**Cost-effectiveness analysis of the NIRUDAK clinical diagnostic model for dehydration severity in patients over five years**

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**Data Sharing:** The deidentified datasets for the NIRUDAK study are freely available with no restrictions via Open Science Framework and can be accessed at https://osf.io/pncms/.

**Abstract**

Purpose: To compare the cost-effectiveness of the World Health Organization algorithm and the NIRUDAK model for treatment of severe dehydration due to diarrhea in patient over five years of age.

Methods:

Results:

Conclusions:

**Introduction**

Accounting for over 6.5 billion cases and 1.4 million deaths in 2019, diarrheal diseases are a major cause of morbidity and mortality and exert a heavy burden on health care systems worldwide.1 Diarrheal-associated morbidity and mortality arise from dehydration and thus treatment involves fluid resuscitation. Existing care guidelines, namely from the World Health Organization (WHO), base treatment recommendations on categorical dehydration classification, e.g., severe or moderate dehydration. More specifically, patients with severe dehydration require immediate resuscitation with intravenous (IV) fluids, while those with moderate dehydration can safely be treated with oral rehydration solution (ORS) and those without any dehydration can be provided with instructions for expectant management at home.2,3 Accurate assessment of dehydration status can thus improve the effectiveness and cost-effectiveness of diarrhea treatment by minimizing the health risks of undertreatment and ensuring that ORS, which can be administered in an outpatient setting, is used for the treatment of appropriate patients instead of more costly IV fluids, which require inpatient beds and skilled nursing staff.

ORS has been previously shown to be highly effective and, as compared to IV fluids, a less expensive treatment option in the management of dehydration.4,5 Moreover, unlike IV fluids, ORS can be administered outside the hospital (i.e., inpatient) setting in developing countries, e..g, in the more cost-effective settings of clinics and patient homes (i.e, outpatient settings).1 In low- and middle-income countries (LMICs), such care is a major strain on societal resources and can lead to a significant, if not catastrophic, financial burden for many households.6,7 Prior cost-analysis conducted in Bangladesh found that the total societal cost of an episode of diarrhea equals a quarter of the average monthly household income in the country and that there is a nearly six-fold increase in average cost per episode when managed an inpatient as compared to an outpatient setting.8 Shifting appropriate patients from inpatient to outpatient management (a roughly 80% reduction in costs) would thus be expected to produce per-episode cost-savings equal to roughly one-third of the national average monthly income without degrading health outcomes.

Yet the under resuscitation of fluid in the setting of acute dehydration can cause the dehydration to persist and lead to a number of other clinical sequalae such as electrolyte abnormalities, cardiac arrhythmias, altered mental status, multiple organ failure.9 Thus, it is critical that any triage system responsible for determining treatment location (i.e., inpatient or outpatient) and type (i.e., ORS or IV fluids) is sensitive enough to ensure that patients with severe dehydration are treated appropriately. Clearly, there is a need to balance the extremely high economic and societal cost burden of diarrheal illness in LMICs with the clinical necessity of adequate treatment of acute dehydration.

The Novel, Innovative Research for Understanding Dehydration in Adults and Kids (NIRUDAK, meaning dehydrated in Bangla) model was developed to more accurately assess the dehydration severity level of patients with acute diarrhea and avoid the potential sequelae of over or under resuscitation.1 Unlike the WHO Integrated Management of Adolescent and Adult Illness (IMAI) algorithm, the NIRUDAK model employs clinical measurements as inputs into a machine learning model.10 Previous analyses have demonstrated that the NIRUDAK model outperforms the current WHO algorithm in terms of accuracy and reliability.11,12 Employing more accurate clinical diagnostic models, like NIRUDAK, is especially critical in settings where resources are limited and the financial burden of treating acute diarrhea in an inpatient versus outpatient setting are significantly higher.

The aim of this study is to determine the cost-effectiveness of the NIRUDAK model compared with the WHO algorithm in treating patients over five years of age experiencing acute dehydration due to diarrhea. [finish paragraph with summary of what we did]

**Materials and Methods**

* State: perspective (e.g., Bangladesh societal or HCS), time horizon (short term, e.g., 1 week)
* Patients are Bangladesh 6+
* Make sure model section
* Outcome section
* Generalization section in the hospitals
* Mention the N in the parent study and that some proportion were unable to be classified (small) by NIRUDAK because of missing data
* Figure out if this cohort was cholera only or if that was most of population

*Study Procedures*

To inform the cost-effectiveness analysis, we used economic data collected as part of the NIRUDAK study, a prospective cohort study of patients over five years of age presenting with acute diarrhea to the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) at Dhaka Hospital in Bangladesh between March 2019 and March 2020 1. All acute diarrhea patients admitted to Dhaka Hospital’s Emergency Ward were screened and randomly selected for participation in the study upon arrival to the hospital. Selected patients were excluded if they met the following criteria: diarrhea lasting more than seven days, having fewer than three loose stools in the past 24 hours, and having a definitive diagnosis other than acute gastroenteritis. Previously enrolled patients were also excluded from the study. Upon consent, two research nurses independently assessed patients for symptoms of dehydration on arrival and continued to collect and record patient weight and the amount of fluid administered every four hours until the patients were discharged. All patients were managed according to icddr,b’s hospital protocols, which follow WHO’s IMAI and Integrated Management of Childhood Illness (IMCI) guidelines.3 Percent weight change with rehydration was used as the criterion standard for percent dehydration, an approach used for patients >5 years old in many other studies.13,14 Percent dehydration was calculated using the following formula:15

Percent dehydration = 100%\*[(Post-illness weight – admission weight)/Post-illness weight]

The two highest consecutive weight measurements that differed by less than 2% were averaged to determine a patient’s stable weight, which was used as their post-illness weight.15 For those who did not reach a stable weight prior to discharge, their return weight was used as their post-illness weight. Based on international guidelines developed by WHO and the United States Center for Disease Control, patients with a percent dehydration >9% were categorized as having severe dehydration, 3-9% as some dehydration, and <3% as no dehydration.

Ethical approval was obtained from icddr,b’s Ethical Review Committee and Rhode Island Hospital’s Institutional Review Board.

The true dehydration status (percent dehydration) was determined based on the patient’s weight at the time of admission to the hospital and their “post-illness” weight at the time of discharge from the hospital. Calculated percent dehydration was stratified into three categories of dehydration severity — no, some, and severe — based on current standards in the literature.16–18 The WHO algorithm and NIRUDAK model both attempt to predict patients’ true dehydration status by classifying patients into one of three predicted categories of dehydration severity — no, some, or severe.

*Data Analysis*

A decision tree (Figure 1) was constructed to demonstrate expected DALYs and expected costs for each possible combination of true dehydration status and model-assigned dehydration status. Expected cost was calculated for each branch of the decision tree by taking the mean cost of all patients in that branch and multiplying by branch probability. Costs for treatment were calculated using data from icddr,b. Total costs for each individual patient in the study were calculated based on the type and total amount of fluid each patient received, associated equipment costs, length of stay at the hospital, and wages lost while in the hospital. All costs were received directly from icddr,b. All exchange rate conversions from Bangladeshi taka (BDT) to United States dollar (USD) were conducted using data from the World Bank 19,20. Costs are summarized in Table 1.

DALYs were calculated as a sum of years of life lost due to illness and years lived with disability. Per convention, years of life lost for each patient were based on Japanese life tables which outline life expectancies at specified ages 21,22. Years lived with disability were calculated based on estimates from the Global Burden of Disease study and prior literature on the effects of over- and undertreatment of severe dehydration 23–25. Expected DALYs for each branch of the decision tree were calculated by taking the mean number of DALYs for all patients in that branch and multiplying by the branch probability.

For the base case analysis, the probability of death from serious cases of undertreatment (i.e., if a patient had severe dehydration but was predicted to have some or no dehydration) and probability of death from serious cases of overtreatment (e.g., if the patient has some or no dehydration but was predicted to have severe dehydration) were estimated based on clinical input from physicians who have practiced at icddr,b and on prior studies of undertreatment in the context of dehydration due to diarrheal illness 25. An initial incremental cost-effectiveness ratio (ICER) was calculated using these data.

Two-way sensitivity analyses were then conducted; here, the probability of death from under- and overtreatment were both taken as variable. Per WHO recommendations, two willingness-to-pay thresholds were used in analysis: two- and three-times the 2019 Bangladeshi gross domestic product (GDP) per capita in USD 26.

**Results**

Median age for enrolled patients was 35. Median household income was $447. Children, adults, and elderly patients each account for about one-third of our study population; age categories were based on WHO classification 27,28. Demographic information is summarized in Table 2.

**Discussion**

1. Findings
2. Benefits/comparison to existing work
3. Limitations/future directions
4. Conclusion/summary

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**Figures and Tables**

**TO-DO**

PARAMETER LIST (look for range/sample size or CI/alpha/bounds if possible)

* **Probability of dying from overtreatment / SEVERE dehydration**
* **Probability of dying from undertreatment / SEVERE dehydration**
* Mean annual wage for Bangladesh around 2020 — empirical econ value, no range needed
* Bangladesh WTP range — empirical econ value, no range needed
  + Can base on per capita GDP (Jonah)

MANUSCRIPT WRITING

* Anagha: Discussion
* Jonah: Methods (other than data collection/trial)
  + Crystalize table/figure list

ANALYSES

* Jonah: add discounting