plus opérationnelle serait de préciser les critères existants.

Les critères cliniques de fréquence cardiaque et de tension artérielle ont l'avantage d'être facilement disponibles car ils font partie de la surveillance habituelle d'un patient lors d'une transfusion. Toutefois, quelles sont les limites de fréquence cardiaque et de tension artérielle à considérer pour pouvoir parler de tachycardie et d'hypertension? Un des signes cliniques de l'anémie est la tachycardie. C'est pourquoi une proportion importante de patients transfusés sont déjà tachycardes avant de recevoir le culot globulaire. Nous proposons donc une autre manière de procéder en utilisant les paramètres du patient lui-même comme valeur de référence. Nous pensons qu'il est préférable de comparer les paramètres du patient après la

transfusion à ceux qu'il présentait dans les six heures précédant celle-ci. Tenir compte ainsi des particularités du patient au moment de la transfusion nous semble cliniquement pertinent puisque les patients présentent déjà certains critères de TACO avant que la transfusion ne soit débutée.

Le critère de détresse respiratoire aiguë pose problème par sa subjectivité. Bien que très pertinent sur le plan clinique et en lien direct avec l'œdème pulmonaire du TACO, il n'est pas défini. Faut-il prendre en compte les difficultés d'oxygénation? De ventilation? La tachypnée? Ou une combinaison de ces éléments? Afin de préciser la définition, il serait opportun de se limiter à un seul paramètre clinique. Puisque le premier signe clinique d'œdème pulmonaire est la tachypnée (42), la fréquence respiratoire semble le meilleur paramètre clinique de la détresse respiratoire aiguë dans le TACO. Le principe de comparaison avec les valeurs pré-transfusion du patient lui-même pourrait alors facilement s'appliquer. Toutefois, ce critère est nettement moins pertinent quand le patient est sous ventilation mécanique : la fréquence respiratoire est alors influencée, voire même imposée par le respirateur. Dans cette situation, la dégradation des paramètres ventilatoires est probablement un critère diagnostique plus approprié.

La présence d'un œdème pulmonaire nouveau ou qui s'aggrave était le facteur limitant principal dans notre étude. En effet, la radiographie pulmonaire n'avait pas été réalisée dans les six heures suivant la transfusion chez plus de 60% des patients. Toutefois, lorsqu'une radiographie était réalisée, elle montrait un œdème pulmonaire nouveau ou qui s'aggrave dans la moitié des cas. Cela représente bien la pratique clinique où le médecin traitant ne prescrit une radiographie pulmonaire que s'il pense que le résultat influencera sa pratique. Il n'est donc pas utile de rendre la radiographie pulmonaire obligatoire dans la définition, mais elle reste un critère important qui, quand il est présent, impacte réellement le diagnostic.

Enfin, le critère de balance liquidienne positive mériterait également d'être plus détaillé. Quel minimum de balance liquidienne positive faut-il prendre en considération? Il semble important de ne pas fixer un seuil absolu de balance liquidienne, mais bien de tenir compte de l'état clinique du patient avant la transfusion. En effet, un patient en surcharge volémique avant la transfusion est plus à risque de TACO qu'un patient en déficit volémique,

et ce, même si leur balance liquidienne respective dans les six heures suivant la transfusion est équivalente.

Bien qu'ayant chacun leurs limitations, tous ces critères sont importants dans la définition car ils représentent tous les aspects de la physiopathologie du TACO. Il est par contre nécessaire de préciser leur interprétation et les critères de positivité. Dans notre étude, nous avons utilisé les paramètres du patient lui-même comme référence pour définir chacun des critères diagnostiques. En utilisant cette méthodologie, nous avons obtenu des taux d'incidence semblables à ceux retrouvés dans la population adulte. Procéder de la sorte permet de rendre la définition du TACO plus opérationnelle et aussi d'uniformiser les critères de recherche afin de pouvoir comparer leurs résultats.

Aucune définition actuelle du TACO n'est satisfaisante. Dès 2014, des critiques ont été émises et ont motivé l'ISBT à créer un groupe de travail composé d'experts dans le but d'améliorer les critères et de rendre ainsi la définition plus opérationnelle. Des propositions de modifications des critères diagnostiques du TACO ont été soumises et testées en milieu clinique. Ce processus de recherche est toujours en cours (43).

Comme cela a été évoqué dans la discussion de notre premier article, il semblerait utile d'ajouter des critères biochimiques à la définition du TACO. Celui que nous avions suggéré, le *Brain Natriuretic Peptide* (BNP), est maintenant repris dans la définition actuelle du TACO par le Center for Disease Control (44). Il est également proposé dans la définition en cours d'élaboration par l'ISBT (43).

Le BNP est une hormone sécrétée par les myocytes cardiaques en cas d'augmentation de la pression de remplissage ventriculaire. Son dosage augmente donc en cas de surcharge volémique. Le *N-terminal-pro hormone* (NT-proBNP) est une pro-hormone inactive produite lors de la synthèse du BNP. Leurs dosages ont donc la même signification clinique mais le NT-pro BNP est plus stable et plus facile à doser en laboratoire.

De plus en plus d'études soulignent l'importance de la prise en compte du BNP ou NT-proBNP dans les critères diagnostiques du TACO (45–52). Une revue de la littérature récente

a recensé tous les articles sur les biomarqueurs étudiés dans les cas de TACO (46). Il en ressort une forte association entre le BNP ou le NT-proBNP et le diagnostic de TACO chez les patients transfusés en dehors des soins intensifs. Un seuil de 300 pg/ml pour le BNP et de 2000 pg/ml pour le NT-proBNP en dessous desquels le diagnostic de TACO est très peu probable est proposé par les auteurs de l'étude. Au sein de la population des soins intensifs, le seuil est moins net. En effet, les taux de BNP et de NT-proBNP ne semblent pas directement corrélés à la pression capillaire pulmonaire et des taux élevés sont fréquemment retrouvés chez les patients sévèrement malades en l'absence d'insuffisance cardiaque (53,54).

Qu'en est-il alors de la population de soins intensifs pédiatriques? Le BNP est de plus en plus étudié en pédiatrie et son utilité clinique est démontrée dans l'évaluation de l'insuffisance cardiaque. Il semble moins influencé par la sévérité globale de la maladie et plus en lien avec la défaillance cardiaque et ce, même dans la population admise aux soins intensifs pédiatriques (55–58). Toutefois, de nombreuses interrogations persistent. Tout d'abord, sa sensibilité et sa spécificité ne sont pas connues dans cette population fréquemment en surcharge. De plus, aucun seuil n'est défini en pédiatrie, encore moins en cas de TACO. Cette problématique est difficile car, pour étudier le BNP dans les cas de TACO et en définir un seuil de positivité, il faut avoir accès à une population à risque de TACO mais pas à risque d'autres complications, en particulier le TRALI. Il est également important d'obtenir un consensus sur la définition du TACO afin de catégoriser correctement les participants à l'étude. Dès lors, bien que l'intérêt clinique du BNP soit grand, de nombreuses étapes doivent encore être franchies avant de pouvoir l'utiliser dans la pratique quotidienne.

D'autres marqueurs cardiaques ou inflammatoires sont encore peu étudiés. Certaines interleukines, leurs récepteurs et différents marqueurs de réaction immunitaire méritent une attention particulière; ils pourraient se révéler très utiles dans le diagnostic différentiel du TACO (46).

Nous nous sommes aussi posé la question de l'impact de la modification de l'intervalle de temps après la transfusion au cours duquel les critères doivent être remplis pour poser le

diagnostic de TACO. Au moment de notre étude, les définitions existantes parlaient d'un intervalle maximal de six heures mais certains auteurs ouvraient déjà la porte à l'élargissement de cette durée (59). Nous avons donc étendu la collecte de données de six heures jusqu'à 12 et 24 heures après la transfusion. Le raisonnement supportant le choix d'un intervalle de six heures est que la surcharge volémique liée au produit sanguin transfusé devrait apparaitre rapidement, dans les premières heures suivant la transfusion. Toutefois, l'insuffisance cardiaque associée à cette surcharge volémique peut, elle, se développer plus lentement. Enfin, il est important de tenir compte des particularités et des comorbidités de chaque patient car ceux-ci ne réagissent pas tous de la même façon. La définition en cours d'élaboration par l'ISBT élargit l'intervalle de temps pour le diagnostic à 12 heures (43). D'autres études prospectives sont nécessaires afin de mieux étudier cet intervalle de temps pour le diagnostic du TACO.

Et d'une manière générale, une définition opérationnelle du TACO pédiatrique ne pourra être obtenue sans d'autres études prospectives.

4.3. TACO versus TRALI

De nombreuses études insistent sur la difficulté de différencier le TACO du TRALI (23,60–62). Apparemment les définitions de ces deux entités semblent bien différenciées : le TRALI exclut la présence d'une augmentation de la pression capillaire pulmonaire, celle-là même qui est l'explication physiopathologique de l'œdème pulmonaire associé au TACO.

Malheureusement, la distinction n'est pas si aisée au chevet du patient. Non seulement le médecin traitant n'a pas toujours à sa disposition toutes les données cliniques et paracliniques utiles au diagnostic différentiel, mais certains patients atteints d'une insuffisance cardiaque peuvent aussi développer un TRALI. Si l'insuffisance cardiaque semble être l'élément clé du diagnostic différentiel entre ces deux entités, il ne peut paradoxalement pas toujours les distinguer clairement.

De plus, certains patients peuvent présenter les deux complications en même temps. La distinction entre les deux devient alors futile.

Au vu de ces difficultés diagnostiques, un consensus d'experts propose d'inclure dans la définition du TRALI une nouvelle entité nommée TRALI/TACO (62). Cette catégorie permettrait de rapporter aux services d'hémovigilance les cas d'œdème pulmonaire post-transfusionnel dont le diagnostic reste incertain.

D'autres proposent d'utiliser le BNP pour aider à différencier le TACO du TRALI (46,63). Une augmentation supérieure des taux de BNP dans les cas de TRALI par rapport aux cas de TACO a été mise en évidence chez les adultes (50). Il est donc crucial d'étudier plus avant le BNP dans les cas de TACO pédiatriques afin d'en évaluer sa pertinence, son importance clinique et son utilité dans le diagnostic différentiel.

4.4. Le TACO existe-t-il vraiment?

Une question plus générale peut se poser. En quoi le TACO se différencie-t-il de la surcharge volémique non liée à la transfusion? S'agit-il de deux entités réellement distinctes avec des définitions différentes ou bien le TACO est-il une sous-catégorie de surcharge volémique? Le type de volume administré a-t-il une réelle importance? L'impact clinique est-il différent s'il s'agit d'une réaction à un produit sanguin ou à un autre liquide?

Pour mieux comprendre, reprenons les caractéristiques de la surcharge volémique. Le pourcentage de surcharge volémique est calculé par la formule suivante (34,37) :

$$\frac{\text{total des apports liquidiens} - \text{total des pertes liquidiennes}}{\text{poids corporel de base}} \times 100$$

Pour tenir compte cliniquement de la surcharge volémique, un minimum de 10% de surcharge est nécessaire. Cette définition est discutée mais reste la plus couramment utilisée en dehors de la période néonatale (34,64).

Plusieurs études pédiatriques ont démontré une association entre la surcharge volémique et une augmentation de la durée de ventilation mécanique, de la durée de séjour aux soins intensifs et à l'hôpital, mais également de la mortalité (31–35,37–40).

Par ailleurs, le TACO est actuellement défini avec des critères plus cliniques incluant la tachycardie, la détresse respiratoire et l'hypertension artérielle, associés à un œdème pulmonaire et une balance hydrique positive. Notre revue de la littérature a montré que le TACO est associé aux mêmes conséquences que la surcharge volémique non liée à la transfusion, c'est-à-dire une augmentation de la durée de ventilation mécanique, de la durée de séjour aux soins intensifs et à l'hôpital, et également de la mortalité.

La question de l'existence du TACO comme entité propre vient sans doute du manque de compréhension de sa physiopathologie. Les manifestations cliniques du TACO sont-elles dues uniquement à la quantité de liquide administré ou existe-t-il une réaction encore méconnue à certaines caractéristiques du produit sanguin lui-même qui en ferait sa spécificité?

D'une part, le TACO et la surcharge volémique non liée à la transfusion sont tous les deux un problème de surcharge avec des symptômes semblables et des conséquences identiques. Cette constatation plaiderait donc pour une confusion entre ces deux entités.

Mais d'autre part, on retrouve dans l'article de Bosboom *et al.* publié en 2018 des résultats montrant une différence entre ces deux diagnostics (65). Il a étudié l'incidence et les conséquences du TACO et de la surcharge volémique non liée à la transfusion dans une population de soins intensifs adultes. Il en ressort une incidence de 5,8% pour le TACO et de 8,5% pour la surcharge volémique non liée à la transfusion. Mais l'élément clé qui différencie les deux entités est la quantité de surcharge volémique nécessaire pour entrainer des symptômes. En effet, la balance liquidienne était moins positive dans le groupe présentant un TACO comparé au groupe contrôle. Les auteurs émettent donc l'hypothèse que les globules

rouges transfusés augmentent la pression oncotique intravasculaire, ce qui entraine un appel d'eau depuis le compartiment extravasculaire et augmente ainsi la quantité de liquide intravasculaire de manière non proportionnelle à la quantité de liquide transfusée.

Une autre hypothèse non évoquée par les auteurs est la présence d'une réaction, inflammatoire ou autre, directement liée aux caractéristiques du produit sanguin transfusé. L'ajout d'adjuvant dans les poches de produits sanguins labiles pourrait-il avoir un impact encore méconnu? Ces questions restent à explorer.

Il semble donc que le TACO est bien une entité à part entière avec ses propriétés spécifiques. Mais d'autres études comparant le TACO et la surcharge volémique non liée à la transfusion sont encore une fois indispensables, surtout en pédiatrie.

4.5. Pourquoi est-il important de diagnostiquer les cas de TACO?

Contrairement aux autres complications des transfusions, le TACO n'est causé ni par une infection, ni par un facteur immunologique majeur, ni par une erreur humaine; il est principalement lié à la condition de l'hôte. Il est donc crucial de diagnostiquer adéquatement les patients atteints de TACO afin de mieux en étudier les facteurs de risque. Ceci nous permettrait ensuite d'adapter nos pratiques transfusionnelles chez les patients à risque afin de prévenir cette complication potentiellement mortelle.

Considérant les facteurs de risque que nous avons mis en évidence dans notre revue exploratoire et les propositions de prévention du TACO publiées par certains auteurs (16,66,67), nous proposons différents éléments à prendre en compte lors de la prescription d'une transfusion.

Premièrement, il est important de s'assurer de la nécessité de la transfusion. Une évaluation rigoureuse de l'état clinique du patient est requise avant toute prescription de produit sanguin afin de ne pas administrer une transfusion uniquement sur base d'un résultat de laboratoire.

Deuxièmement, la quantité de produit sanguin prescrit doit être adéquate, en lien avec les besoins du patient. À l'exception des situations d'hémorragie massive, il est important de prescrire une unité à la fois et d'évaluer la tolérance du patient avant de prescrire d'autres unités supplémentaires.

Troisièmement, à l'exception de l'hémorragie active, la transfusion doit être perfusée lentement afin d'en favoriser la tolérance hémodynamique. Il peut être nécessaire de séparer les poches en aliquots moins volumineux afin de pouvoir prolonger le temps de transfusion sans gaspiller de produit sanguin.

Finalement, chez les patients les plus à risque, il peut être approprié de leur administrer un diurétique avant la transfusion afin de limiter la surcharge volémique.

L'application de toutes ces mesures pratiques basées sur les facteurs de risques connus de TACO permettrait d'en diminuer la survenue et donc potentiellement la mortalité post-transfusionnelle.

4.6. Critique de la méthodologie utilisée

L'objectif de ce projet de maitrise était de répondre à deux questions principales : quelle est la définition du TACO à utiliser en pédiatrie, et quelles sont les connaissances actuelles du TACO aux soins intensifs.

Afin de répondre à la première question, nous avons mené une étude observationnelle rétrospective. Ce type d'étude comporte plusieurs avantages mais également certaines limitations.

Tout d'abord, son caractère rétrospectif peut entrainer un biais de sélection qui est présent lorsque le recrutement des participants ne se fait pas de manière aléatoire ou systématique. Ceci peut donc signifier que la population étudiée n'est pas représentative de la population réelle. Toutefois, dans notre étude, ce biais est peu vraisemblable puisque la collecte de données a été réalisée de manière prospective.

Néanmoins, le caractère rétrospectif permet une réalisation plus rapide et à moindre coût. Les études rétrospectives observationnelles sont souvent utilisées comme première étape, pour décrire la problématique actuelle, avant d'entamer une étude prospective idéalement multicentrique. En effet, notre étude a permis de mettre en lumière les limites de l'application de la définition du TACO à la population de soins intensifs pédiatriques, et pourra servir à l'élaboration d'étude prospectives de validation de critères diagnostiques et d'implémentation.

Ensuite, il s'agit d'une étude descriptive, observationnelle. Ce type de devis, associé au caractère rétrospectif, augmente le nombre de données manquantes. Cette limite est en partie balancée par le caractère prospectif de la collecte de données de notre étude. Néanmoins, la quantité non négligeable de radiographies du thorax non réalisées dans l'intervalle étudié en est la meilleure illustration. Toutefois, les études observationnelles permettent de mieux refléter les pratiques cliniques réelles, sans interférence du protocole de recherche. Dans notre étude, le peu de radiographies du thorax réalisées représentent la réalité de la pratique clinique aux soins intensifs pédiatriques.

Enfin, il s'agit d'une étude monocentrique incluant peu de patients (136 enfants transfusés). Cela pourrait limiter la validité externe de notre étude, c'est-à-dire la généralisabilité des résultats obtenus. Notre étude a été menée dans une unité de soins intensifs pédiatriques d'un hôpital universitaire. Bien que la population admise soit assez polyvalente pour être comparable aux autres unités, nos résultats ne peuvent s'appliquer qu'aux patients hospitalisés dans une unité de soins intensifs pédiatriques dans un pays occidentalisé.

Pour répondre à la deuxième question de notre projet de recherche, nous avons choisi de réaliser une revue exploratoire de la littérature. Pour mieux expliquer notre choix, voici une

comparaison entre une revue exploratoire, une revue narrative et une revue systématique (68,69).

Une revue systématique a pour objectif principal de répondre à une question précise en analysant la littérature pertinente internationale, et synthétisant les résultats pour orienter la pratique clinique ou les recherches futures. Une attention particulière est portée à l'évaluation de la qualité des études incluses dans la revue afin de limiter les biais et d'en ressortir les données les plus fiables possibles.

Une revue narrative, quant à elle, ne suit aucune méthodologie systématique et est donc nettement plus sujette aux biais liés à la sélection des études. Ce type de revue est souvent considéré comme moins rigoureuse et leur validité scientifique est parfois limitée (70).

Finalement, une revue exploratoire a pour objectif de faire un état des lieux de la littérature actuelle. Contrairement à la revue systématique qui cherche à répondre à une question précise, la revue exploratoire sert à recenser toute la littérature existante à propos d'un sujet. Elle est donc particulièrement utile lorsque le sujet est encore peu décrit. Elle permet également de déterminer les devis de recherche utilisés dans le domaine, et d'en identifier les lacunes afin de guider les recherches futures. Puisque l'objectif est de décrire toute la littérature existante, toutes les études retrouvées répondant aux critères d'inclusion doivent être retenues, sans qu'une évaluation de leur qualité ne soit faite.

Bien qu'exploratoire, ce type de revue suit un processus rigoureux qui assure la validité des résultats obtenus.

4.7. Prochaines étapes

De nombreuses questions ne sont pas résolues et nécessitent de réaliser d'autres projets de recherche.

Premièrement, l'absence de définition adaptée à la population pédiatrique reste un problème important. Des études sont requises afin de préciser les critères diagnostiques chez l'enfant. Comme nous l'avons proposé, une comparaison des paramètres du patient avant et après la transfusion doit être étudiée de manière plus systématique. Il est également nécessaire d'évaluer différents intervalles de temps après la transfusion afin de déterminer la durée de surveillance à conseiller pour diagnostiquer un TACO. Une définition plus opérationnelle permettrait d'uniformiser les différentes recherches et donc de pouvoir comparer leurs résultats. Ceci ne peut se faire sans la réalisation d'études prospectives permettant de valider la définition élaborée. Une étude avec un devis pré-/post- implémentation serait également intéressante afin d'objectiver l'impact clinique de la nouvelle définition.

Deuxièmement, nous pensons qu'il est nécessaire d'inclure certains biomarqueurs dans la définition. Bien que le BNP et le NT-proBNP soient de plus en plus étudiés dans la population adulte, il reste à vérifier ces résultats chez l'enfant à l'aide d'études prospectives.

Avant de pouvoir inclure le BNP dans la définition du TACO, il est important d'en établir les normes pédiatriques et de définir un seuil de positivité dans le TACO. Ceci amène d'autres défis importants. En effet, afin de pouvoir établir ce seuil, il faudrait mesurer les taux de BNP chez des patients souffrant de TACO et les comparer à des patients contrôles. Pour ce faire, il est important d'avoir une population de TACO « pure », c'est-à-dire une population chez qui le diagnostic de TACO est certain, et qui ne souffre d'aucune autre pathologie pouvant potentiellement influencer les résultats, en particulier le TRALI. Malheureusement, définir une telle population semble très difficile. Comment, à l'heure actuelle, obtenir une population à risque de TACO sans être à risque de TRALI ou d'autres complications transfusionnelles? Une hypothèse serait de prendre en compte uniquement des patients souffrant de surcharge volémique avant la transfusion, partant du principe qu'ils seront dès lors à plus haut risque de TACO. Toutefois, ceci ne permettrait pas d'exclure toutes autres complications de la transfusion. D'autre part, les taux de BNP dosés chez ces patients en surcharge avant la transfusion sont-ils réellement fiables et utilisables comme valeur de référence? Ou sont-ils déjà augmentés de par la surcharge volémique? Les critères d'inclusion d'une telle étude

prospective ne sont pas évidents mais celle-ci permettrait une avancée importante dans le domaine du TACO et plus particulièrement du TACO aux soins intensifs pédiatriques.

Il faudrait également s'intéresser davantage à d'autres biomarqueurs qui pourraient aider au diagnostic et au pronostic du TACO.

Troisièmement, il est important de comparer le TACO et la surcharge volémique non liée à la transfusion. L'étude publiée récemment par Bosboom *et al.* (65) apporte des résultats significatifs chez l'adulte et offre des perspectives de recherche. Il nous paraitrait intéressant de mener un projet comparable en pédiatrie.

Toutes ces pistes de recherche ont un même objectif : mieux comprendre et décrire le TACO pédiatrique, sa définition et son épidémiologie.

5. Leçons apprises durant ce projet de recherche

Cette recherche menée pendant ma maitrise s'est révélée une expérience pour le moins enrichissante. J'ai parcouru pas à pas les étapes nécessaires pour mener à terme un projet de recherche.

Tout d'abord, j'ai appris à utiliser une base de données, à comprendre comment elle a été construite, à en vérifier l'exactitude, et à l'exploiter pour en retirer les éléments nécessaires à mon projet. J'ai compris que l'attention qu'il faut donner à la récolte des données, vrai travail de fourmi, est primordiale pour la validité de l'étude.

J'ai découvert la richesse des différentes analyses statistiques que j'ai mises en œuvre pour faire parler les données récoltées. Les statistiques nécessitent une connaissance précise et une pratique rigoureuse afin de choisir le test statistique adapté aux circonstances.

C'était la première fois que je rédigeais un protocole de recherche avec tout ce que cela implique comme préparation, anticipation et rigueur scientifique. J'ai réalisé l'importance d'un protocole bien construit et détaillé; il trace le chemin à suivre durant tout le projet.

Une revue de la littérature est faite de méandres. J'ai appris comment élaborer une stratégie de recherche, sélectionner les articles les plus pertinents pour le sujet traité avec la rigueur requise. Ceci est un travail long et fastidieux; j'ai compris l'importance d'être entourée d'une équipe qualifiée et aidante.

Enfin, est venue l'étape de la mise en forme des résultats obtenus avec la rédaction d'articles et la formulation prudente d'hypothèses et de voies de recherche futures. Ce travail m'a permis de tester ma persévérance en le corrigeant sans cesse, en le remaniant pour atteindre le résultat souhaité.

Mes directeurs de recherche, avec leur regard à la fois critique et bienveillant, m'ont transmis une méthode rigoureuse de questionnement nécessaire à tout travail de recherche.

6. Conclusion

L'objectif initial de notre travail était de mieux décrire le TACO aux soins intensifs pédiatriques.

Dans notre première étude, nous avons mis en évidence les limites de la définition adulte du TACO au sein de la population de soins intensifs pédiatriques. Ceci a permis de soulever les adaptations qu'il faut y apporter pour la rendre cliniquement opérationnelle dans cette population spécifique et ce qu'il faut peut-être y ajouter en termes de marqueurs biologiques tels que le BNP ou NT-proBNP.

Dans notre deuxième étude, nous avons réalisé une revue exploratoire de la littérature du TACO aux soins intensifs adultes et pédiatriques. Seules neuf études correspondaient à nos critères d'inclusion et démontraient une incidence de TACO plus élevée aux soins intensifs que dans la population générale avec des conséquences néfastes importantes.

Ce travail nous a mené à poser la question de l'existence du TACO en tant que diagnostic spécifique ou comme sous-catégorie de surcharge volémique non liée à la transfusion. Il ressort de la littérature récente que le TACO semble plus être une entité à part entière, avec ses caractéristiques propres.

Le TACO reste malgré tout trop peu étudié en pédiatrie, et surtout aux soins intensifs pédiatriques. D'autres études sont dès lors nécessaires afin d'approfondir nos connaissances de cette complication fréquente et potentiellement mortelle.

Nous avons proposé quelques pistes pour guider les futures recherches.

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Annexe 1.

Transfusion-associated circulatory overload in a pediatric intensive care unit: different incidences with different diagnostic criteria.

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CME/SAM

Transfusion-associated circulatory overload in a pediatric intensive care unit: different incidences with different diagnostic criteria

Lise De Cloedt, Guillaume Emeriaud, Émilie Lefebvre, Niina Kleiber, Nancy Robitaille, Christine Jarlot, Jacques Lacroix, and France Gauvin

BACKGROUND: The incidence of transfusion-associated circulatory overload (TACO) is not well known in children, especially in pediatric intensive care unit (PICU) patients.

STUDY DESIGN AND METHODS: All consecutive patients admitted over 1 year to the PICU of CHU Sainte-Justine were included after they received their first red blood cell transfusion. TACO was diagnosed using the criteria of the International Society of Blood Transfusion, with two different ways of defining abnormal values: 1) using normal pediatric values published in the *Nelson Textbook of Pediatrics* and 2) by using the patient as its own control and comparing pre- and posttransfusion values with either 10 or 20% difference threshold. We monitored for TACO up to 24 hours posttransfusion.

RESULTS: A total of 136 patients were included. Using the "normal pediatric values" definition, we diagnosed 63, 88, and 104 patients with TACO at 6, 12, and 24 hours posttransfusion, respectively. Using the "10% threshold" definition we detected 4, 15, and 27 TACO cases in the same periods, respectively; using the "20% threshold" definition, the number of TACO cases was 2, 6, and 17, respectively. Chest radiograph was the most frequent missing item, especially at 6 and 12 hours posttransfusion. Overall, the incidence of TACO varied from 1.5% to 76% depending on the definition.

CONCLUSION: A more operational definition of TACO is needed in PICU patients. Using a threshold could be more optimal but more studies are needed to confirm the best threshold.

Transfusion-associated circulatory overload (TACO) is the most frequent serious transfusion adverse reaction in adult populations[1] and was the second leading cause of transfusion-related fatalities reported by the Food and Drug Administration in 2015.[2] It is associated with increased mortality and morbidity and a longer length of stay in hospital.[3]

TACO is underdiagnosed and underreported.[3] This is due to the lack of recognition of the diagnosis, the underestimation of its severity, the confusion between TACO and transfusion-related acute lung injury (TRALI),[4] and probably to the absence of an operational definition.

The best diagnostic criteria for TACO is still a matter of debate.[5] There are at least two lists of diagnostic criteria of TACO in adults, one advocated by the National Healthcare Safety Network of the Centers for Disease Control and Prevention,[6] the other one advocated by the British Hemovigilance Scheme and the International Society of Blood Transfusion (ISBT).[7] Recently, the ISBT submitted

ABBREVIATIONS: FiO_2 = inspired fraction of oxygen; IBST = International Society of Blood Transfusion; PICU = pediatric intensive care unit; TACO = transfusion-associated circulatory overload.

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another list of diagnostic criteria.[8] None of these diagnostic criteria are adapted to children as they do not define cutoffs for age-adapted vital sign values. Moreover these definitions ignore the effect of critical illness that can per se influence vital signs: for example, tachycardia is prevalent among pediatric intensive care unit (PICU) patients. The diagnosis of TACO is therefore challenging in critically ill children and a definition adapted to the PICU is highly needed as this population often receives transfusions and is prone to the adverse effects of circulatory overload.[9] The objectives of this study were 1) to compare different criteria or abnormal values for TACO in the PICU and 2) to compare the incidence of TACO in the PICU using those different criteria.

MATERIALS AND METHODS

Study design

This retrospective observational study of consecutively transfused children is based on a previous prospective study, which aimed to describe the respiratory dysfunction associated with red blood cell (RBC) transfusions.[10] This study was undertaken in the PICU of CHU Sainte-Justine, a 24-bed unit of a quaternary university-affiliated pediatric hospital, from April 2009 to April 2010. All patients consecutively admitted to the PICU over 1 year were eligible if they received at least one RBC transfusion during their PICU stay. The exclusion criteria were gestational age less than 40 weeks, age less than 3 days or more than 18 years, pregnancy, transfusion on extracorporeal membrane oxygenation, transfusion in operating room, admission to PICU just after labor, and death within 1 hour of first RBC transfusion.

Any administration of RBC units in the PICU was considered a transfusion, regardless of the volume given. Only prestorage leukoreduced AS-3 RBC units were used. Time 0 was defined as the time the first RBC transfusion was started in the PICU. Data were collected on the first RBC transfusion administered for each included patient. This TACO study is a secondary study undertaken in 2013 using the database of the prior study mentioned.

Data collection

Patient's data were recorded in a validated case report form by research assistants. Data were collected from 6 hours before Time 0 until 24 hours after Time 0. Three periods were set: 6, 12, and 24 hours after Time 0. In this article, the terms pretransfusion and posttransfusion always refer to Time 0 (beginning of the transfusion).

The following data were collected: demographic data, diagnosis of cardiac disease, post–cardiac surgery, duration of transfusion, transfusion volume, use of vasopressive or inotropic agent, highest inspired fraction of oxygen (FiO_2), highest respiratory rate, highest positive end-expiratory pressure and peak inspiratory pressure, lowest arterial partial pressure of oxygen/FiO_2 or oxygen saturation measured by pulse oximetry or FiO_2, noninvasive or invasive ventilation required, mean and highest heart rate, mean and highest blood pressure (systolic and mean pressure), mean and highest central venous pressure, mean and highest left atrial pressure, and fluid balance. The worst values of each variable were recorded for each period.

For each ventilated patient, a chest radiograph is done every morning in the PICU; another chest radiograph can be ordered by the physician when judged necessary. For nonventilated patients, chest radiograph is ordered when judged necessary by the physician. A pediatric radiologist (CJ) retrospectively and independently reviewed all chest radiographs to evaluate if any pulmonary edema was present, and if it had worsened after RBC transfusion compared to before transfusion. The radiologist was blinded to the time of administration of transfusion, to the clinical condition of the patient, and to the presence or not of other TACO criteria. The radiologist was also blind to the results of other previous reports by intensivists or radiologists who interpreted the radiographs during the stay of the patient.

TACO criteria

We used the criteria proposed by the ISBT,[7] which diagnose TACO when any four of the five following criteria are observed within 6 hours of completion of transfusion: 1) acute respiratory distress, 2) tachycardia, 3) increased blood pressure, 4) acute or worsening pulmonary edema on frontal chest radiograph, and 5) evidence of positive fluid balance. Since there is no clear definition to specify each criterion, we decided to compare two ways to define abnormal values for those criteria (as detailed in Table 1). The first way was to use the upper limit of the normal pediatric values according to age, as published in the *Nelson Textbook of Pediatrics*;[11] this was used for respiratory distress, tachycardia, and high blood pressure. The two other criteria consisted of edema found on chest radiograph, according to the radiologist, and a positive fluid balance. For positive fluid balance, since there is no available normal value in the literature, we decided to use the absolute value of at least 1 mL as threshold. The second way was to use the patient's worst values after transfusion compared with his baseline values (observed within 6 hr before transfusion) and seek thresholds of 10 and 20% deterioration; this was used for respiratory distress, tachycardia, and high blood pressure. For example, a threshold of 10% deterioration is reported for a patient who shows an increased heart rate (between 10% and 20%) after transfusion compared to before transfusion (maximal heart rate of 140/min after transfusion compared to 120/

TABLE 1. Detailed variables that we used to diagnose cases of TACO

Criteria (TACO = 4/5 criteria)	1) Normal pediatric values (at least one positive value necessary to confirm criteria)	2) Comparison of patient's values before and after transfusion, using a threshold of 10% or 20% (at least one positive value necessary to confirm criteria)
Acute respiratory distress	Maximal respiratory rate according to age* $PaO_2/FiO_2 \leq 300$ or $SpO_2/FiO_2 \leq 315$	Values found in patient: Maximal FiO_2 Maximal respiratory rate Maximal PEEP† and PIP† Minimal PaO_2/FiO_2 or SpO_2/FiO_2
Tachycardia	Maximal heart rate according to age*	Maximal heart rate in patient
Increased blood pressure	Maximal systolic blood pressure according to age*	Maximal blood pressure in patient: Systolic and mean blood pressure Central venous pressure‡
Edema on chest radiograph	Edema found on posttransfusion chest radiograph, according to radiologist	Edema found on posttransfusion chest radiograph and worsened compared to pretransfusion chest radiograph, according to radiologist
Positive fluid balance	Positive fluid balance (≥1 mL)	Patient's posttransfusion fluid balance − pretransfusion fluid balance

* According to the *Nelson Textbook of Pediatrics*.[11]
† If patient on mechanical ventilation.
‡ If central venous catheter in place.
PaO_2 = arterial partial pressure of oxygen; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; SpO_2 = oxygen saturation measured by pulse oximetry.

min before transfusion, which gives a difference of 140-120/120 = 16%). A threshold of 20% is reported if the deterioration is more than 20%. The two other criteria consisted of: 1) edema on chest radiograph that had worsened after transfusion compared to before transfusion according to the radiologist (there was no difference between 10 and 20% deterioration as it is impossible to specify such a specific deterioration on chest radiograph) and 2) a fluid balance that was increased after transfusion compared to before transfusion (with a 10 or 20% deterioration). Since other definitions suggest that TACO can appear later than 6 hours posttransfusion,[8] we decided to evaluate all these criteria at 6, 12, and 24 hours posttransfusion even though it is not part of the ISBT definition.

Statistical analysis

Continuous variables are presented as mean with standard deviation or median with interquartile ranges according to the distribution. Categorical variables are presented as number with proportion (%). The incidence of TACO was calculated separately for each group of patients and for each studied period (6, 12, or 24 hours posttransfusion) as followed: total number of TACO per total number of patients transfused. Data were collected on a computer spreadsheet (Microsoft Excel 2010, Microsoft Corp.) and analyzed with statistical software (SPSS Statistics Version 24, SPSS, Inc.).

Ethical approval

This observational study was approved by the institutional review board who waived informed consent.

RESULTS

As detailed in Fig. 1, a total of 916 consecutive patients were admitted to the PICU from April 2009 to April 2010, including 144 who received at least one RBC transfusion. Eight patients were excluded while 136 (14.8%) were retained in the study. Demographic characteristics are detailed in Table 2. Most patients (62.5%) were younger than 3 years (median, 12 months). Mean duration of the first RBC transfusion was 126 minutes and half of our patients had more than one blood product transfused during the 24 hours after the first RBC transfusion.

The number of patients with TACO based on the three distinct periods is detailed in Tables 3, 4, and 5. At 6 hours posttransfusion, 63 patients (46%) had a TACO using the "normal pediatric values" criteria, while only four patients (3%) had a TACO using the "10% threshold" criteria and two patients (1.5%) using the "20% threshold" criteria. At 12 and 24 hours posttransfusion, TACO was observed in 88 (65%) and 104 patients (76%), respectively, using the normal pediatric values criteria, 15 (11%) and 27 patients (20%) using the 10% threshold criteria, and six (4%) and 17 patients (12%) using the 20% threshold criteria.

Missing data are described in Tables 3, 4, and 5. Chest radiograph was the most frequent missing item; no chest radiograph was done at 6 hours posttransfusion in most patients (86/136 = 63%). Pretransfusion fluid balance was also frequently unavailable (15/136 = 11%). Those missing data made the diagnosis of TACO impossible in 11 patients at 6 hours posttransfusion, eight patients at 12 hours posttransfusion, and six patients at 24 hours posttransfusion. Overall, depending on the criteria used and

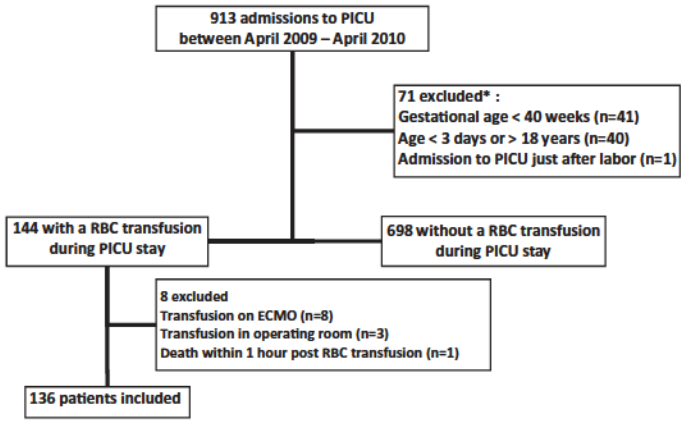

Fig. 1. Patients' flow chart. ECMO = extracorporeal membrane oxygenation. *Some patients presented more than one exclusion criterion.

TABLE 2. Demographic data

All subjects	n = 136*
Population	
Age (months)	12 (3-128)
Female	67 (49)
Initial diagnosis of cardiac disease	48 (35)
Post–cardiac surgery	35 (26)
Description of first RBC transfusion	
Transfusion volume (mL/kg)	10.5 (7-15)
Duration of transfusion (min)	126 ± 61
Rapid transfusion (<30 min)	7 (5)
Slow transfusion (>180 min)	36 (26)
Rate of transfusion (mL/kg/hr)	5.4 (3.6-9.4)
Length of stay in PICU before transfusion (day)	1.3 ± 2.1
Any other blood product transfused†	69 (51)
Total volume of all blood product transfused (mL/kg/patient)‡	15 (10-27)

* Continuous data are presented as mean ± SD or median (interquartile range); categorical data are presented as number (%).
† During the 24 hours after the first RBC transfusion.
‡ During the 24 hours after the first RBC transfusion and including this first transfusion.

the interval posttransfusion used, the incidence of TACO varies from 1.5% to 76%.

New cases of TACO per period, using the different criteria studied, are shown in Fig. 2. No case of TACO diagnosed in this study was reported by the attending physician to the Quebec Hemovigilance System.

DISCUSSION

In our study, the incidence of TACO differed significantly when using different values for diagnostic criteria and different posttransfusion intervals; using the normal pediatric values criteria, the incidence of TACO varied from 46% to 76% depending on the posttransfusion interval; using the 10% threshold criteria, the incidence varied from 3% to 20%; and using the 20% threshold criteria, it varied from 1.5% to 12%. Thus, this study about TACO in PICU raises many questions.

First, can we use the definition suggested by the different scientific societies to diagnose TACO in children? The results of our study suggest that it might not be appropriate, because this definition is too vague and not adapted to children. In our study, we used the adult definition with different criteria or abnormal values and found that the incidence of TACO varied widely.

Second, which criteria or abnormal values should be used to diagnose TACO in PICU patients? The incidence of TACO with the normal pediatric values definition was very high (46%-76%). Is this high incidence due to overdiagnosis (unsuitable and too sensitive criteria) or is it due to the fact that PICU patients were more at risk of TACO because of previous overload and/or cardiac failure?

If we compare to the adult literature,[12,13] the incidence we found using a comparison between pre- and posttransfusion values (threshold) seems to be more appropriate. This study does not allow to determine the best threshold (10% or 20%) since there are no reference standards. However, this approach is also supported by Lieberman and colleagues[14] who showed significant differences in the values of vital signs before and after the diagnosis of TACO in adult populations.

In this study, the incidence rate of TACO ranges from 1.5% to 11% using the 10% threshold and the 20% threshold at 6 and 12 hours of transfusion, which is similar to the literature from critically ill adults.[12,13] This could suggest that a threshold of 10% to 20% could possibly be an

TABLE 3. Number of patients with TACO at 6 hours posttransfusion according to different diagnostic criteria*

	Number of patients with positive criteria using normal pediatric values		Number of patients with positive criteria using comparison in patient's values (before and after transfusion)		
Diagnostic criteria for TACO	Patients with positive criteria	Patients with missing data	Patients with positive criteria (threshold set at 10%)	Patients with positive criteria (threshold set at 20%)	Patients with missing data
Acute respiratory distress	125 (92)	0	78 (57)	58 (43)	0
Tachycardia	111 (82)	0	19 (14)	10 (7)	2
Increased blood pressure	96 (71)	0	66 (49)	46 (34)	3
Edema on chest radiograph	24 (18)	86	7 (5)	7 (5)	86
Positive fluid balance	99 (73)	0	70 (51)	69 (51)	15
TACO (≥4/5 criteria)	63 (46)	0†	4 (3)	2 (1.5)	11†

* Data are presented as number (%). Total number of transfused patients, n = 136.
† Number of patients with at least two unavailable criteria which made the diagnosis of TACO impossible.

TABLE 4. Number of patients with TACO at 12 hours posttransfusion according to different diagnostic criteria*

	Number of patients with positive criteria using normal pediatric values		Number of patients with positive criteria using comparison in patient's values (before and after transfusion)		
Diagnostic criteria for TACO	Patients with positive criteria	Patients with missing data	Patients with positive criteria (threshold set at 10%)	Patients with positive criteria (threshold set at 20%)	Patients with missing data
Acute respiratory distress	130 (96)	0	104 (76)	81 (60)	0
Tachycardia	116 (85)	0	33 (24)	15 (11)	2
Increased blood pressure	106 (78)	0	87 (64)	62 (46)	3
Edema on chest radiograph	39 (29)	57	14 (10)	14 (10)	57
Positive fluid balance	117 (86)	0	78 (57)	77 (57)	15
TACO (≥4/5 criteria)	88 (65)	0†	15 (11)	6 (4)	8†

* Data are presented as number (%). Total number of transfused patients, n = 136.
† Number of patients with at least two unavailable criteria which made the diagnosis of TACO impossible.

appropriate choice. The optimal threshold comparing pre- and posttransfusion values to diagnose TACO remains to be determined in prospective studies in this PICU population.

Third, what should be the best posttransfusion interval to define TACO: 6, 12, or 24 hours? At present, definitions of TACO suggest that the diagnosis must be done during the first 6 hours after transfusion, but could be done beyond 12 hours.[5] The rationale supporting a shorter period of onset for TACO is that RBC transfusion—associated fluid overload should occur within a few hours. However, longer intervals could be expected due to the interaction between fluid status and cardiac function as fluid overload could lead to cardiac insufficiency that may progress more slowly. Furthermore, different patients with different comorbidities and fluid balances are expected to demonstrate the clinical effects of volume overload at different times suggesting that there is not a single ideal time to define TACO. In our study, incidence of TACO varies widely according to posttransfusion period and it was impossible to choose the best posttransfusion interval. Nevertheless, it is interesting to note that many cases of TACO appeared at 12 and 24 hours posttransfusion. Again, further studies should determine the peak onset of vital sign disturbances in all patients. Moreover, these studies should ideally be done using invasive and echocardiographic hemodynamic criteria that could help differentiating cardiac overload from other etiology producing a similar clinical picture.

Fourth, how frequent is TACO in children? Some papers reported that TACO is more frequent in children younger than 3 years and in people older than 60 years.[3,12,15,16] On the other hand, the literature reports very few TACO in children.[17,18] Moreover, in this study, no case of TACO was reported to the Quebec Hemovigilance System. The most probable explanations are that TACO is underdiagnosed and underreported.[4] Other reasons may be due to a lower risk of TACO in children compared to adult, to the inadequacy of the current diagnostic criteria in pediatrics or the clinician's lack of awareness of this condition. Another reason is that the difference between respiratory transfusion reactions like TACO and TRALI is more difficult to establish in critically ill patients because of their pulmonary status. Furthermore, the differentiation between the diagnosis of TRALI and TACO is sometimes difficult.[15,19-22]

TABLE 5. Number of patients with TACO at 24 hours posttransfusion according to different diagnostic criteria*

	Number of patients with positive criteria using normal pediatric values		Number of patients with positive criteria using comparison in patient's values (before and after transfusion)		
Diagnostic criteria for TACO	Patients with positive criteria	Patients with missing data	Patients with positive criteria (threshold set at 10%)	Patients with positive criteria (threshold set at 20%)	Patients with missing data
Acute respiratory distress	130 (96)	0	112 (82)	97 (71)	0
Tachycardia	119 (88)	0	37 (27)	21 (15)	2
Increased blood pressure	115 (85)	0	102 (75)	83 (61)	3
Edema on chest radiograph	57 (42)	15	27 (20)	27 (20)	15
Positive fluid balance	123 (90)	0	87 (64)	85 (62)	15
TACO (≥4/5 criteria)	104 (76)	0†	27 (20)	17 (12)	6†

* Data are presented as number (%). Total number of transfused patients, n = 136.
† Number of patients with at least two unavailable criteria which made the diagnosis of TACO impossible.

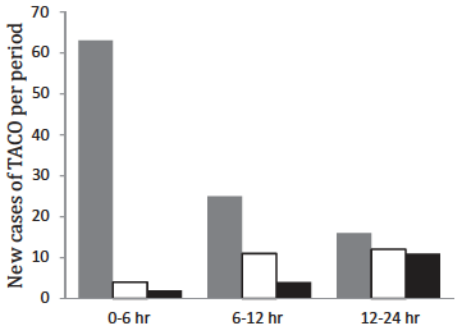

Fig. 2. New cases of TACO per period. Figure shows the new cases of TACO diagnosed using the different criteria, during each period (at 6, 12, and 24 hours posttransfusion). (▒) Using the normal pediatric values criteria; (□) using the 10% threshold criteria; (■) using the 20% threshold criteria.

Finally, the best clinical criteria to diagnose TACO are still a matter of debate. A review of the different definitions made by SHOT showed large variations in incidence of TACO depending on the definition used.[5] They concluded that all the definitions presently used are unsatisfactory. In 2016, the ISBT proposed new criteria including increased blood level of natriuretic peptide (BNP or NT-pro-BNP) levels.[8] A high BNP level is an additional clue to the diagnosis of TACO as it supports the diagnosis of fluid overload and cardiac dysfunction.[23] Nevertheless, BNP has so far rarely been measured in PICU patients since we do not have baseline values; it was developed for adult congestive heart failure and the test requires a large amount of blood for analysis in small children. The usefulness of BNP to diagnose TACO in PICU patients must be evaluated in prospective studies. Perhaps the use of a 50 or 100% increase in BNP/NT-pro-BNP at 6, 12, and 24 hours as the gold standard for the diagnosis of TACO could be studied.

Another problematic criterion is the chest radiograph. First, in our study, the chest radiograph, which is necessary to ascertain lung infiltrates and is one of the five diagnostic criteria, was unavailable in most instances (86/136) at 6 hours posttransfusion. These missing data made the diagnosis of TACO impossible in many patients and may contribute to the variation in the incidence rate. Second, the x-ray must be read by a radiologist as it can sometimes be difficult to differentiate pulmonary edema from another type of infiltrate and to adequately determine worsening of preexisting pulmonary edema.

This study has some limitations. The TACO definition was meant for patients who develop acute frank respiratory distress as part of obvious transfusion reaction; thereafter, the criteria are applied to help differentiate TACO from TRALI or another transfusion reaction. Since we used the database of a previous prospective study, it is impossible to assume that all patients developed respiratory distress as part of transfusion reaction, even though deterioration was after transfusion.

Diagnostic criteria could not always be fulfilled due to missing criteria. However, this reflects the clinical practice since some tests or vital signs are not routinely performed during the time surrounding RBC transfusion.

There was only one radiologist to diagnose pulmonary edema; expert opinion and clinical judgment were used without specific criteria. This could introduce bias and weaken the results of this criterion. Furthermore, the interpretation of chest radiographs was conducted a posteriori by an independent radiologist. Although the radiologist was blind to the clinical criteria, it is possible that fluid overload was more frequently diagnosed because of the study context.

For positive fluid balance, we used the absolute value of at least 1 mL as threshold. This threshold is probably too sensitive but there is no clear published definition and no optimal threshold has been validated in the literature.[24-27] The results of this study will serve as preliminary data to prepare further validation studies.

Our study was not designed to validate a new list of diagnostic criteria; its principal aim was to compare different criteria or abnormal values for diagnosis of TACO and it is only generating hypotheses. Indeed our results provide some hints on which values could be considered to diagnose TACO in critically ill children and to elaborate more operational diagnostic criteria.

Finally, we do not have the data on other blood products and fluids that the patient received before their TACO was diagnosed; this could have been a useful guide as to when patients in the ICU become at risk of having a TACO. We also do not have data about TACO prevention strategies employed in any child (slow rate of transfusion, pre- or posttransfusion furosemide administered), as this would have been very helpful data.

In conclusion, the incidence of TACO in PICU differs widely depending on the diagnostic criteria used. The current definitions of TACO (SHOT, ISBT, National Healthcare Safety Network) might not be adequate for PICU patients. Prospective multicenter studies are required to develop and validate a new list of diagnostic criteria for pediatric TACO and to determine the real incidence and clinical impact of TACO in critically ill children.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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Annexe 2.

Transfusion-associated circulatory overload (TACO) in intensive care units: a scoping review of incidence, risk factors, and outcomes.

De Cloedt L, Savy N, Gauvin F, Taylor S, Lacroix J, Emeriaud G.

Crit Care Med. 2019 Jun;47(6):849–56.

Review Articles

Transfusion-Associated Circulatory Overload in ICUs: A Scoping Review of Incidence, Risk Factors, and Outcomes*

Lise De Cloedt, MD[1]; Nadia Savy, MD, MSc[1,2]; France Gauvin, MD, MSc, FRCPC[1]; Stephen Taylor, MD[3]; Jacques Lacroix, MD, FRCPC, FAAP[1]; Guillaume Emeriaud, MD, PhD[1]

Transfusion-associated circulatory overload is the most frequent serious adverse transfusion reaction, with an incidence close to 1% of transfused patients in the general adult population. Patients in ICUs are probably more at risk of transfusion-associated circulatory overload as they are more frequently transfused and associated with more comorbidities. However, the epidemiology of transfusion-associated circulatory overload in ICU is not well characterized, leading to a risk of underdiagnosis.

Objectives: We conducted a scoping review to describe the incidence, risk factors, and outcomes of transfusion-associated circulatory overload in PICU and adult ICU.

Data Sources: PubMed, Ovid Medline, Ovid All EBM Reviews, Ovid Embase, and EBSCO CINAHL COMPLETE.

Study Selection: Two reviewers independently screened each article for inclusion criteria. Studies were eligible if they reported data on incidence, risk factors, or outcomes of transfusion-associated circulatory overload in at least 10 ICU patients.

Data Synthesis: Among 5,926 studies identified, nine were included. Five studies were prospective, and four were retrospective. The definition of transfusion-associated circulatory overload varied among studies. The pooled incidence of transfusion-associated circulatory overload was of 5.5% (95% CI, 2.6–9.4%) in adult ICUs (four studies, 2,252 patients, high heterogeneity). In PICUs, two studies (345 patients) reported 0 cases, and a third study (136 patients) reported variable incidences between 1.5% and 76%, depending on diagnostic criteria. Risk factors for transfusion-associated circulatory overload included positive fluid balance, the number and type of products transfused, rate of transfusion, and cardiovascular and renal comorbidities. Transfusion-associated circulatory overload was associated with increased ICU and hospital lengths of stay, whereas the association with mortality was not consistent.

Conclusions: Transfusion-associated circulatory overload is frequent in ICU patients and is associated with adverse outcomes. The lack of a pediatric-adjusted definition of transfusion-associated circulatory overload may lead to a risk of underdiagnosis of this condition in PICUs. Further research is warranted to improve the knowledge of transfusion-associated circulatory overload and the safety of transfusion in ICU patients. (*Crit Care Med* 2019; 47:849–856)

Key Words: hemovigilance; intensive care unit; safety; transfusion; transfusion-associated circulatory overload

*See also p. 878.

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Transfusion-associated circulatory overload (TACO) is an important adverse transfusion reaction. It is defined as acute respiratory distress associated with signs of fluid overload, including tachycardia, hypertension, pulmonary edema, positive fluid balance, or elevated levels of brain natriuretic peptides (1). According to the Food and Drug Administration, it was reported in 2012 to be the second cause of death attributable to transfusion (2). In the general population, TACO has an incidence close to 1% of transfused patients (3–5). It is associated with increased mortality, a longer duration of postoperative mechanical ventilation, and a longer length of stay in hospital (6, 7). Risk factors associated with TACO include a positive fluid balance, the number of blood products transfused, transfusion of plasma, preexisting cardiac or renal dysfunction, and older age (6, 8–10).

The risk of TACO seems greater in patients in ICUs. Transfusion is very common during critical illness, with

25–45% of patients being transfused during their ICU stay (11–13). Additionally, ICU patients frequently have at-risk comorbidities, in particular, a high prevalence of fluid overload, cardiac failure, and systemic inflammation. Nevertheless, TACO still seems to be an under-diagnosed complication from transfusion in ICUs (4, 14–16). This is probably due to the condition not being recognized, but also to diagnostic criteria which are not adapted to critically ill patients, and to the severity and clinical impact of this complication being underestimated.

We conducted a scoping review in order to highlight the importance of this complication in ICU patients. The primary objective was to describe the incidence, risk factors, and outcomes of TACO in PICU and adult ICU. The secondary objective was to identify knowledge gaps and potential future research directions.

MATERIAL AND METHODS

Search Strategy

The search strategy was established by two intensivists (L.D.C., G.E.) in collaboration with a scientific librarian (**Annexe 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/E472). Systematic searches of the databases PubMed, Ovid Medline, Ovid All EBM Reviews, Ovid Embase, and EBSCO CINAHL COMPLETE were performed by a librarian of Centre Hospitalier Universitaire Sainte-Justine with special training and skills in medical literature searches in May 2018.

In 2018, all that was indexed in the MeSH and subheading "Blood Transfusion/adverse effects" was re-indexed with the heading "Transfusion Reaction." Both terms were taken into account to avoid any bias in the methodology of the research

Study Inclusion and Exclusion Criteria

Studies were eligible if they reported data at least on incidence, risk factors, or outcomes of ICU patients with TACO. Both adult and PICU studies were eligible. The definition used for TACO was up to the discretion of the authors, with no specific inclusion criteria, although this information was collected (**Annexe 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/E472). As TACO has not always been a common acronym, studies reporting cases of cardiogenic (noninflammatory) pulmonary edema were included as TACO. Studies looking at any adverse transfusion reactions were reviewed, and eligible if TACO specific incidences were clearly identified. Similarly, studies conducted in a general population could be included if some data were provided for ICU patients. We did not restrict the study selection to the type of blood product (transfusion of RBCs, plasma, and/or platelets were eligible).

We included all published observational, interventional, retrospective, and prospective studies (17). We excluded abstracts and posters as the information provided was insufficient to assess the incidence of TACO and also to rule out any risk of overlap with a published study. We also excluded studies including fewer than 10 transfused patients.

In case of doubt about the ICU subgroup or the incidence calculation, we contacted the authors of the study to obtain the original information.

Systematic and narrative reviews were not included in the scoping review but were evaluated to look for other eligible references. Only articles in English or French were included.

Study Selection and Data Extraction

Two reviewers (L.D.C., N.S.) independently screened each title and abstract of the search results to determine whether the article should be fully read, based on prespecified criteria. If there was insufficient information to warrant inclusion or exclusion, reviewers included the article for further analysis.

The full manuscripts of the remaining studies were fully read independently by the two reviewers, and inclusion/exclusion criteria were noted. Discrepancies regarding study eligibility were resolved by consensus, and with a third reviewer if needed (G.E.).

Data were then extracted from included articles using a standardized report form. Quality assessment of individual studies was not done, according to the methodologic framework for scoping reviews provided by Arksey and O'Malley (17).

Statistical Analysis

The characteristics of the studies retained for the scoping review, including time and place where the study was conducted, study design, population assessed, type(s) of blood products evaluated, as well as the definition and strategy used to diagnose TACO, were taken into account.

Incidence of TACO was reported as the percentage of cases in transfused ICU patients. A pooled incidence was calculated separately in pediatric and adult studies, and reported with a 95% CI, using random effects modeling. Heterogeneity in the study data was assessed with I^2 statistics. The analysis was conducted with MedCalc (MedCalc, Ostend, Belgium). Identified risk factors and outcome data were reported using descriptive statistics.

RESULTS

Results of the Search

The initial literature extraction identified 5,926 potentially eligible articles (**Fig. 1**). Of those, 5,892 were eliminated based on the review of the title and abstract. Thirty-four full manuscripts were read. The authors from seven articles with missing data were contacted; this permitted us to keep one additional study in the analysis (18). Of the 34 full texts read, 26 were excluded because of exclusion criteria or insufficient information, as detailed in Figure 1. One article that was not found in the initial literature search was identified from the references of another article. Finally, nine studies met the inclusion criteria and were included in the scoping review (14, 18–25).

Study Characteristics

As detailed in **Table 1**, included studies were published between 1999 and 2018. Most studies were conducted in North America, one in The Netherlands. Six were conducted in adult ICUs, and three in PICUs. Five studies were prospective, four

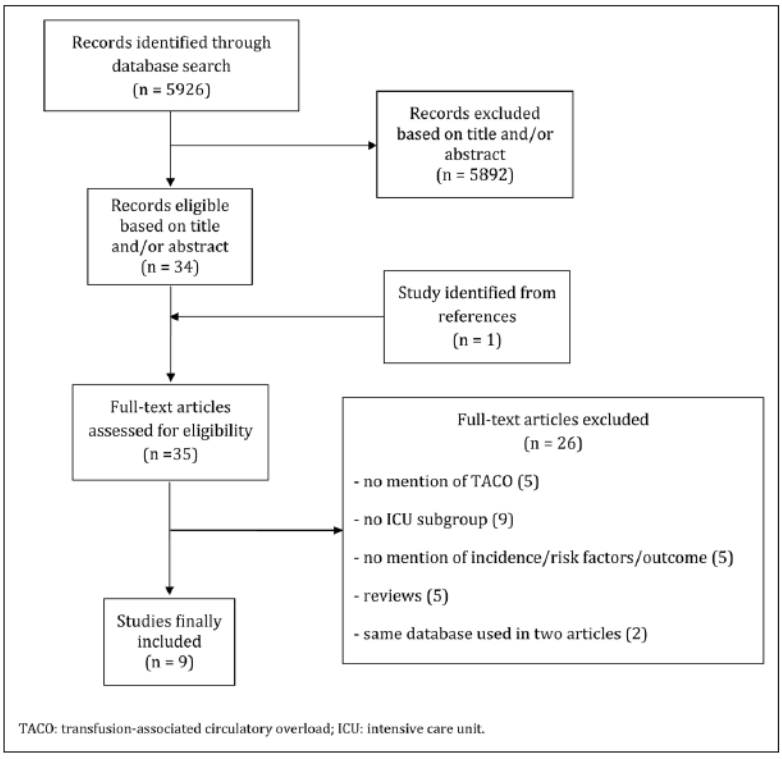

Figure 1. Study selection. TACO = transfusion-associated circulatory overload.

were retrospective including one retrospective study with prospective screening for TACO (20). Eight studies considered transfusion of any blood products, whereas one study considered only RBC transfusions.

Hébert et al (19) conducted a randomized controlled study to compare the safety of two different transfusion thresholds; we only kept the liberal arm of transfused patients so we could determine an accurate incidence of TACO.

Many sets of criteria were used to diagnose TACO, as detailed in the Appendix. Two studies used the definition of the International Society of Blood Transfusion definition (1) or of the Centers for Disease Control definition (26) while the others used locally developed definitions.

Two studies screened for cases of TACO with an electronic surveillance system (20, 24); the other ones reviewed the clinical and paraclinical data collected in the medical files.

Incidence of TACO in ICU

Seven studies reported the incidence of TACO in ICUs (Table 1 and **Fig. 2**) (14, 18–20, 22, 23, 25).

In adult ICUs, four studies including respectively 420, 901, 1,351, and 1,140 transfused patients reported 45, 51, 25, and 66 cases of TACO. The pooled incidence was 5.5% (95% CI, 2.6–9.4%), with a significant heterogeneity ($I^2 = 95.2\%$).

In PICUs, two studies that enrolled 40 and 305 transfused patients reported no cases of TACO (18, 23). A third pediatric study of 136 transfused patients reported between 2 and 104 cases of TACO according to the diagnostic criteria used (14). The pooled incidence was 0.56 % (95% CI, 0.0–2.24%) when retaining only two cases of TACO in the latter study, with nonsignificant heterogeneity ($I^2 = 53.6\%$). When we estimated the pooled incidence using the more liberal diagnostic strategy in De Cloedt et al (14) (104 cases of TACO), heterogeneity was very high ($I^2 = 99.5\%$) and the pooled incidence was 14.4% (95% CI, 11.2–82.2%).

To explore the variability in the incidence of pediatric TACO, we analyzed the methods for collecting data and the patient characteristics. The three pediatric studies diagnosed TACO using clinical and paraclinical data collected by bedside nurses (heart rate, blood pressure, respiratory rate, oxygen saturation, and fluid balance). In the study of Gauvin et al (18), nurses prospectively collected data for every patient transfused up to 4 hours posttransfusion; transfusion reactions were reviewed by experts only if reported by the nurses. In the study by De Cloedt et al (14), nurses prospectively collected data for every patient transfused but up to 24 hours posttransfusion, and the authors reviewed each case even if it was not reported as an adverse event. Agrawal et al (23) conducted a retrospective chart review to compare slow and liberal transfusion groups in stable patients only (no acute blood loss or hemolysis).

Risk Factors for TACO in ICU

As detailed in **Table 2**, four studies (20, 22, 24, 25) described risk factors of TACO in ICU patients, including two prospective and two retrospective studies. None were in PICUs.

The reported risk factors reflect both the patients' poor tolerance to fluid administration and the characteristics of transfusion. Regarding patient tolerance to fluid, positive fluid balance was a risk factor in the four studies, and preexisting cardiac or renal comorbidity was associated with TACO in three studies.

Regarding transfusion characteristics, the number, volume, and rate of transfusions were associated with TACO.

TABLE 1. Characteristics of Included Studies

References	Design	Population	Country	Blood Product Transfused	No. of ICU Patients Transfused (Cases of TACO); Incidence
Hébert et al (19)	Randomized controlled trial—liberal arm	Adult	Canada	All blood products	420 (45 TACO); 10.7%
Gauvin et al (18)	Prospective, observational	Pediatric	Canada	All blood products	305 (0 TACO); 0%
Li et al (21)	Prospective, observational	Adult	United States	All blood products	NA (51 TACO)
Li et al (22)	Prospective, observational	Adult	United States	All blood products	901 (51 TACO); 6%
Agrawal et al (23)	Retrospective, observational	Pediatric	United States	RBCs	40 (0 TACO); 0%
Murphy et al (24)	Prospective, observational	Adult	United States	All blood products	NA (22 TACO)
Bosboom et al (25)	Retrospective, observational	Adult	The Netherlands	All blood products	1,140 (66 TACO); 5.8%
De Cloedt et al (14)	Retrospective, observational	Pediatric	Canada	All blood products	136 (2 to 104 TACO [1.5–76%], depending on the diagnostic criteria used)

NA = not available, TACO = transfusion-associated circulatory overload.

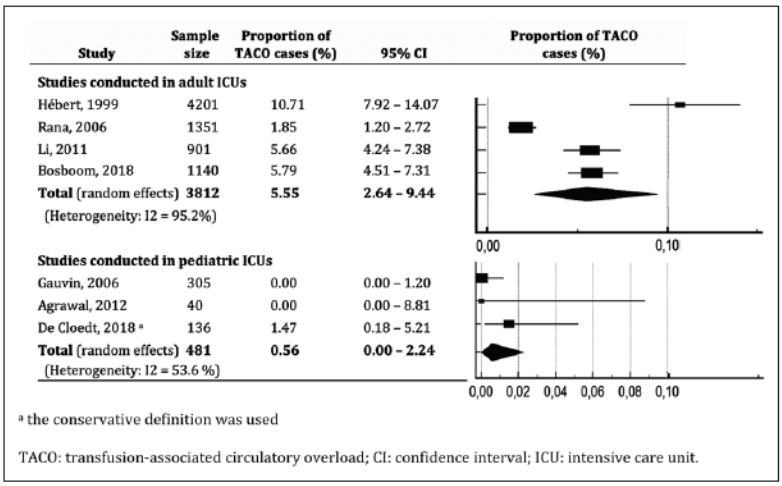

Figure 2. Estimates of incidence of transfusion-associated circulatory overload (TACO) in adult ICU and PICU. The size of the squares in the figure reflects the relative weight of each study in the global estimate (random model), determined by the study sample size and TACO prevalence. [a]The conservative definition was used.

Hemorrhagic shock was also found to be a risk associated with TACO. Two studies analyzed the type of blood products transfused (RBCs, plasma, and platelets). Plasma (two studies) and platelets (one study) transfusions were associated with TACO.

Outcomes of TACO in ICU

As detailed in **Table 3**, four studies (20, 21, 24, 25) reported outcomes of TACO in adult ICUs. TACO was associated with an increased length of stay in ICUs and in hospital. One study reported that the impact on mortality was significant in TACO, whereas two other studies reported no significant difference in mortality.

DISCUSSION

There are more and more studies about TACO, but very few studies address the problem of TACO in ICU.

In the literature, the incidence of TACO in the general population is close to 1% (3–5). In our studies, we found a pooled incidence of 5.5% in critically ill adults. This suggests that ICU patients be more at risk to developing TACO than the general population. This is probably due to the fact that ICU patients have more preexisting comorbidities that increase the risk of TACO. Furthermore, as ICU patients are often unstable, they are probably transfused more rapidly. However, it is possible that this increased frequency of TACO is attributable to a closer monitoring of ICU patients' complications posttransfusion (ascertainment bias). The studies included had significant heterogeneity and all of them reported a higher incidence of TACO in ICU patients compared with the

TABLE 2. Risk Factors of Transfusion-Associated Circulatory Overload in ICUs

Risk Factor	References	Risk
Positive fluid balance	Rana et al (20)	5.9 L vs 2.0 L ($p < 0.01$)[a,b]
	Li et al (22)	OR 1.38 (1.12–1.71)[a]
	Murphy et al (24)	Adjusted OR 9.4 (3.1–28.0)[c]
	Bosboom et al (25)	Adjusted OR 1.15 (1.07–1.24)[c]
Transfusion		
Number of transfused products	Rana et al (20)	6 U vs 2 U ($p < 0.01$)[a,b]
	Li et al (22)	OR 1.45 (1.12–1.88)[a]
	Murphy et al (24)	Adjusted OR 1.10 (1.01–1.22)[c]
Transfusion rate	Li et al (22)	OR 1.88 (1.06–3.33)[a]
Transfusion of plasma	Li et al (22)	OR 1.39 (1.07–1.80)[a]
	Rana et al (20)	40% vs 14% ($p < 0.01$)[a,b]
Plasma transfused for anticoagulation reversal	Li et al (22)	Adjusted OR 4.31 (1.45–14.30)[c]
Volume of plasma transfused	Li et al (22)	OR 4.88 (1.55–15.36)[c]
	Rana et al (20)	(Female) 0.17 L vs 0.04 L ($p < 0.01$)[a,b]
		(Male) 0.33 L vs 0.07 L ($p < 0.01$)[a,b]
Transfusion of platelets	Rana et al (20)	32% vs 7% ($p < 0.01$)[a,b]
Cardiovascular comorbidities		
History of heart failure	Murphy et al (24)	Adjusted OR 6.6 (2.0–21.0)[c]
	Bosboom et al (25)	Adjusted OR 2.4 (1.2–4.6)[c]
Preexisting left ventricular dysfunction	Li et al (22)	Adjusted OR 8.23 (3.36–21.97)[c]
Cardiology referral	Bosboom et al (25)	Adjusted OR 13.6 (5.1–35.7)[c]
Cardiothoracic surgery referral	Bosboom et al (25)	Adjusted OR 8.8 (3.7–20.7)[c]
Renal comorbidities		
Chronic renal failure	Murphy et al (24)	Adjusted OR 27 (5.2–143.0)[c]
	Li et al (22)	OR 2.87 (0.89–11.08)[a]
Continuous venovenous hemofiltration before transfusion	Bosboom et al (25)	Adjusted OR 3.2 (1.2–8.9)[c]
Hemorrhagic shock	Murphy et al (24)	Adjusted OR 113 (14–903)[c]
Age	Murphy et al (24)	Adjusted OR 0.78 (0.62–0.99)[c]
	Li et al (22)	OR 0.99 (0.96–1.02)[a]

OR = odds ratio (95% CI).
[a]Univariate analysis.
[b]Transfusion-associated circulatory overload vs controls.
[c]Multivariate analysis.

1% observed in the general population. The study by Hébert et al (19) reported the highest incidence (10.7%). This could be partly explained by the fact that these patients were treated using the liberal transfusion strategy (every patient was transfused if the hemoglobin level fell under 9 g/dL). Furthermore, as the study was a randomized controlled trial, patients were probably very closely monitored for any adverse reactions.

Contrastingly, two pediatric studies reported no cases of TACO (incidence of 0%). This absence of pediatric TACO cases could be explained by the fact that the definition is not adapted to pediatric patients (14) which makes the diagnosis much more difficult. This is supported by the study by De Cloedt et al (14), which reported major differences in incidence rates (from 1.5% to 76%) depending on the diagnostic

TABLE 3. Association Between Transfusion-Associated Circulatory Overload and Outcomes

Outcome	References	Risk
Increased ICU length of stay	Rana et al (20)	7.1 d vs 1.6 d ($p < 0.05$)[a,b]
	Li et al (21)	3.0 d vs 1.7 d ($p < 0.05$)[a,b]
	Murphy et al (24)	HR for discharge 0.37 (0.26–0.53)[c]
	Bosboom et al (25)	7.2 d vs 4.3 d ($p < 0.01$)[a,b]
Increased ventilation time	Bosboom et al (25)	118 hr vs 61.5 hr ($p < 0.01$)[a,b]
Increased hospital length of stay	Li et al (21)	9.4 d vs 6.1 d ($p < 0.05$)[a,b]
	Murphy et al (24)	HR for discharge 0.64 (0.48–0.86)[c]
	Bosboom et al (25)	15.9 d vs 14 d (p = NS)[a,b]
Mortality		7.8% vs 11.8% ($p = 0.73$)[a,b]
In-hospital mortality	Li et al (21), Murphy et al (24)	HR 3.20 (1.23–8.10)[c]
Mortality at 28 d	Bosboom et al (25)	22.7% vs 18.8% (p = NS)[a,b]
Mortality at 90 d	Bosboom et al (25)	27.3% vs 24.4% (p = NS)[a,b]
1-yr mortality	Li et al (21)	38% vs 28% ($p = 0.37$)[a,b]
2-yr mortality	Li et al (21)	44.9% vs 38.8% ($p = 0.51$)[a,b]

HR = hazard ratio (95% CI), NS = not significant.
[a]Univariate analysis.
[b]Transfusion-associated circulatory overload vs controls.
[c]Multivariate survival analysis.

criteria used. This retrospective study confirms that TACO exists in PICUs and seems quite frequent, in stark contrast to what we found in the other studies. Furthermore, the two pediatric studies reporting no cases of TACO included relatively few patients as compared with the adult studies (40 and 305, respectively) and did not use an electronic surveillance system; TACO cases could thus have been missed by bedside nurses or attending physicians. Furthermore, Agrawal et al (23) included only stable patients with no acute blood loss; no patient presented with cardiopulmonary dysfunction before transfusion and nearly half of them received diuretics close to the transfusion. This excludes an important part of at-risk population.

All studies included in this review detailed the TACO definition they used and we observed many variations. Only two of them (14, 24) used published definitions by the Centers for Disease Control and the International Society of Blood transfusion. The seven others used diagnostic criteria of TACO like circulatory overload and cardiac congestion. Such variation in TACO definitions is a limit of our study, but it can explain part of the spectrum of reported TACO incidences and TACO-related outcomes. A universally accepted definition of TACO in ICU patients is required to standardize future studies.

The ISBT definition (27) that is in the process of development seems to be the most adequate as it includes clinical, paraclinical variables, and also biomarkers such as brain natriuretic peptide. More studies are required to validate this definition in pediatrics, in particular as no one has looked into brain natriuretic peptide in pediatric TACO. Nevertheless, operational criteria should be specified, in particular with specific thresholds to define clinical variables like tachycardia, hypertension, or positive fluid balance. As suggested by De Cloedt et al (14), the use of pre- and post-transfusion changes in the variables instead of absolute values may improve the discrimination performance of the definition.

TACO and transfusion-related acute lung injury (TRALI) are both clinical syndromes that share several characteristics: acute respiratory distress following a transfusion and pulmonary edema. They, however, differ in other aspects. Fluid overload is one cornerstone for TACO diagnosis, although it is an exclusion criterion for TRALI, in which the lung edema is inflammatory. Cardiovascular changes are part of TACO criteria but not of TRALI. The studies included in this review all distinguished TACO from TRALI. However, there is a potential overlap between both conditions, and we cannot exclude that some reported TACO were misdiagnosed. The development of a future definition for TACO should also take this aspect into account and facilitate the distinction between both entities.

Only two studies used an electronic surveillance system to detect TACO. As ICU patients are extensively monitored, computerized screening based on electronic medical records may help to detect cases more rapidly and efficiently. Further studies should explore this potential avenue for the identification of TACO in ICUs.

We found four studies describing the risk factors of TACO in ICU with relatively consistent results. Factors that are mostly associated with TACO were positive fluid balance,

characteristics of the transfusion linked with fluid overload (volume and speed of transfusion), and comorbidities (cardiovascular and renal). As TACO is defined as pulmonary edema due to circulatory overload, the importance of preexisting positive fluid balance and cardiovascular dysfunction is not surprising. Thus, it is reasonable to pay particular attention to the development of respiratory distress when transfusing patients with these conditions. The volumes transfused and the transfusion rates are also reported as risk factors of TACO. We may therefore speculate that ICU patients should be transfused less frequently and as slow as possible. It has been well established that lower transfusion thresholds in ICUs are safe in both adult and PICUs (19, 28–30). Decreasing the amount of blood transfusions should be a priority and will limit the population at risk of transfusion-related complications, including TACO.

Furthermore, the type of blood product transfused is detailed in only two studies (20, 22). Transfusion of plasma is reported to be a risk factor for TACO in both studies. The existing data do not permit to ascertain if this association is related to specific properties of the plasma, or rather explained by a confounding association (e.g., the plasma being transfused in conditions at higher risk of TACO). In addition, transfusion of plasma may be different in terms of volume and rate (in addition to different indications). Future studies should further explore the respective importance of the different blood product characteristics regarding their association with TACO.

There are no studies reporting risk factors for TACO in PICUs. The risk factors reported in adults are also often present in PICU patients. We may speculate that in their presence, critically ill children might be at higher risk for TACO. However, PICU and adult ICU patients have important pathophysiologic differences. Further research is warranted to explore specific pediatric risk factors of TACO.

We observed that TACO was associated with adverse outcomes. Importantly, those outcomes are difficult to interpret, as ICU patients are already critically ill, and performing transfusions is correlated with the severity of the patient's underlying condition. The included studies reported associations but no causalities. However, the four studies describing outcomes of TACO reported consistently an increased length of ICU stay, and two reported an increased length of stay in hospital. Concerning mortality, results were not consistent, with one study reporting a significant increase in mortality rate (24) and two others reported no significant difference (21, 25).

Even if these are only associations, it remains that all studies included in this scoping review reported less favorable outcomes in patients with TACO, which justifies improving not only the prevention but also the diagnosis and management of TACO.

CONCLUSIONS

We found only few studies describing incidence, risk factors, and outcomes of TACO in ICU patients even if this population seems to be at higher risk. The pooled incidence of TACO in adult ICUs was particularly high, compared with the general population. TACO is associated with adverse outcomes. The identification of TACO in PICUs appears suboptimal.

We need more studies concerning TACO in ICU patients, more so in PICU patients. A more operational definition of TACO adapted to pediatric patients is crucially needed.

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