TRANSFUSION COMPLICATIONS
Acute transfusion reactions at a national referral hospital in Uganda: **a prospective study**

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ABBREVIATIONS

FNHTR(s) = febrile nonhemolytic transfusion reaction(s);
MNRH = Mulago National Referral Hospital;
TACO = transfusion-associated circulatory overload;
LR = leukoreduction;
SSA= sub-Saharan Africa;
UBTS = Uganda Blood Transfusion Services;
WB = whole blood.

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ABSTRACT

BACKGROUND

Very little has been published about acute transfusion reactions (ATRs) in developing countries. This study was undertaken to determine the incidence, type, imputability, severity, and possible associated factors of ATRs observed in a university- affiliated hospital in Uganda.

STUDY DESIGN AND METHODS

We prospectively followed the transfusion of blood units issued over a 7-week period from the hospital blood bank during regular working hours to nonbleeding patients. For each transfusion, we recorded the patient's status before, during, at the end of, and 4 hours after transfusion. Three physicians independently reviewed all reports of suspected ATRs and related hospital charts. Using pre- defined criteria, the presence, type, imputability, and severity of ATRs were adjudicated by consensus of two of three physicians. Factors potentially associated with ATRs were analyzed for statistical significance.

RESULTS

A total of 507 transfusions were analyzed. Fifty-three acute transfusion events were recorded and 49 of 53 or 9.6% of the 507 transfusions were con- firmed to be ATRs by physician consensus: 24 febrile, seven allergic, five hypertensive, three hypotensive, three transfusion-associated circulatory overload, two acute hemolytic, and five others. Imputability of ATRs was definite, probable, or possible in 45 of 49 ATRs (92% of ATRs or 8.9% of transfusions) and judged to be severe in nine of 45. No significant associated factors were identified.

CONCLUSIONS

Our findings suggest that ATRs may occur more commonly in resource-limited settings than in high-income countries. Although some reactions are unavoidable, improved surveillance of transfusions and implementation of transfusion guidelines could improve the safety of transfusions in these settings.

INTRODUCTION

Blood transfusion is an indispensable component of clinical medicine in both high-income and resource-limited countries. Nevertheless, transfusion can lead to serious adverse events.

Acute transfusion reactions (ATRs) are defined as adverse events associated with transfusion that occur within 24 hours of the transfusion, with most occurring during or within 4 hours of a transfusion. Over the past 20 to 30 years ATRs have been extensively studied in high-income countries. The incidence, including trends over time, as well as the etiology and pathophysiology are now known for several types of ATRs. Such studies, together with educational and hemovigilance programs, have contributed to increased transfusion safety, for example, through changes on the blood supplier side such as the introduction of prestorage leukoreduction (LR) of cellular blood components, transfusion-associated acute lung injury (TRALI) reduction measures and bacterial testing of platelet (PLT) components and, on the hospital side, through increased awareness of the importance of transfusion administration protocols, transfusion monitoring, and the reporting of adverse transfusion events. However, there have been very few published studies addressing ATRs in resource-limited settings, in general, and in sub-Saharan Africa (SSA) in particular, and those that are available report extremely different results. In retrospective studies from Uganda and Ghana, transfusion reactions were recorded for 0.6 and 0.8% of patients who received transfusions, respectively, while the investigators of prospective studies performed in Nigeria and Cameroon reported that ATRs occurred in, respectively, 8.7 and more than 50% of transfusions.1-4 This study was undertaken to determine the incidence, type, imputability, severity, and possible associated factors of ATRs observed in a university- affiliated hospital in Kampala, Uganda.

MATERIALS AND METHODS

Study design

This was a prospective observational study conducted between November 1 and December 24, 2011.

Study site and population

The study site was Mulago National Referral Hospital (MNRH) in Kampala, Uganda. MNRH, a publically funded hospital, is Uganda's major referral hospital and the teaching hospital for Makerere University Medical School. The study targeted pediatric and adult patients on the medical, surgical, obstetrical, and gynecological wards who were not acutely bleeding and who could be monitored before, during, and for 4 hours after the end of the transfusion. Neonates; patients with acute bleeding, including patients with surgical, obstetrical, or traumatic bleeding; and patients in the intensive care unit were not included due to the difficulty of monitoring all phases of the transfusion episode. Patients receiving cancer chemo- therapy and patients with cardiac illnesses are served by two separate entities located within the MNRH complex; these sites were not included in this study. Patients to be approached for inclusion in the study were identified in the blood bank when a request for transfusion was received. Patients were consecutively recruited during daytime hours (0800-1800 hr) on regular working days (Monday to Friday). The periods were chosen to ensure that all transfusions could be monitored up to 4 hours after the end of transfusion; available resources did not allow us to perform this monitoring outside these time periods. Patients were not enrolled more than once in any 24-hour period but could be enrolled more than once if the transfusions were separated by more than 24 hours.

Transfusions

A transfusion was defined as single transfusion episode of red blood cells (RBCs) or whole blood (WB). No other blood products were included in this study. All blood was supplied by Uganda Blood Transfusion Services (UBTS). All UBTS donations are provided by anonymous, volunteer blood donors; all units are tested serologically for human immunodeficiency virus, hepatitis B and C, and syphilis (and found negative) before issue to hospitals. No testing for malaria is performed. WB is stored in CPDA-1. RBCs are prepared by UBTS in a closed system: 3 RBC units, stored in additive solution (AS), are made from one WB donation. The blood collection sets do not include diversion pouches and units are not LR. Whenever possible, young children are transfused with RBCs rather than WB. Pretransfusion testing consists of determining the blood recipient's ABO and RhD group/type and performing a room temperature cross-match using the tile technique. (Such limited pretransfusion testing is common practice in Uganda and many other low-income settings.) Three units included in this study were given before completion of pretransfusion procedures.

Clinical data

Clinical data were collected and recorded on a detailed case report form at the time of transfusion by research assistants (three nurses, one physician assistant), all of whom were trained and supervised by one of the physician investigators. For each patient, the following patient data were recorded: name, age, clinical ward, major diagnosis, and blood group. For each transfusion, the following transfusion data were recorded: unit type (WB or RBCs), group, unique number, and expiry date; patient's vital signs (respiratory rate, heart rate, blood pressure, and temperature) immediately before beginning the transfusion, at 15 minutes and 1 hour after the start of the transfusion, at the end of transfusion, and at 4 hours after the end of the transfusion. A transfusion event was defined as an increase in temperature of at least 1°C, a change in systolic or diastolic blood pressure of at least 20 mmHg, or any other change in vital signs that the research assistant considered potentially clinically significant and/or the occurrence of any new symptom(s) or sign(s) during or in the 4 hours after the completion of the transfusion. For all transfusion events the patient was also evaluated at 24 hours after the transfusion.

Management of transfusion events

In case of occurrence of a transfusion event, the research assistant stopped the transfusion and informed the primary care staff responsible for the patient. Venous access was maintained and verification of patient identity and blood component was performed. Patients received further treatment depending on the type of transfusion event using published algorithms and according to the orders of the attending physician5. In selected cases pretransfusion testing was repeated. However limited resources did not allow us to perform full transfusion reaction investigations such as blood cultures, biochemistry testing, or chest X-rays.

Diagnosis of ATR

The diagnosis of ATR was adjudicated by three physicians (an internal medicine trainee with specific training related to ATRs, an internist with hematology and transfusion medicine training and experience, and a hematologist with transfusion medicine expertise) who independently reviewed the case report forms of all transfusion events and the corresponding patient charts. Using predefined criteria based on published definitions, the physicians reported independently, on an adjudicating form, their opinion as to whether or not the reported transfusion event represented an ATR and if so the type of ATR.[6,7] With respect to febrile reactions,

fever due to transfusion was defined as an increase in temperature of at least 1°C to a temperature of at least 38°C not considered to be due to the underlying illness. However, because recording of a patient's evolution in the chart notes often lacks details, and laboratory investigations for bacterial or malarial contamination were not performed, febrile reactions (other than those considered to be hemolytic ATRs) were not further categorized as febrile nonhemolytic transfusion reactions (FNHTRs) versus septic (or other) reactions but were simply called febrile reactions. The adjudicating physicians determined the imputability and severity of each ATR using definitions shown in Table 1. Final diagnosis was confirmed by the adjudicating process (Delphi method) with a consensus of at least two of the three physicians.8

TABLE 1: Definitions of imputability and severity of ATRs

Imputability	
Definite:	Conclusive evidence beyond reasonable doubt that the adverse reaction can be attributed to the transfusion.
Probable:	Evidence is clearly in favor of attributing the adverse reaction to the transfusion.
Possible:	Evidence is indeterminate for attributing the adverse reaction to the transfusion or to an alternate cause
Doubtful:	Evidence is clearly in favor of attributing the adverse reaction to causes other than transfusion.
Ruled out:	Conclusive evidence beyond reasonable doubt that the adverse reaction can be attributed to causes other than the transfusion.
Severity	
Grade 1:	No treatment or requires only symptomatic relief (nonsevere).
Grade 2:	Prolonged hospitalization and/or medical treatment to prevent injury (severe).
Grade 3:	Major intervention required, e.g., vasopressors or transfer to intensive care unit.
Grade 4:	Death after an ATR.

The following factors were analyzed, using bivariate and multivariate analysis to determine if they were significantly associated with the occurrence of an ATR: age less than 13 or 13 years or more, sex, presence or absence of a history of previous transfusion or pregnancy, type of blood component (WB or RBCs), and blood unit storage duration of less than 15 or 15 or more days. Continuous variables were compared with a t test; categorical variables were compared using the chi-square statistic. Results were considered significant with a p value of less than 0.05. Statistical analyses were performed with computer software (STATA, Version 11.0, StataCorp, College Station, TX).

Ethical approval

The study was approved by the institutional review board of the Makerere University College of Health Sciences. Written informed consent/assent was obtained as required by the institutional review board.

RESULTS

Patient and transfusion data

A total of 2336 WB or RBC units were issued over the study period of which 507 were included in the study. Figure 1 shows the reasons for exclusions. Table 2 shows patient characteristics and blood unit type.

Acute transfusion events and reactions

Of the 507 transfusions evaluated, a transfusion event was reported by the research assistants in 53 transfusions. ATRs were confirmed by physician consensus in 49 (9.7%) of the 507 transfusions; in four cases an ATR was ruled out. The 49 ATRs occurred in 46 patients: 43 patients had one ATR and three patients had two ATRs. Of the 49 ATRs, 45 (or 8.9% of the 507 transfusions) were considered to be definite, probable, or possible ATRs. The type, imputability, and severity of the ATRs as confirmed by physician consensus are summarized in Table 3.

Factors associated with ATRs

Of the possible associated factors analyzed using bivariate analysis only patient age ($p = 0.001$) and blood component type ($p = 0.003$) were significant; however, neither of these factors retained significance in multivariate analysis ($p = 0.093$ and $p = 0.102$, respectively).

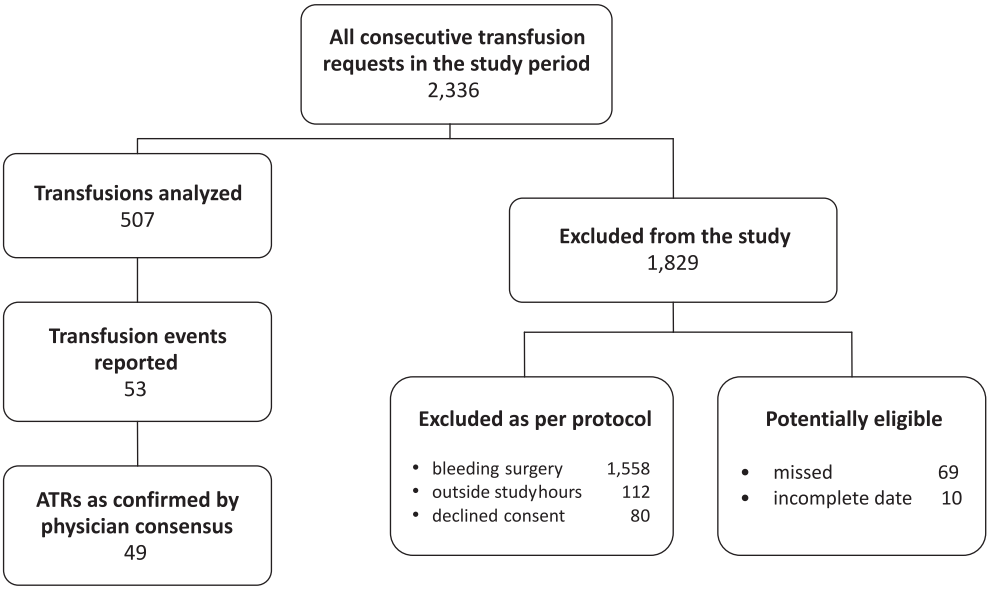
DISCUSSION

To the best of our knowledge, this is the first study in SSA to prospectively evaluate in detail ATRs among a variety of WB or RBC recipients. In a total of 507 transfusions, 49 ATRs were confirmed by expert consensus, resulting in an incidence rate of 9.7 ATRs per 100 transfusions of RBCs components (or 8.9 per 100 units if only ATRs of definite, probable, and possible imput ability are considered).

Febrile and allergic reactions were the most prevalent at 49% (24/49) and 14% (7/49) for an overall rate of 4.9 and 1.4 per 100 transfusions, respectively. The two most serious types of reactions, transfusion-associated circulatory overload (TACO) and acute hemolytic accounted for 6% (3/49) and 4% (2/49) or a rate of 0.6 and 0.4 per 100 transfusions, respectively. The remainder of the ATRs accounted for 26% (13/49) of the reactions.

Overall, these rates are higher than those generally reported in developed countries, even when considering only prospective studies (which almost always observe higher ATR rates than retrospective studies). For example, in a prospective study of ATRs in a pediatric intensive care unit, the incidence of ATRs was much lower at 1.6 per 100 transfusions.[9] Overall rates in the general transfused population are more difficult to discern from the literature but the rates of individual reaction types or reactions associated with specific blood components have been reported. The rate of FNHTRs (as determined in prospective studies) is estimated to be 0.04 to 0.44 per 100 RBC units transfused, with the higher rates occurring in non-LR units.[10] TACO is estimated to occur in one in 700 transfusions, with figures varying depending on the patient mix and physician awareness in its identification.[11] A recent prospective study evaluating all types of ATRs occurring with the transfusion of LR RBCs stored in ASs reported ATR rates of less than 1%.[12] All of these reaction rates are considerably lower than the ATR rates observed in our study. However, the incidence of allergic ATRs in our study is similar to that in developed countries where allergic reactions have been reported to occur in approximately 0.5 to 3% of transfusions with the higher rates occurring with plasma-containing components.[13,14]

FIGURE 1: Diagram of transfusions included and analyzed in the study.



Very few studies examining the rates of ATRs in SSA have been published but those that have report highly variable results. Two studies, one from Uganda and the other from Ghana, that determined the ATR rate by reviewing clinical notes, reported that transfusion reactions were recorded for only 0.6 and 0.8% of transfused patients, respectively.[1,2] However, these reports, which do not ensure any active monitoring or reporting of ATRs, almost certainly underestimate the true incidence of ATRs in SSA. At the other end of the spectrum, a prospective study conducted in Cameroon of 26,973 blood units transfused from 1994 to 1998 reported that ATRs occurred in more than 50% of the transfusion episodes - febrile reactions in 40% of cases and allergic reactions in 19%, with some overlap between the two types of ATRs.[4] This study did not appear to have been as detailed as ours and, in particular, the investigators did not appear to have been as diligent in attempting to distinguish fever occurring in a temporal relationship with transfusion as being truly associated with transfusion versus being due to the underlying illness. A high rate of allergic reactions was also reported in a prospective study of obstetrical patients in Nigeria in which 12.6% of patients had allergic ATRs.[15]

The SSA study with the results most similar to ours was conducted over a 1-year period (2004) in a Nigerian university-affiliated hospital.3 The investigators determined the frequency and nature of ATRs using a questionnaire administered within 24 hours of transfusion. A total of 462 transfusions were evaluated of which 72% were WB, 19% RBCs, and the remaining 19% PLT or plasma transfusions. ATRs were determined to have occurred in 40 or 8.7% of the transfusions with the reaction types being FNHTR alone 65%, allergic reactions alone 15%, FNHTR with allergic reactions 17%, and acute hemolytic reactions 3%. Unlike our study no TACO reactions were reported. However, TACO may well not have been identified both as a result of the lack of awareness of TACO as an ATR at the time the study was performed and as a result of the methods used to identify ATRs in that study.

TABLE 2: Patient and transfusion characteristics*

Transfusion and patient characteristics	All Transfusions (n = 507)	ATRs (n = 49)
Wards		
Pediatric medical	162 (32)	5 (10)
Adult or adolescent medical	212 (42)	29 (59)
Surgical, obstetrical, or gynecology†	133 (26)	15 (30)
Sex		
Male	198 (39)	20 (41)
Female	309 (61)	29 (59)
History of transfusion or pregnancy		
Yes	355 (70)	40 (82)
No	152 (30)	9 (18)
Blood component		
WB‡	239 (47)	33 (67)
RBCs§	268 (53)	16 (33)
Age of blood component (days)		
<15	357 (70)	35 (71)
≥15	150 (30)	14 (29)

* Data are reported as number (%).
† Includes four patients less than 13 years old, one of whom had an ATR.
‡ Of the 239 WB transfusions, 227 were given to patients at least 13 years old and 12 to patients less than 13 years old; all 33 ATRs occurred in patients at least 13 years old.
§ Of the 268 RBC transfusions, 114 were given to patients at least 13 years old and 154 to patients less than 13 years old; of the 16 ATRs, 10 occurred in patients at least 13 years old and six in patients less than 13 years old.

Most of the febrile reactions in our study were likely FNHTR. They were all of Grade 1 severity, only one was associated with a decrease in blood pressure (of 20 mmHg), only four occurred within 15 minutes of beginning the transfusion and only one was accompanied by tachypnea. We cannot, however, rule out the possibility that some may have been due to bacterial contamination since we did not perform bacterial cultures in any of the implicated patients or units and many patients were receiving broad-spectrum antibiotics. The possibility that some were manifestations of a mild hemolytic ATR also cannot be eliminated as complete transfusion reaction work-ups were also not performed although bedside checks of patient identity and unit numbers were done in all cases. Finally none were considered to be TRALI.

The high rate of febrile reactions (at least when compared to rates reported from developed countries) observed in our study is likely due to a combination of factors. The fact that the units were not LR is almost certainly an important factor. Although the history of a previous transfusion or pregnancy did not reach significance as a risk factor for the occurrence of an ATR, 70% (355 of 507) of transfusions in this study were given to those with a history of previous transfusion or pregnancy and 82% (40 of 49) of ATRs occurred in patients with a history of previous transfusion or pregnancy. Thus, this may have contributed to the high rate of febrile ATRs via an antibody-mediated mechanism. However, even without LR, FNHTR rates of 4% to 5% with RBCs or WB are not usually seen. Thus additional factors would seem to be necessary to explain the 4.9% incidence of febrile ATRs that we observed (assuming that the majority were in fact FNHTR). In SSA it is often difficult to adhere strictly to temperature control for the storage and transport of blood units. Thus, although not documented, it is possible that WB and RBC units in many SSA settings spend sufficient accumulated time outside refrigerated storage (at any step along the path from collection to the end of transfusion) to allow leukoderived cytokine production in that could be sufficient to contribute to the occurrence of FNHTRs. Alternately (or in addition), this problem might lead to a higher rate of clinically significant bacterial contamination. Finally, it is also possible that patient factors could have contributed to this high rate of febrile ATRs: transfused patients in SSA often have infectious or inflammatory conditions and therefore might have higher endogenous plasma cytokine levels than is the case for patients in other settings.

TACO, while not common (three cases in the 507 transfusions) was nevertheless observed more frequently in our study than is reported in either non-resource-limited settings or in other SSA studies. In spite of the fact that we could not perform chest X-rays or laboratory investigations, these three ATRs were all unanimously considered by the physician evaluators to be TACO: all developed tachypnea or new or worsening respiratory distress from 1 to 2 hours after the onset of the transfusion, all had blood pressure increases, none had fever, and all responded to diuretic therapy. There are a variety of reasons why TACO could occur more frequently in SSA than in high- or middle-income countries. Patients in SSA often present with advanced illness, severe chronic anemia, and un- or undertreated conditions such as hypertension. These patient factors together with the absence of guidelines for infusion rates, the lack of infusion pumps, and limited nursing oversight all likely place SSA transfusion recipients at higher risk for TACO. In addition to the three TACO cases, it is possible that some of the cases of tachycardia or hypertension could have been manifestations of mild circulatory overload.

The two hemolytic ATRs observed in this study occurred in the same recipient, a group O woman who in both instances received group AB blood. Her ABO group was initially determined to be AB; the first unit she received was apparently cross-match compatible but no cross-match was performed for the second unit. She was subsequently found to be group O. It was not clear from the documentation available where the error occurred in the pretransfusion testing for the first unit nor why a cross-match was not performed for the second unit, but given that the blood bank laboratory (as is probably the case for the majority of public health facilities in SSA) has not fully implemented quality systems, there are many opportunities for errors to occur. One particular concern is that pretransfusion testing is often performed by physicians rather than appropriately trained laboratory personnel. In addition to these laboratory errors, in the course of the study, we did prevent one episode of mistransfusion due to incorrect recipient identification, highlighting the potential for clinical as well as laboratory errors.

There were three ATRs that fulfilled criteria for hypotensive reactions. No bedside LR filters were used and only one of the three recipients was receiving acetylcholine esterase inhibitor medication. Blood cultures to eliminate the possibility of bacterial contamination were not done. It is therefore not clear whether these reactions were bradykinin-mediated reactions or due to other causes.

We did not observe any reactions that were considered to be TRALI. However, given that we studied 507 transfusions and that TRALI occurs with a frequency that is considerably less than one in 500 transfusions, it is not surprising that this did not occur over the study period. However, there may be an additional consideration. In Uganda (as in many low-resource settings), there are more donations from male than female donors and donors tend to be younger than in higher-income countries.[16] It is therefore likely, although undocumented, that relatively few blood donations are from multiparous female donors.

This study has several strengths. First, we studied a reasonably large number of transfusion events, prospectively, with monitoring by research assistants trained in the recognition of ATRs. Second, a team of three physicians, all with knowledge of ATRs and familiarity with the study setting, individually evaluated each adverse transfusion event using predefined, internationally accepted ATR criteria with final ATR designation being determined by a consensus process. However, there were two major limitations to our study. The first was lack of available resources to perform complete transfusion reaction investigations. As discussed, it is possible that some of the ATR classifications might have changed if we had been able to perform these investigations. Second, while we attempted to review the charts of all patients with adverse transfusion events, in a few cases the charts could not be located and in many cases where charts were available only limited information was available, in particular, patients' vital signs were not routinely recorded. Nevertheless, the evaluators applied ATR definitions as rigorously as possible given these limitations.

Another limitation to our study is the fact that we did not evaluate transfusions given intraoperatively or for other acute hemorrhage nor transfusions given to oncology patients undergoing chemotherapy. Thus, the results of this study cannot be generalized to those patient populations or settings. Finally, we did not evaluate any transfusions administered at night or on weekends or public holidays. Since hospital errors in general occur more frequently outside regular working hours or days it may well be that the ATR rate would be even higher in those situations.[17]

While the prevention of some ATRs is likely beyond the current resource capabilities of low-income countries - for example, the provision or pre- or poststorage LR units - there are still several strategies that could be implemented in these settings to reduce the rate of ATRs. In particular, life-threatening hemolytic ATRs and TACO could almost entirely be eliminated through education and the implementation of appropriate transfusion procedures and policies. Indeed the second hemolytic ATR and the TACO reactions observed in this study may all have had more serious outcomes had the patients not been undergoing monitoring for the study. It is also possible that the incidence of FNHTR (and possibly even some reactions due to bacterial contamination) could be decreased by relatively simple measures such as improving transport boxes and ensuring that blood remains refrigerated at all times that it is not in transit.

As was the case in high-income countries in the 1980s and 1990s, in SSA in the past decade much attention and most of the funding has been, necessarily, directed to the production of safe blood units. However, as has been more recently emphasized in developed countries, safe transfusion therapy also requires having safe practices within the transfusing facility. Our study demonstrates that this is also, not surprisingly, the case in SSA and provides information that can be used for transfusion medicine education of health care professionals in SSA and to inform potential transfusion recipients about the risk of ATRs, information that has been greatly lacking in SSA. Our study has also identified areas that merit further study in SSA such as studies to determine the causes of febrile and hypotensive ATRs, studies to determine the incidence and nature of ATRs in other recipient groups, and studies to investigate ways to prevent ATRs.

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