

## RESEARCH ARTICLE

## Acute Unfavourable Transfusion Outcomes in Children: Frequency and Pattern in Resource Limited Settings

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### Abstract

Unfavourable transfusion outcomes (UTOs) compromise the efficiency and safety of blood transfusion in sub-Saharan Africa burdened by financial inaccessibility to advanced transfusion reaction prophylaxis. To provide less sophisticated solutions, it is important to know the frequency and pattern of these unfavourable transfusion outcomes especially amongst children who account for more than half of transfusions here. This study monitored the occurrence of acute unfavourable transfusion outcomes in paediatric blood receivers at the Mother and Child center of the Chantal Biya foundation. A retrospective and descriptive cross-sectional design was employed. A structured data extraction form was used to collect information from 831 complete patient files of transfused children during the study period. Data was processed using IBM-SPSS version 22.0 . Variables were analysed using descriptive statistics and associations were derived with inferential statistics. UTOs occurred after 20% of blood transfusions. In decreasing order of frequency; Febrile non-haemolytic reactions (10.2%), allergies (3.3%), circulatory overload (2.6%), acute lung injury (1.2%), sepsis (1.2%), Dyspnoea (1.0%) and unclassifiable transfusion reactions (0.4%) were observed. Their pattern of occurrence varied with the nature of UTO, being observed as early as four minutes following transfusion or as late as 39 hours after. This variation also concerned their duration, disappearing as soon as four minutes after for some kinds of UTOs or lasting up to six days for others. One third of UTOs were severe, almost all being highly imputable to the transfusion process. UTOs occurred more in younger children and always lengthened hospital stay. This indicates that transfused children in our setting manifest six times more transfusion unfavourable outcomes and suffer 200 times more from severe hazards of transfusion than do transfused children in richer settings. Organisation commitment and good blood transfusion practices should be fostered to improve paediatric blood transfusion safety.

**Keywords:** Unfavourable Transfusion Outcomes; Pediatric Transfusion Safety; Hemovigilance

## Introduction

The occurrence of acute unfavourable transfusion outcomes (UTOs) continues to mar the alleviation of blood transfusion indications. [1] In sub Saharan Africa, financial inaccessibility to advanced transfusion reaction prophylaxis such as pre storage leucocyte reduction, red cell washing and pathogenic inactivation is characteristic and often accused for the alarming levels of UTOs.[2] Meanwhile, blood transfusion services are not sufficiently committed to the provision of even affordable blood banking equipment that may reduce the occurrence of transfusion reactions. [3] In order to accurately propose less sophisticated methods of preventing UTOs in sub-Saharan Africa, their pattern of occurrence in this setting must first be known. Especially amongst children blood receivers who alone account for 63.5% of transfusions here. [2] Unfortunately, the rareness of hemovigilance systems in sub-Saharan Africa limits the reporting of UTOs such that indicators of blood transfusion safety are inadequate. [4,5] This study was conducted to fill in this gap by monitoring the occurrence of acute unfavourable transfusion outcomes in paediatric blood receivers at the Mother and Child Center of the Chantal Biya Foundation (MCC/CBF). Specific objectives were to describe the different kinds of UTOs and their pattern, to grade their severity, to assess their imputability to transfusion as well as to identify any possible determinants of their occurrence.

## Materials and Methods

We carried out a retrospective cross-sectional study over a 25-month period from 1<sup>st</sup> January 2016 to 31<sup>st</sup> January 2018. Ethical clearance was gotten from the ethics committee of the Faculty of Medicines and biomedical sciences. Administrative authorisation was obtained from the directorate of the MCC/CBF. Upon admission of children, a written informed consent had been gotten from their parents allowing for use of their data for research purposes. For this study, the identity of patients was kept confidential. We Used hospital ward registers to create a list of transfusions carried out during our study period, then searched for patient records in hospital archives. We screened all records of admitted children who received blood transfusion and retained only those with complete patient and blood bag identity and with records of patient follow up before, during and after their blood transfusion. Using the ISBT (International society of blood transfusion) adverse event definitions, [7] we classified unfavourable transfusion outcomes, monitored their pattern, graded their severity and assessed their imputability to the transfusion process. Information for each patient was copied into pre-established data extraction forms. Data was entered and analysed using IBM-SPSS version 22.0 and exported to Microsoft Excel 2013 for table and figure representation. Results were presented as mean and standard deviation for quantitative variables and as frequencies and percentages for qualitative variables. Association was done using Fischers Exact and Chi-square test. All P values less than 0.05 were considered statistically significant.

## Subjects Studied

Of the 1312 registered transfusions, we found 1018 records in the archives. 187 Files were excluded for incompleteness, leaving us with 831 transfused children files to study. Patient age ranged from one day to 17 years with an average of three years old. More boys were transfused than girls with a sex ratio (male:female) of 1.4:1. Hospital stay of transfused children ranged from 2 to 13 days with most transfused children staying in hospital for three days. severe malaria accounted for 65.9% of transfusions. Respiratory tract infections for 9.8%, sepsis for 9.7% , complications of sickle cell anaemia for 7.8% and other pathologies accounted for 6.8% of transfusions.

Donor blood was banked in five different hospital blood banks. Only 1.1% of transfused blood bags were voluntarily donated. Donor blood storage age ranged from 0 to 35 days with an average of 7 days. Transfusion delay ranged from 55 minutes to 240 minutes with an average of 103 minutes. 93.3% of transfusions were indicated for management of severe anaemia, 5.5% for severe pancytopenia, 1.1% for hypovolemic shock and 0.1% for severe thrombocytopenia. However, no erythrocyte concentrate was administered because resources for component separation of whole blood into packed red blood cells were rare. As such, 99.9% of patients received whole blood and 0.1% received platelet concentrates.

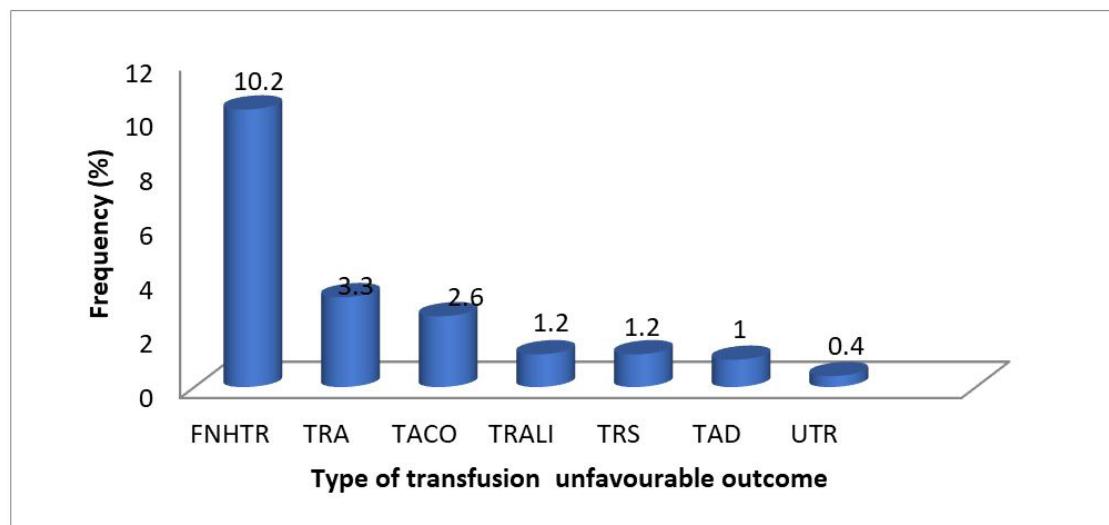
Of 831 transfusions, 769 (92.6%) were isogroup-isorhesus, 53 (6.4%) were aniso group-isorhesus, 7 (0.9%) were isogroup-aniso rhesus and 1 (0.1%) was anisogroup-anisorhesus.

Pre transfusion blood bag temperatures were unknown as they were transported from the blood bank to hospital ward in coolers or trays with neither thermostat nor thermometer. Blood transfusion protocols varied from one hospital ward to another. In general, 86% of donor blood units were cross matched with patient's blood at bedside prior to transfusion. 16.1% of patients received transfusion adverse reaction prophylaxis: 7.5% received furosemide in the course of transfusion, 5.7% received dexamethasone 15 minutes prior to transfusion and 1.8% received both furosemide and dexamethasone. Blood units were transfused for one to 12 hours with average transfusion duration of 4 hours. After transfusion, 94% of children were discharged healthy, 4.8% were discharged on parent request against medical advice and 1.2% died.

## Results

### Frequency of UTO's

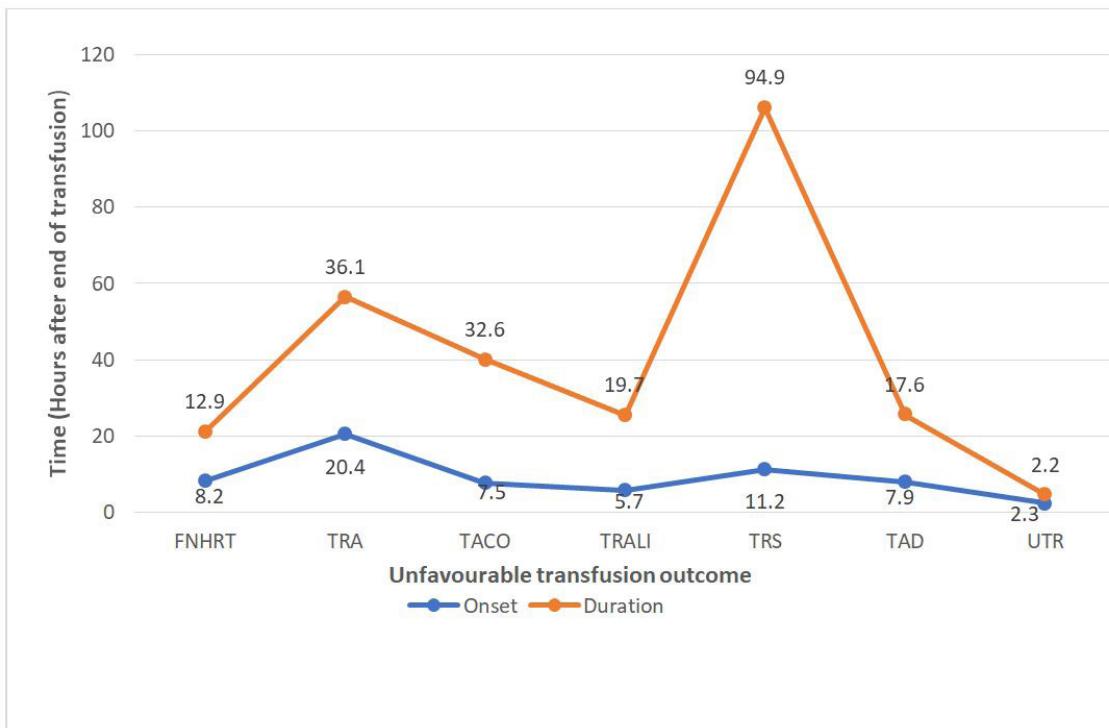
Of 831 transfused children, 166 (20%) presented unfavourable outcomes. In decreasing frequency of occurrence, we observed 10.2% Febrile non haemolytic transfusion reactions (FNHTR), 3.3% Transfusion Related Allergies (TRA), 2.6% Transfusion associated circulatory overload (TACO), 1.2% transfusion related acute lung injury(TRLI), 1.2% transfusion related sepsis (TRS), 1.0 % transfusion associated dyspnoea (TAD) and 0.4 % unclassifiable transfusion reactions (UTR). See Figure 1.



**Figure 1:** Occurrence of unfavourable transfusion outcomes in decreasing order of frequency

### Pattern of UTOs

FNHTR averagely occurred 8.2 (range: 0.7 – 17.1) hours after the onset of transfusion and lasted 12.9 (range 3.3 – 22.6) hours. TRA occurred 20.4 (range 3.3 – 39.2) hours following the start of transfusion and subsided 36.1 (range 15.4 – 56.6) hours after. TACO begun 7.5 (range 2.3 – 12.7) hours after the start of transfusion and was averagely relieved 32.3 (range: 6.5 – 58.1) hours after. Occurrence of TRALI was observed averagely 5.7 (range 2.6 – 8.8) hours after the launch of transfusion and ended 19.7 (range 4.2 – 35.2) hours after. TRS occurred 11.2 (range 0.6 – 21.8) hours after the start of transfusion and was remedied 94.9 (range 50.9 – 138.9) hours after. TAD averagely occurred 7.9 (range 4.7 – 11.1) hours following the start of transfusion and subsided 17.6 (range 4.2 – 31) hours after. UTR occurred 2.3 (range 1 – 3.6) hours following the start of transfusion and lasted averagely 2.2 (range 0.7 – 3.7) hours. See Figure 2.



**Figure 2:** Onset and duration of observed unfavourable transfusion outcomes

### Severity and Imputability of UTO

Generally, 71.2% of unfavourable transfusion outcomes were of low severity (Grades 1 and 2) and 28.8% of moderate to high severity (grades 3 and 4). 92.8% of observed unfavourable outcomes were highly imputable (definite and likely) to the transfusion process and 7.2% were of low imputability (possible). See Table 1.

	Imputability			Severity			
	Definite	Likely	Possible	Grade1	Grade2	Grade3	Grade4
FNHTR	34	46	5	48	31	4	1
TRA	<b>14</b>	14	0	1	26	1	0
TRALI	6	4	0	0	0	10	0
TACO	15	5	2	0	6	<b>16</b>	0
TAD	2	5	1	0	3	5	0
TRS	1	8	1	0	1	9	0
UTR	0	0	3	0	1	1	1
Total n (%)	72 (43.4)	82 (49.4)	12 (7.2)	50 (30.1)	68 (41.0)	46 (27.7)	2 (1.2)

**Table 1:** Imputability and severity of observed unfavourable transfusion outcomes

### Determinants of UTOs

The general occurrence of unfavourable transfusion outcomes in this study was significantly associated to patient age ( $p=0.01$ ), transfusion duration ( $p=0.0$ ) and hospital stay ( $p=0.0$ ). Meanwhile, the overall occurrence of an unfavourable transfusion outcome was not associated to the following variables: Patient gender( $p=0.15$ ); patient blood group ( $p=0.05$ ); patient history of transfusion ( $p=0.33$ ); transfusion indication ( $p=0.09$ ); blood product received ( $p=0.50$ ), blood quantity ( $p=0.16$ ) blood bag source ( $p=0.97$ ); blood storage age ( $p=0.10$ ) and transfusion delay( $p=0.51$ ).

## Discussion

In this study, classification of unfavourable transfusion outcomes was done according to standard ISBT definitions. As such, the UTO diagnosis of the health care worker was not always in accordance with ours. From patient records, we noticed that most cases of FNHTR, immediate transfusion allergies and TACO were un recognised.. This often occasioned prescription of several workups, the extra cost for which, often caused parents to withdraw their children from the hospital. It is thus necessary to sharpen the consciousness of health care providers on the recognition of all kinds of UTO and to establish a contextualised, standard transfusion reaction panel which is key to cost effective management of UTOs in settings where even financial access to blood transfusion is a challenge. [8]

The 20% occurrence of UTOs we observed is a regression when compared to prior studies conducted in Cameroon. [2,9] However, the preponderance of FNHTR and TRAR has remained. FNHTR are defined by a  $\geq 1^{\circ}\text{C}$  increase in temperature from pre-transfusion temperature associated or not to chills, myalgia and/or nausea within four hours of completion of transfusion. [10] FNHTR are known to occur when antibodies in recipient plasma and Human leucocyte antigens and /or granulocyte antigens interact to release endotoxins that act on the hypothalamus to stimulate a fever. [11] This hypothalamic stimulation can also be induced by leucocyte cytokines that are produced during storage of blood especially in warmer temperatures [12]. No doubt the chance of occurrence of FNHTR increases by 6.7% after every extra day of blood storage beyond three days. [13,14] This association between occurrence of UTO and blood shelf was not observed in our study, probably because most blood units transfused had been stored for only two days.

TRA on the other hand is the occurrence of two or more of :rashes, urticaria, flushing, bronchospasm, angioedema, hypotension and anaphylaxis four hours on cessation of transfusion. [15] These reactions are usually caused by hypersensitivity to allogeneic proteins in plasma, on leukocytes or platelets or, uncommonly, to soluble allergens found in the transfused blood component. [16] Many studies have shown greater incidence of TRA in patients with a history of transfusion. [17] That this was not the case in our study may be due to the quasi-systematic administration of dexamethasone to children who had been transfused before.

In our study severe hazards of transfusion (SHOTs) were observed after 5% of blood transfusions. Here shots included TACO (2.6%), TRALI(1.2%) and TRS(1.2%). Other studies amongst adult blood receivers in Cameroon found the frequency of SHOTs to range between 0.05% [2] to 2.04%[9]. These findings are similar to those of Oakle et al in richer settings who found SHOTs to occur three times more in children than in adults (0.029% VS 0.077%).[18] However, after transfusion of children, SHOTs occur 200 times more frequently in our setting than it would in Oakle's setting. This stresses the need for SSA to catch up with the global strive for paediatric blood transfusion safety.

TACO is defined as new acute respiratory distressed , tachycardia, increased blood pressure, evidence of positive fluid balance and/or pulmonary oedema[7] during or within -six hours after transfusion[19]. TACO is usually caused by transfusing a large volume of blood too rapidly [15]. During our study period, pediatric blood bags were lacking and all children were transfused from adult blood units. Transfusion was halted, and the remaining blood discarded, after a visually estimated fraction of blood, supposedly corresponding to the child's need had been infused. Apart from gross wastage of already rare blood [20], this malpractice holds the risk of transfusing a larger than required volume of blood to the child. This volume overload is increased with transfusion from blood bags potentially overfilled during collection without automatic cut-off meters, as is routine in our resource limited setting [21]. Also, the absence of resources to separate whole blood into components imposed the TACO -predisposing malpractice of addressing severe anaemia with whole blood rather than with erythrocyte concentrates [22].

The diagnosis of TRALI was made when we observed during or within six hours following transfusion, acute onset hypoxemia with bilateral infiltrates on frontal chest radiograph (when present) without signs of circulatory overload in a patient without prior risk factors for acute lung injury [7] Although transfusion related acute lung injury has been hypothesised to be caused by cytokines and antibodies in donor blood that lead to neutrophil activation in blood recipient with underlying endothelial and genetic

factors, [23] the actual mechanism is still unclear. [24] That this SHOT most accused globally for post transfusion mortality [25] accounted for 6% of UTOs in our context raises concern. Could it be that besides the acknowledged underreporting of TRALI [26] sub Saharan children, especially those suffering from malaria, lack or possess endothelial factors that favour the occurrence of TRALI? However, more research is needed in sub Saharan Africa to throw light on this question.

Transfusion related sepsis was recognised when high grade fever greater than 39.5°C , tachycardia, tachypnea and signs of organ dysfunction were observed. [27] This accounted for 6% of UTOs in our study and is consistent with studies in sub Saharan Africa which reveal that 8.8% of blood bags destined to children are bacterial contaminated. [5] Although the risk of symptomatic TRS in adults has been reported to be as low as 1: 250000 units of packed red blood cells [28], we believe that owing to lower levels of immune competence, children of SSA will be less resilient to bacteria from contaminated blood units.

We recognised UTOs as transfusion associated dyspnoea when acute respiratory distress occurred within 24 hours of cessation of transfusion and did not meet the definitions of an allergic reaction, transfusion associated circulatory overload nor transfusion related acute lung injury.[29] These were mainly mild, overlap transfusion reactions and accounted for 4.8% of UTO in our study. However mild, UTO should be avoided as they add to the suffering of the patient.

Unclassifiable transfusion reactions were observed adverse effects temporally related to transfusion which could not be classified according to an already defined transfusion reaction and with no other risk factor nor cause other than transfusion.[7] This accounted for 1.2% of UTOs and mainly presented as first-time afebrile convulsions in children who were not at risk of doing so. More research to define the pathogenesis of such convulsions will be useful.

We found low patient age and weight to be associated with UTO occurrence. Similar findings by other researchers [30] indicate a need to adjust formulae for blood requirements in paediatrics.

In consistency with other studies [31], we found that the occurrence of UTOs lengthened hospital stay and increased morbidity of transfused children. Meanwhile post transfusion deaths in this study could not be imputed to the transfusion process, but rather to a complication of the disease for which the patient was admitted. This emphasizes the need for timely access to blood transfusion which when delayed may no longer save the life of the recipient. [32,33]

Nevertheless, The six fold occurrence of UTOs in children we observed compared to those of authors in more developed settings [34] points out the need for extra effort towards blood safety in sub-Saharan Africa. In richer settings, leucocyte filtration, volume reduction, red cell washing and/or pathogen inactivation have brought down the occurrence of UTOs to only 0.03- 2.11% . [35] That resources are limited and organisation commitment is lacking in sub-Saharan Africa is no acceptable excuse. We do not necessarily need sophisticated mechanisms to reduce UTOs and their burden .[2] Who can say if only the consistent use of paediatric blood bags and of automatic cut-off meters for blood collection will not decrease the occurrence of pulmonary UTO in children? Who knows if strict observance of good blood banking practices alone would suffice to curb bacteria associated UTOs?... As it is, the importance of more research in the quest for blood safety in SSA cannot be overstated.

## Conclusion

In a nutshell, UTO followed 20% of blood transfusions in children. The seven types observed in decreasing frequency of occurrence were FNHTR, TRA, TACO, TRS, TRALI, TAD and UTR. Their pattern varied with the nature of UTO, being observed as early as four minutes following onset of transfusion for some or as late as 39hours after the start of transfusion for others. This variation also concerned their duration, disappearing as soon as four minutes after for some kinds of UTOs or lasting up to six days for others. One third of UTOs were of high severity, almost all being highly imputable to the transfusion process. UTOs occurred more in younger children and always lengthened hospital stay.

## **Data Availability**

The corresponding author will be ready to provide all data obtained from this study.

## **Conflict of Interest**

We declare no conflict of interest regarding this study or its publication.

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