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Title: Assessment of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) to Predict Acute Kidney Injury (AKI) in Children Receiving Multiple Nephrotoxic Medications (NINJA NGAL)

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1. Background/Preliminary Studies

Nephrotoxic medication (NTMx) exposure is one of the most commonly cited causes of acute kidney injury (AKI) in hospitalized children[1], and is the primary cause of AKI in 16% of cases. Recent data from Texas Children's Hospital reveal more than 80% of non-critically ill children receive at least one NTMx (e.g., aminoglycosides, non-steroidal anti-inflammatory agents) during their hospitalization[2]. NTMx-AKI is associated with increased hospital length of stay and associated health care costs; we found patients with NTMx-AKI secondary to intravenous aminoglycoside exposure spent a median of five additional days in hospital (additional cost of $17,000) compared to children who were exposed but did not have AKI[3]. Furthermore, 10-49% of adults and children who survive an AKI episode develop chronic kidney disease[4-7], which puts them at risk for hypertension and progression to kidney failure, requiring dialysis or a kidney transplant.

Through our initial work at Cincinnati Children's Medical Center, **we have found that NTMx exposure is potentially modifiable and the associated AKI is an avoidable adverse safety event.** In our single center systematic screening system to identify children at-risk for AKI called Nephrotoxic Injury Negated by Just in time Action (NINJA), we utilized an electronic health record trigger to improve near real-time clinical decision support collaboration between rounding physicians, pharmacists, nurses and patient families[8]. With this systematic screening, we found our baseline NTMx-AKI rates (2.96 per 1000 patient-days)[8] were similar to published baseline central line blood stream[9] and catheter associated urinary tract infection[10] rates, suggesting that NTMx-AKI is as important as these US hospital acquired conditions which are national priorities. We recently published the 3½ year NINJA experience, demonstrating sustained decreases in NTMx exposures (38% reduction) and NTMx-AKI (68% reduction).[11] We calculated that CCHMC patients avoided more than 600 exposures and almost 400 NTMx-AKI episodes over that time period as a result of the NINJA program.

As a result of our single center success, we have been funded by the Agency for Healthcare Research and Quality to disseminate NINJA at nine other US pediatric hospitals. In the first 18 months of this project, we already observed a 30% reduction in NTMx-AKI rates. Four additional pediatric hospitals have joined the NINJA collaborative and have started to submit data. In aggregate, the Collaborative centers observe a monthly average of 200 patients with NTMx exposure leading to 35 NTMx-AKI episodes from 20,000 patient-days screened. In September 2016, NINJA was accepted as the next Hospital Acquired Condition (HAC) for the Solutions for Patient Safety (SPS); the SPS is a national harm reduction network of more than 100 pediatric institutions in the US and Canada funded by the Centers for Medicare and Medicaid Services. The HAC designation provides significant additional resources to disseminate NINJA to all SPS member hospitals starting in Winter 2017. Thus, the disseminated NINJA program provides a current unparalleled foundation and infrastructure for clinical-translational research to improve outcomes in children with, or at-risk for NTMx-AKI. With the integration of NINJA into SPS, the potential for clinical application of any diagnostic or therapeutic intervention to modify NTMx-AKI will expand exponentially.

While the NINJA quality improvement research related AKI reductions have been important, one in six children exposed to NTMx still develop AKI. In a pilot study assessing the ability of the novel AKI damage urine biomarker NGAL to predict AKI in a cohort of children with cystic fibrosis, we discovered that higher uNGAL levels predicted the AUC for the nephrotoxic medication tobramycin as well as predicting AKI.[12] Thus, we suggest that uNGAL may have a pivotal role in detecting AKI early as well as mitigating AKI with appropriate NTMx-dose adjustment. The proposed project will leverage the clinical infrastructure of NINJA to determine if NGAL could replace serum creatinine as the marker of choice in the epidemic of NTMx-AKI.

2. Rationale

Despite the success outlined above, one of the negative aspects of the NINJA program voiced by clinicians, nurses, families and patients stems from the pain and difficulty in obtaining daily blood samples on patients who meet high-NTMx exposure criteria. As most of the blood samples are performed in the early morning hours, blood draws not only cause pain, but can disrupt nighttime sleeping patterns and reduce patient satisfaction with medical care. In some programs, daily blood monitoring of high-risk patients is not performed limiting our ability to detect AKI and improve the ability of daily screening. Improving our ability to screen for NTMx-AKI with non-invasive urine biomarkers will make a tremendous impact in our ability to detect harm from NTMx medications and at the same time, reduce the difficulty and pain associated with daily blood draws.

In order to incorporate the use of urine NGAL into clinical practice we must first demonstrate that urine NGAL will not miss cases of serum creatinine based AKI (express a high sensitivity and a very low negative predictive value). If successful, we believe we can alter the approach to screening for NTMx-AKI as shown in the figure below. Our central hypothesis is that daily urine NGAL can replace daily serum creatinine measurements in children who meet criteria for high exposure risk according to standard NINJA criteria.

Hypothesis 1: Urine NGAL is highly sensitive to detect NTMX-associated AKI

A. Methods - We will continue to measure serum creatinine values daily according to current NINJA protocol. A once daily urine sample will be obtained for 7 days from each participant who meets the high nephrotoxic medication exposure criteria (receiving 3 or more NTMx on the same day, or 3 or more days of an intravenous aminoglycoside). We will collect urine using a urine bag, or collected as a natural void. Urine will be processed, frozen and banked for future testing. Urine NGAL will be measured in batch in the CCHMC Clinical Lab which has the NGAL assay on their platform. These results will not be posted in EMR.

Hypothesis 2: Bedside testing of urine from high risk NTMx-exposed participants are adequate and reliable compared to uNGAL measured from the clinical platform.

A. Methods - using the urine collected above, we will evaluate urine NGAL using the Bioporto bedside POC test at the time of urine collection. The POC assay is a

colorimetric assay and a “low-risk” reading correlates with the clinical lab based NGAL reading of < 50 ng/ml.

3. Study Design:

This study is a multicenter prospective observational study.

Using the Electronic Medical Record (EMR) generated report, at-risk patients will be identified which is part of our standard of care. At-risk patients are defined as patients meeting high-NTMx exposure criteria. Once identified as a potential research participant one of the research investigators will then contact the primary medical team to ask their permission to approach the participant and family. Once the research team has approval to approach the participant and family, one of the research study coordinator’s will then approach the participant/participant’s family regarding potential enrollment and to obtain informed consent and assent as indicated. Once informed consent is given, a detailed medical record review will be performed on these participants; which may include demographic information, medical history, medications, laboratory values, vital signs, and urinary biomarkers. Data from medical records will be abstracted into an electronic research database. Data collection sheets will be identified by a unique study identification number not based on PHI. A key linking participant names and medical record numbers to study identification numbers will be stored on a password-protected computer, separate from the study data, by the principal investigator or his designee.

3A. Bone Marrow Transplant Repository

Urine samples will be obtained from the Bone Marrow Transplant Repository who meet the NINJA criteria of 3 or more NTMx in a day or IV aminoglycosides given for three or more consecutive days. For those participants enrolled in the BMT Repository that meet NINJA criteria, once daily urine samples will be obtained from the Repository.

4. Consent/HIPPA Authorization

Non-BMT Participants: We plan to obtain informed consent from parents and directly from of-age participants if applicable- as well as assent from participants over the age of 11- to participate in the study at the time of NTMx exposure. Before enrollment, permission from the attending physician caring for the participant will be obtained. After permission is granted from the attending physician, consent will be obtained from the parents, legal guardian, or legally authorized representative in their primary language. An interpreter will be provided if necessary. A short form consent in Spanish will be available for Spanish speaking subjects. If a subject speaks a language other than English or Spanish, a short form consent in their native language will be submitted to the IRB and approved prior to enrollment. Because standard safeguards will be employed to protect PHI, this study represents no more than minimal risk to participants. The consent process and HIPAA authorization will not adversely affect the rights or welfare of participants.

BMT Participants: ***Justification of Waiver of Consent & HIPAA Authorization****:* We are requesting a waiver of the informed consent process and requirement to obtain HIPAA authorization from participants enrolled in the BMT repository at CCHMC. Use of their urine for NGAL involves the review of information that is already in existence at the time this research is being submitted and study staff will not have any direct contact with the research participants enrolled in the BMT repository. We believe the request for a waiver of consent and HIPAA authorization from BMT participants who have consented to provide urine to the BMT repository meets the necessary criteria for a waiver of consent and HIPAA authorization per 45CFR46.116(d) as follows:

a. The use or disclosure of Protected Health Information (PHI) represents no more than minimal risk because:

    i. An adequate plan exists to protect the identifiers from improper use and disclosure. See "Potential risks, discomforts, and inconveniences: Mechanism proposed to minimize the participant's potential risks involving confidentiality" and "Security."

    ii. There are adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted. See "Security."

b. The research could not practically be conducted without the access to and use of the PHI. Critically ill patients receiving care from BMT are eligible for multiple studies, both interventional and observational. This patient population is also understandably under a great deal of stress and the BMT repository has been created to minimize multiple requests for study participation, specifically those involving collection of samples collected by non-invasive means, such as urine.

5. Statistical Analysis Plan: We plan to enroll at least 100 subjects, 30 of whom will need to develop AKI by the KDIGO serum creatinine criteria (50% rise over baseline or a 0.3 mg/dl rise over baseline within 48 hours). If we have not enrolled at least 30 participants with AKI after a 100 participant total enrollment, we will continue to enroll up to another 100 participants to achieve a total of 30 AKI participants. Our current data from the NINJA project show that 15% of exposed participants develop AKI. For hypothesis 1, we will determine the sensitivity, specificity, positive predictive value and negative predictive value of urine NGAL to detect NTMx-AKI. Our goal is to achieve a NPV of >98% using an uNGAL concentration of <50 ng/ml to rule out serum creatinine based AKI development. For hypothesis 2, we will also assess sensitivity, specificity, PPV and NPV for the POC "low-risk" test to predict a clinical lab based NGAL level of <50 ng/ml.

Sample size estimates: With an assumption that 70 participants will not develop AKI in the first 7 days, we will have 490 samples for comparative analysis if we are able to stop at 100

participants. If we need to enroll 200 participants to achieve enroll 30 AKI participants, we would have 1190 samples (170x 7 days) for participants without AKI. Sample size analysis for non-inferiority (of NGAL to serum creatinine, of POC NGAL to clinical lab NGAL) reveals that we need 143 samples to be confident that we will not see a >2% discordance rate between the reference and test data set with a power of 0.8 and an alpha of 0.05. Clearly, we will have enough samples in the dataset. If we analyze the data on a per participant basis, again we will have enough participants if we enroll 200 total. At the minimum of 100 participants, our power is 0.67.

6. Security

Participant confidentiality will be maintained throughout the study, through the use of a numeric coding system. Data will be stored using a secure EDC system (REDCap) and access will be limited to study staff.

The records from this study will be kept confidential to the extent allowed by law. Representatives of Cincinnati Children's Hospital Medical Center ("CCHMC"), the Investigator and CCHMC employees involved with the research study including the Institutional Review Board and the Office for Research Compliance and Regulatory Affairs, and any sponsoring company or their appointed agent as well as National Institutes of Health / National Institute of Child Health and Human Development, and the United States Food and Drug Administration may also be allowed to inspect the medical and research records related to this study. If the results of this study are published, no Protected Health Information (PHI) will be disclosed, and subjects will not be identified by name. Research data will be stored in a secure location, with limited access.

7. Future Use

The data obtained from sites will be saved according to HIPPA guidelines and will be maintained in a de-identified format in REDCap. No PHI will be used for future research without prior IRB approval. Urine samples will be maintained for a minimum of five years and will not be used for future research without prior IRB approval.

Figure 1: Current Screening for NTMx-AKI

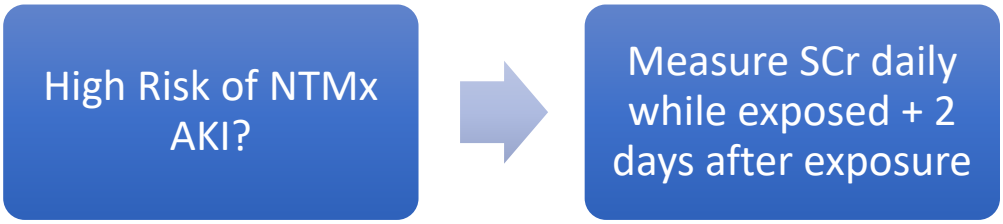


Figure 2: Screening for NTMx-AKI during study

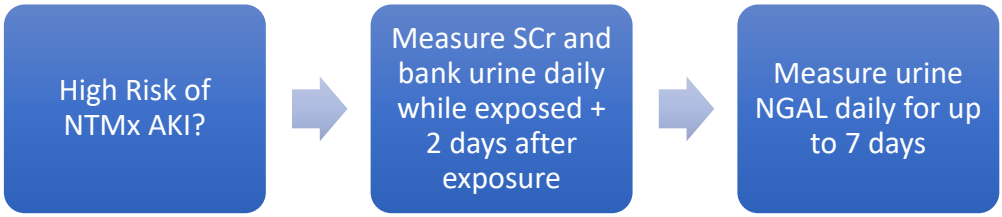
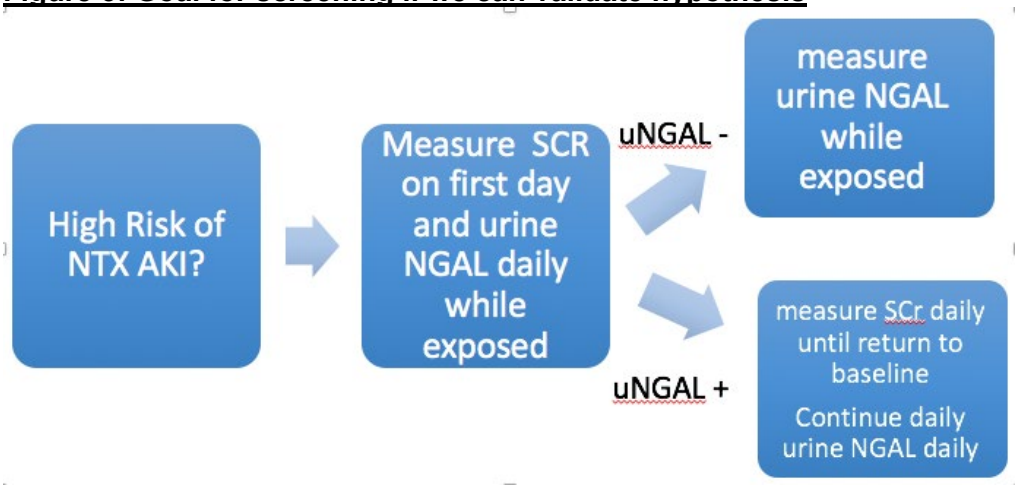


Figure 3: Goal for screening if we can validate hypothesis



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