

Improvement in Hospital Indicators after Changes in Dengue Case Management in Nicaragua

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Abstract. Dengue is a major problem worldwide, and improving case management is a significant priority. In consultation with colleagues in Thailand, changes in management of hospitalized dengue cases were introduced in Nicaragua, including oral rather than intravenous (IV) fluids upon admission, continuous monitoring of clinical and laboratory signs, and use of IV fluids principally during the critical phase and colloids in management of shock. Two periods were compared, before (2003) and after (2005) their implementation, to assess impact. In 2003, 182 hospitalized laboratory-confirmed dengue cases 0–14 years of age who presented ≤ 5 days post-symptom onset were included in the study; 46 were enrolled in 2005. Outcomes included significant reductions in days of IV fluid administration ($P = 0.0001$), number of patients receiving IV fluids ($P < 0.0001$), and duration of hospitalization ($P < 0.0001$), and a non-significant reduction in the number of admissions to the intensive care unit from 8 in 2003 to 0 in 2005 ($P = 0.36$). This study demonstrates concrete gains in dengue patient care and case management.

INTRODUCTION

Dengue is an acute viral febrile illness transmitted by the mosquitoes *Aedes aegypti* and *Ae. albopictus*. Dengue virus (DENV) infection can result in asymptomatic infection or a range of disease severities: dengue fever (DF), noted for intense joint and muscle pain and high fever; dengue hemorrhagic fever (DHF), with signs of vascular leakage, thrombocytopenia, and hemorrhagic manifestations; and dengue shock syndrome (DSS), in which the vascular leakage has increased to the point of causing shock. Although DF has been recognized for hundreds of years, it was not until after World War II that epidemic and fatal DHF/DSS spread in Southeast Asia,^{1,2} where it is now one of the leading causes of hospitalization and death. The pattern of endemic and epidemic DF and emerging DHF/DSS is currently being repeated in Latin America³; all four serotypes of DENV have expanded throughout the region. DHF/DSS first emerged in Cuba in 1981⁴ and has since been reported in most Latin America countries. In Nicaragua, dengue has been an important public health burden since the introduction of DENV-1 and DENV-2 in 1985,⁵ and it became hyperendemic in 2000, by which time all four serotypes had been introduced.^{6–8}

Symptomatic DENV infection is characterized by three phases. The febrile phase lasts between two and seven days. During this period, early warning signs may lead to hospitalization for careful monitoring and in some instances to decisions to implement resuscitation. Upon defervescence, the patient may spontaneously recover, or significant plasma leakage can occur (the critical phase). Lastly, there is the convalescent phase in which patients have stable vital signs and increased appetite and urine production, but may continue to have persistent exanthema and petechiae.

The principal feature of DHF/DSS is vascular permeability, which can lead to shock and death if appropriate treatment is not received in a timely manner.^{2,9} As such, the protocols for case management, as evolved by certain countries in Southeast Asia,

notably Thailand^{10,11} and Vietnam,¹² involve careful monitoring of vital signs combined with judicious and responsive fluid management. Physicians from the Queen Sirikit National Institute for Child Health (QSNICH) in Bangkok, Thailand, who have treated and managed DHF/DSS since its recognition in the 1960s, have trained numerous clinicians throughout Thailand and Asian countries in clinical management of severe dengue, with tangible effects in reducing fatality rates.^{10,13} More challenging has been the transfer of this experience from the Asian region to the Americas, where dengue continues to spread as a major public health problem.

In 2004, a team of clinicians from Nicaragua traveled to Thailand to gain familiarity with the clinical management of severe dengue as performed by physicians from the QSNICH. We report the result of applying fluid treatment and case management protocols garnered from the experience in Thailand at the National Pediatric Reference Hospital in Nicaragua. A number of outcomes were evaluated, including duration of hospitalization, number of patients receiving intravenous (IV) fluid, days of IV fluid administration, and intensive care admission. Although there were no fatalities in either year, we observed tangible improvements in outcome, including a reduced length of hospitalization, fewer patients requiring IV fluids, and a reduction in intensive care in pediatric dengue cases.

MATERIALS AND METHODS

Study population. Two studies with similar protocols were performed in 2003 and 2005 on hospitalized pediatric suspected dengue cases in the Nicaraguan National Pediatric Reference Hospital, Hospital Infantil Manuel de Jesús Rivera (HIMJR). These studies were reviewed and approved by the Institutional Review Boards of the University of California Berkeley, the Ministry of Health of Nicaragua, and the HIMJR. Inclusion criteria for this retrospective analysis were laboratory confirmation of dengue virus (DENV) infection and presentation to the HIMJR ≤ 5 days after onset of symptoms.

Laboratory tests. Laboratory confirmation of DENV infection consisted of seroconversion of DENV-specific IgM antibodies¹⁴ or a four-fold or greater increase in total antibody titer, as measured by inhibition enzyme-linked immunosorbent assay (ELISA),^{15,16} between acute-phase and convalescent-

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phase serum samples; isolation of DENV in C6/36 *Aedes albopictus* cells⁷; and/or reverse transcription–polymerase chain reaction amplification of viral RNA.⁶ Identification of DENV serotype (1–4) was achieved by virus isolation and/or reverse transcription–polymerase chain reaction directed to the capsid^{6,17} and/or nonstructural protein 3 genes.¹⁸ Primary DENV infections were defined by an antibody titer by inhibition ELISA < 20 in acute-phase samples and/or < 2,560 in convalescent-phase samples, and secondary DENV infections were defined by an antibody titer by inhibition ELISA \geq 20 in acute-phase samples and/or \geq 2,560 in convalescent-phase samples.^{6,16} All serologic and virologic assays were performed in the National Virology Laboratory at the National Diagnosis and Reference Center (CNDR) of the Nicaraguan Ministry of Health. With the exception of the on-ward microhematocrit, all clinical laboratory tests were performed in the Department of Clinical Chemistry at the CNDR or at the clinical laboratory at the Health Center Sócrates Flores Vivas¹⁹ in Managua.

Clinical management and definitions. World Health Organization (WHO) criteria were strictly applied to classify dengue disease severity.²⁰ Hospitalization criteria, intensive care unit (ICU) transfer criteria, discharge criteria, and clinical laboratory testing were maintained unchanged in 2003 and 2005. For case definitions and hospital discharge criteria, only clinical laboratory hematocrits were used.

An intervention consisting of modified fluid management guidelines and staff training occurred between the two studies. In 2003, most patients received crystalloid IV fluids. All patients received maintenance fluid when they were admitted to the hospital; the rate of IV fluid administration was constant. Rapid IV fluid replacement was conducted in all patients with hemodynamic instability. If patients had not improved after 2 or 3 loads (10–20 mL/kg), they were given dopamine (4–10 μ g/kg/minute) to treat profound shock (virtually no pulse pressure, weak pulse, cold clammy skin, altered mental state); if available, dextran was administered under these conditions. If improvement was not observed, the patient was transferred to the ICU. Hematocrit was determined every 24 hours by the CNDR laboratory.

Post-intervention in 2005, all patients received oral fluids, and crystalloid IV fluids were given to patients with hemodynamic instability (narrowing pulse pressure \leq 20 mm of Hg, hypotension for age, or increased hematocrit), or intolerance of oral fluids. The rate of IV fluid administration was adjusted by weight as necessary for all patients, according to the Halliday-Segar formula. Colloid IV fluids (Dextran 40), were given to patients who did not improve after initial rapid infusion with crystalloid solution.²¹ If after one infusion of colloid administration patients did not improve and/or stabilize, they were to be transferred to the ICU; however, none met this criteria. In addition to the daily clinical laboratory results, hematocrit was determined every 1 to 2 hours using an on-ward microhematocrit centrifuge at the start of defervescence or when any other vital signs, physical inspection, or clinical laboratory tests showed worsening conditions. Additional signs and symptoms recorded by the nursing and medical staff were largely the same in the two study years. However, a strict log and calculation sheet of fluid intake and output was incorporated to assess fluid balance in 2005. Furthermore, staff training and accountability and standardization of protocols and procedures were prioritized and monitored in 2005.

Statistical analysis. All analyses were conducted in STATA version 9 (STATA Corp., College Station, TX). *P* values were

determined using a two-tailed *t*-test, Pearson's chi-square test, or Fisher's exact test as indicated. A multivariate model of days of hospitalization was fit using a backward stepwise procedure. A combination of *P* > 0.20 as the cut-off for significance and an insignificant change in coefficients of remaining variables in the model was used to determine variables that should be included in the final model. The model included the following significant predictors: day of illness when hospitalized and severity (DF, DHF, DSS). Age and sex were not found to be significant.

RESULTS

Study participants. In 2003 and 2005, 182 and 46 patients, respectively, met the inclusion criteria. The two populations did not differ significantly with respect to sex or immune status or in the proportion of participants with DF, DHF, and DSS (Table 1). No overall difference in disease severity was observed between the two study periods; 29% of hospitalized dengue patients were classified as DHF/DSS in 2003 versus 26% in 2005. The two populations differed somewhat in age distribution among persons 1–4 year of age and 10–14 years of age. Among the patients studied, the percent of primary and secondary DENV infections in participants more than one year of age was 35% and 60% in 2003 and 24% and 70% in 2005, respectively. Serotype identification was achieved in 28% of participants in 2003 and 80% in 2005, with 24 (83%) DENV-1, 2 (7%) DENV-2, 2 (7%) DENV-4, and 1 (3%) coinfection (DENV-2/DENV-4) in the 2003 participants, and 7 (19%) DENV-1 and 30 (81%) DENV-2 in 2005.

Days of hospitalization and illness. The difference in mean days of hospitalization in the two populations was significant for all patients (*P* < 0.0001), DF (*P* < 0.0001), and DHF (*P* = 0.0018), but was not significant for DSS (*P* = 0.0927) (Figure 1A). Similar results were obtained when total days of illness were examined (day of onset of symptoms until day of discharge from the hospital) (Figure 1B). The difference in the day of illness when hospitalized was not significant for DF, DHF, or DSS (*P* = 0.17, *P* = 0.06, and *P* = 0.78 respectively), but was significant for the population overall (*P* = 0.04), with patients

TABLE 1

Characteristics of participants in dengue case management study, Nicaragua

Characteristic	2003 (n = 182), No. (%)	2005 (n = 46), No. (%)	<i>P</i> *
Sex			
Male	86 (47)	21 (46)	0.96
Female	96 (53)	25 (54)	0.96
Age, years			
> 1	13 (7)	3 (6)	0.93
1–4	42 (23)	3 (6)	0.02
5–9	76 (42)	16 (35)	0.49
10–14	51 (28)	24 (52)	0.004
Immune status			
Primary dengue infection	63 (35)	11 (24)	0.245
Secondary dengue infection	110 (60)	32 (70)	0.245
Indeterminate	9 (5)	3 (6)	
Severity			
Dengue fever	128 (70)	34 (74)	0.73
Dengue hemorrhagic fever	46 (26)	8 (17)	0.28
Dengue shock syndrome	8 (4)	4 (9)	0.31

* *P* values were calculated using Pearson's chi-square test or Fisher's exact test as appropriate.

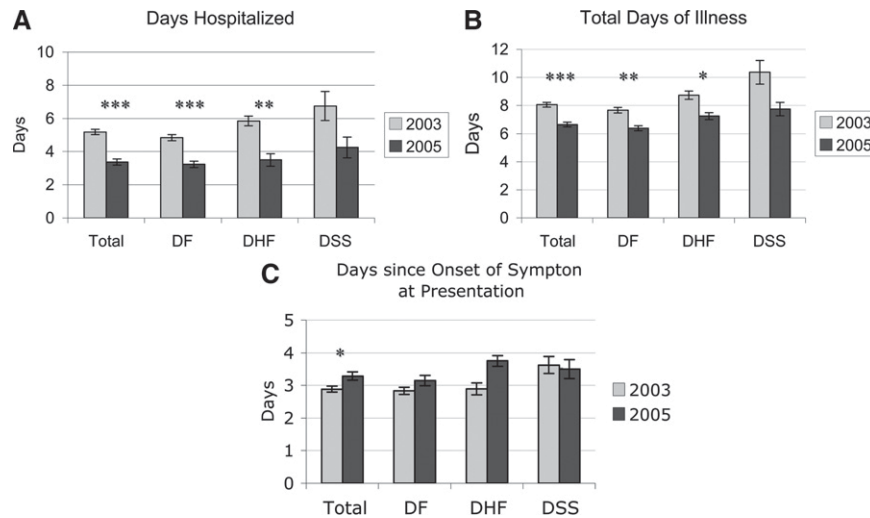


FIGURE 1. Impact of modified dengue case management on days of hospitalization. **A**, Decrease in number of days hospitalized. The number of days of hospitalization were compared among all patients (Total), and patients with dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) in 2003 (light gray) with those in 2005 (dark gray). **B**, Decrease in total days of illness. The number of days of illness (from onset of symptoms to hospital discharge) were compared as in **A**. In **A** and **B**, the differences were statistically significant for all categories with the exception of DSS patients. **C**, Days since onset of symptoms at presentation. The number of days since onset of symptoms at presentation to the study hospital were compared as in **A**. *** $P < 0.0001$; ** $P < 0.01$; * $P < 0.05$ (see text for details), as calculated using the *t*-test.

admitted slightly earlier in 2003 than in 2005 (Figure 1C). A multivariate regression analysis was performed to investigate the relationship between days of hospitalization and year (pre-/post-intervention). When adjusted for day of illness upon hospitalization and disease severity, study participants in 2003 spent an average of 1.68 (95% confidence interval = 1.07–2.29) more days in the hospital than in 2005. Admissions to the intensive care unit decreased from 8 in 2003 to 0 in 2005 ($P = 0.36$).

Fluid management. The percentage of patients receiving IV fluids was significantly less across all categories except DSS in 2005 when compared with 2003 (Figure 2A). In 2003 and

2005, 100% of DSS patients received IV fluids (Figure 2A). The overall mean days of IV fluid decreased from 3.87 days in 2003 to 0.96 in 2005. This decrease was significant overall ($P = 0.0001$) and in the DF and DHF categories ($P < 0.0001$ and $P < 0.001$, respectively) (Figure 2B). In 2005, a significant decrease in mean amount of fluid administered was observed overall and in the DF and DHF categories ($P < 0.0001$, $P < 0.0001$, and $P < 0.01$, respectively) (Figure 2C). All DSS patients in both years received IV fluids, and there was no significant difference in mean days of IV fluid or mean amount of fluid ($P = 0.35$ and $P = 0.50$, respectively) (Figure 2B and C). The mean quantities of IV fluids per person administered in 2003

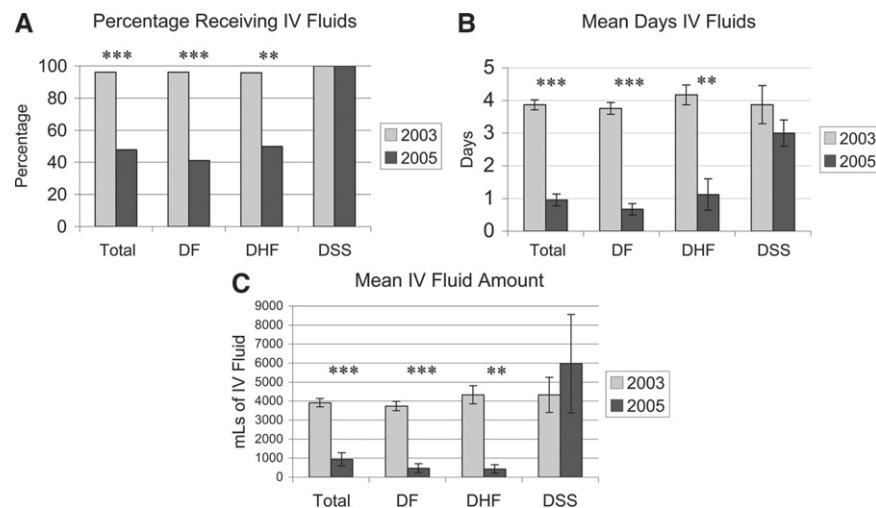


FIGURE 2. Impact of modified dengue case management on use of intravenous (IV) fluids. **A**, Decrease in percentage of patients receiving IV fluids. The percentage of patients receiving IV fluids was compared among all patients (Total), and patients with dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) in 2003 (light gray) with those in 2005 (dark gray). **B**, Decrease in mean days of IV fluids. The mean days that patients received IV fluids were compared as in **A**. **C**, Decrease in mean amount of IV fluids. The amount of IV fluids administered to patients was compared as in **A**. *** $P < 0.0001$; ** $P < 0.01$ (see text for details), as calculated using the *t*-test. Differences were statistically significant for all categories with the exception of DSS patients.

and 2005 were 3,917 mL and 937 mL, respectively. In 2003 and 2005, 3 (1.6%) and 9 (20%) $P < 0.001$ of patients received IV colloid fluids. In 2003, colloid was not prioritized and thus was not readily available.

DISCUSSION

Case management of dengue has evolved independently in Asia and the Americas as the virus became endemic to each region. The Asian experience with DHF/DSS dates from the 1950s; DHF/DSS was introduced into the Americas in 1981. For the time being, although the presence of DHF/DSS in the Americas is unequivocal, Asia experiences more severe disease than the Americas,²²⁻²⁵ with greater possibility of severe complications. As such, treatment protocols that focus on severe dengue illness are well established in Asia.^{11,12,26-29} In 2004, a team of clinicians from Nicaragua traveled to Thailand for intensive training in fluid management of suspected dengue cases. The significant differences in management implemented in the HIMJR in 2005 involved the use of oral rehydration therapy (ORT) instead of intravenous therapy (IVT) until IVT was indicated, adjustment of IVT per individual patient characteristics, strict monitoring of fluid intake and output, frequent monitoring of hematocrit using a bedside microcapillary centrifuge, the use of rapid IV infusion, and standardized use of colloids before ICU admission. This retrospective study analyzes various outcome measures before and after the intervention. We observe tangible improvements in outcome, including a reduced length of hospitalization, fewer patients requiring intravenous fluids, and a reduction in ICU admission in pediatric dengue cases. Including and beyond clinical outcome, these results provide significant benefits to developing countries such as Nicaragua.

Dengue patients are susceptible to dehydration and hypovolemia because of high fever and concomitant anorexia, together with the pathophysiologic vascular leakage associated with the illness, for which children are inherently more susceptible.³⁰ Supportive therapy focuses on maintaining intravascular pressure. However, in severe dengue cases, treatment must avoid the serious complication of fluid overload. Even in the absence of specific studies supporting its benefit, ORT and increased fluid intake became the recommended standard outpatient management of WHO in its 1997 guidelines.²⁰ In 2003, Harris and others³¹ reported that increased fluid intake within 24 hours prior to presentation to a hospital or clinic is protective against hospitalization. Likely caused by the lack of controlled studies in inpatients, guidelines have been more equivocal in advocating for a shift from IVT to ORT for treatment of non-critical inpatients with dengue, with some advocating ORT³² and others advocating studies to provide supporting evidence.³³ Nonetheless, many medical centers administer inpatient ORT until IVT is indicated,^{10,12} given the empirical success of ORT for inpatient dengue management (until IVT is indicated), the invasiveness of IVT, and the increased cost of IVT for a disease that primarily impacts resource-poor settings.

In our study, the change in case management between 2003 and 2005 demonstrated striking outcome differences for patients with DF and non-shock DHF, which made up approximately 70% and 20%, respectively, of hospitalized patients during both years. First, the mean days of hospitalization and total days of illness decreased by more than 1.5 days in both

groups, substantially reducing cost and the burden of bed space. Second, the significant decrease in number of patients using parenteral liquids and the decrease in volume and duration of parenteral liquids between pre-intervention and post-intervention periods also translates into substantial cost savings and improved patient care. Interestingly, two independent meta-analyses of randomized controlled trials concluded that ORT is associated with a significantly shorter hospital stay and fewer major adverse events when compared with IVT in treating dehydration caused by diarrheal illnesses in children in developed and developing countries.^{34,35} In our study, changes in case management, including more frequent monitoring of the patient and use of an on-ward microhematocrit centrifuge to monitor hematocrit more often, were directed to decision-making regarding fluid treatment of dengue vascular permeability syndrome. Thus, the outcomes of IVT administration and concomitant changes in duration of hospitalization that were measured were a direct reflection of the increased monitoring as well as customized fluid administration.

The mechanistic details of the pathogenesis of plasma leakage in dengue remain poorly understood and as such, novel therapies have not yet emerged. Thus, the treatment of severe dengue patients has undergone a slow progression since seminal pathophysiologic studies in the 1960s established the fundamental principles of fluid and case management.¹¹ The concept of rapid infusion of a crystalloid solution for treatment of dengue shock and the use of a colloid solution for those who fail to respond dates back almost to the emergence of DHF/DSS in Asia.¹¹ These principles were formally adopted by WHO after a technical advisory committee meeting for South-East Asia and the Pacific Regions.^{21,36} In the past decade, well-designed studies examining the benefits and temporal appropriateness of rapid infusion of crystalloids and colloids have validated their use and provided clarity for best practices.^{12,28-30,37,38} Less risk and equal clinical benefit of starch in lieu of dextran as the colloid of choice¹² may further improve clinical care and decrease costs.

As expected for patients with shock, all patients with DSS in both years of this study received IV fluids. The mean number of days of illness, hospitalization, and IV fluid administration decreased in 2005, and the amount of IV fluid increased, although none to a significant degree. The 2005 HIMJR practices are in agreement with other studies using a similar protocol, where non-shock DHF patients receive much less IV fluid than DSS patients.³⁹ Patients with DSS are the most severe and therefore at greatest likelihood to be transferred to ICUs. Although not statistically significant, the decrease from eight to zero ICU admissions between the two years suggests that the fluid management changes resulted in either more responsive management and/or fewer complications. The criteria for ICU admission, failure to regain or maintain hemodynamic stability, did not change between the pre-intervention and post-intervention. However, bedside monitoring for hemoconcentration, the use of rapid infusion, adjusting the IV fluid rate accordingly, and the application of colloid fluids did change and likely reduced the need for ICU admission.

As shown by the experience in Thailand and Vietnam, nationwide pre-graduate and post-graduate training of physicians and medical staff in dengue case management and resuscitation has led to striking decreases in case-fatality rates.^{10,13} We demonstrate that application of dengue treatment protocols from Thailand had beneficial outcomes in the Nicaraguan

National Pediatric Reference Hospital. Since this study was conducted, the Nicaraguan Ministry of Health has supported training programs for numerous physicians from different hospitals throughout the country to learn from our experience with the new case management protocols. The Ministry also produced new manuals and pocket guides describing the most important aspects of treatment and resuscitation of dengue vascular permeability syndrome. Although these are important steps forward, it is necessary to maintain the continuing education of physicians who treat dengue patients and to monitor the impact. In addition, we strongly recommend that countries in the Americas newly endemic for dengue share strategies for improvement of dengue case management and invest in post-graduate training and continuing education designed to standardize improved protocols for treatment of dengue vascular permeability syndrome.

This retrospective study compares treatments from two different periods, invoking certain study limitations. First, circulating serotypes and infection history can affect dengue severity.⁴⁰ Although the principal infecting serotypes were different between the two years, with DENV-1 predominating in 2003 and DENV-2 in 2005, the immune status of patients was not significantly different between the two years, although the sequence of infecting serotypes was likely distinct. However, the analysis circumvents this bias as best as possible by directly comparing the categories of disease severity between the two years. Our previous studies showed differences in clinical manifestations by serotype, specifically, increased vascular permeability associated with DENV-1 infections and increased shock with DENV-2 infections, with a shorter period of hospitalization for DENV-1 than for DENV-2 infections.⁴⁰ In this study, we found the opposite; namely, shorter hospitalization periods for 2005 (DENV-2), possibly reflective of improved treatment protocols in 2005 when DENV-2 infections predominated. Second, as the change in protocol involved alterations in early management and severe management, differences in treatment might have diminished the progression of some cases to more severe forms of the illness. However, the overall burden of severe disease was similar in the two years.

The updated clinical practices implemented in the HIMJR in 2005 resulted in tangible benefits, including the reduction in days of hospitalization and associated cost and stress on the hospital during an epidemic when bed space is sparse, and material use of IV catheters and IV fluids. These cost savings are greater than the cost of implementing and sustaining the new management protocol, which involves staff training, a microcapillary centrifuge and tubes, and sparing use of colloids. Overall, the exchange between geographic regions to improve dengue case management provides benefits to developing countries, such as Nicaragua, that extend well beyond clinical outcome.

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