Drug Induced Kidney Injury: Prevention and Management Strategies

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Cincinnati Children's Hospital Medical Center

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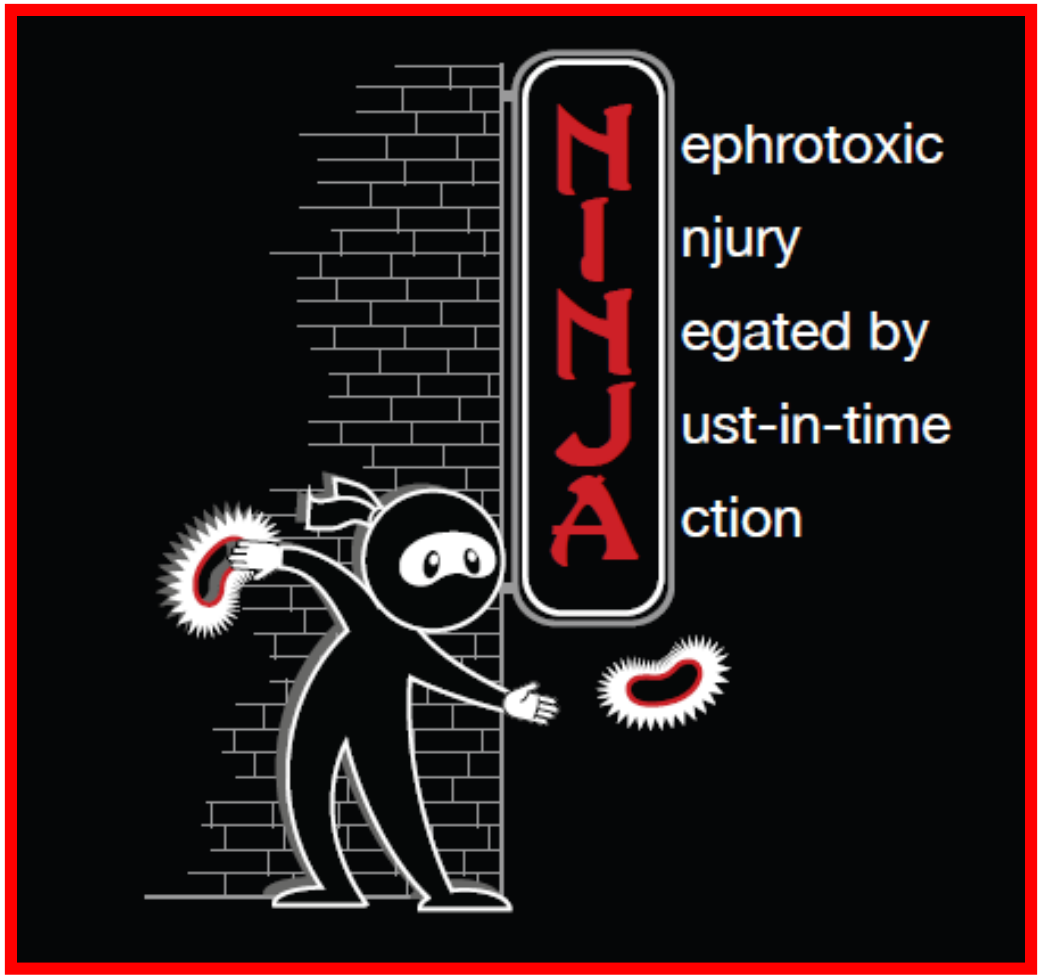
NINJA
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Conflicts of Interest

- Baxter Healthcare
  - Speaker's Bureau
  - Grant support
  - Consultant
- Consultant
  - AM Pharma
  - Astute Medical
  - Bioporto
  - Fresenius
  - MediBeacon
  - Medtronic
  - Reata
  - Renibus

High Level Rationale for NINJA

- One of the most common causes of AKI in non-critically ill hospitalized children
- A portion of NTMx-AKI goes unnoticed due to lack of systematic kidney function surveillance in exposed children
  - Multiple studies show SCr measured at least every four days only 50% of the time in children receiving multiple NTMx
- NTMx-AKI may be a potentially modifiable adverse safety event if
  - At-risk patients are identified
  - Systematic SCr monitoring is instituted reliably in at-risk patients
  - AKI is avoided and/or mitigated by reducing unnecessary NTMx exposure

NINJA Vision Statement

Children should only get the nephrotoxic medications they need for the duration they need them

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Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study

Michael Zappitelli[1], Brady S. Moffett[2], Ayaz Hyder[3] and Stuart L. Goldstein[4]

- Patients receiving IV AG ≥ 5 days
- Primary renal diagnoses excluded
- One year of study
  - 557 children
  - 95% > 3 months of age
  - AKI occurred in
- SCr measured at least q4 days only 50% of the time

Nephrol Dial Transplant (2010) 1 of 7

Acute Kidney Injury and Increasing Nephrotoxic-Medication Exposure in Noncritically-Ill Children

Brady S. Moffett and Stuart L. Goldstein†*

- 350 non-critically ill children with AKI by pRIFLE
- 350 matched children without AKI
- 38 potential NTMx
- Compared NTMx exposure rate between AKI vs. non-AKI patients
- 86% exposed to at least 1 NTMx
- Patients with AKI had 1.7 OR for exposure to a NTMx
- PPV for AKI doubles for patient with 3+ NTMx

Clin J Am Soc Nephrol 6: 856–863, 2011.

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Background

Nephrotoxic medication (NTMx)-associated Acute Kidney Injury (AKI) is one of the most common causes of AKI in hospitalized children.

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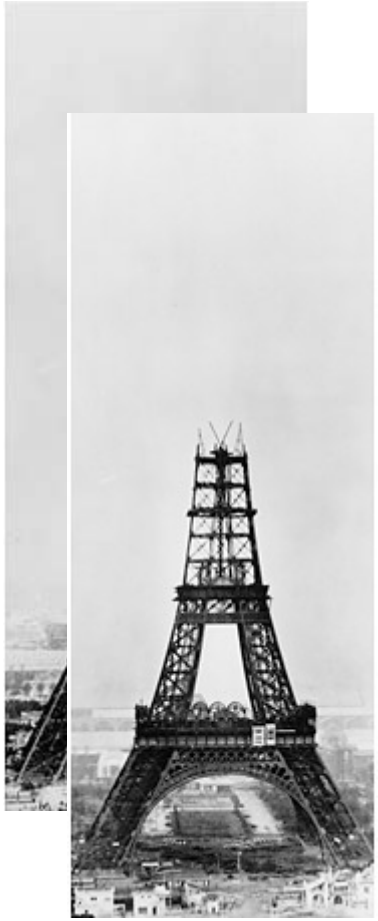
Recent studies demonstrate that NTMx-AKI occurs at higher than previously recognized rates.



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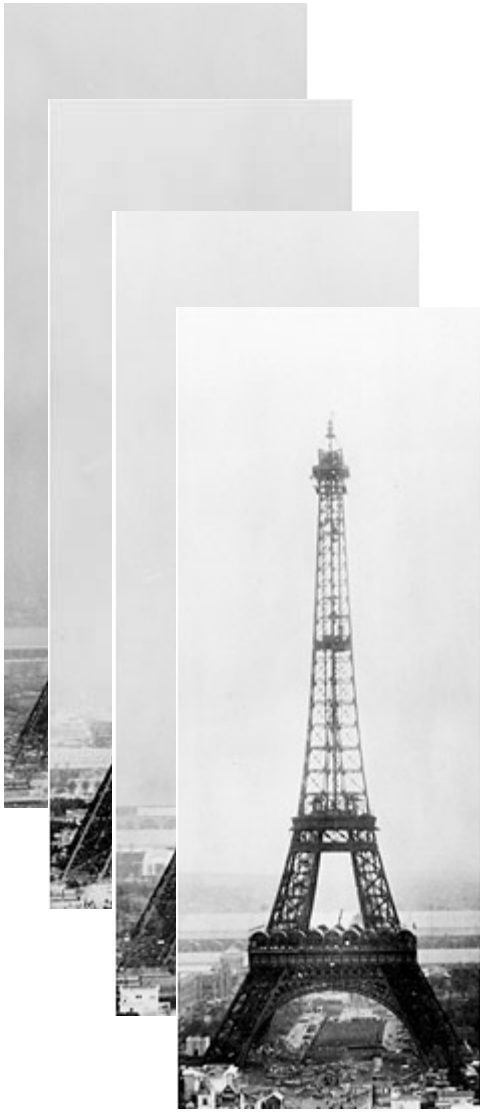
Recent studies demonstrate that NTMx-AKI occurs at higher than previously recognized rates.

A portion of NTMx-AKI goes unnoticed due to lack of kidney function surveillance in susceptible children.



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Background

Nephrotoxic medication (NTMx)-asso
Injury (AKI) is one of the most
hospitalized children.

Hypothesis:
More reliable surveillance of NTMx exposure and injury would demonstrate that rates of AKI are high, and that…
an epidemic exists.

unnoticed due to lack of
k eillance in susceptible children.

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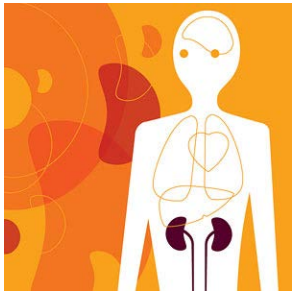
Objectives of NINJA



- Develop and EHR-based AKI screening intervention to assess changes in AKI prevalence, or duration (intensity)

- **RELIABLY QUANTIFY** the rate of *High NTMx exposure* and *NTMx-AKI* in the non-critical care population.

High NTMx-exposure Criteria

Patient receiving 3 or more nephrotoxic medications (NTMx) concomitantly*

or

On an aminoglycoside for 3 or more days

*IV radiology contrast, amphotericin, or cidofovir in previous week is counted for the week following administration

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Nephrotoxic Medication List

TABLE 1 List of Nephrotoxic Medications

Acyclovir	Enalaprilat	Mesalamine
Ambisome[a]	Foscarnet	Methotrexate
Amikacin	Gadopentetate dimeglumine[a]	Nafcillin
Amphotericin B	Gadoxetate disodium[a]	Piperacillin/tazobactam
Captopril	Ganciclovir	Piperacillin
Carboplatin	Gentamicin	Sirolimus
Cefotaxime	Ibuprofen	Sulfasalazine
Ceftazidime	Ifosfamide	Tacrolimus
Cefuroxime	Iodixanol[a]	Ticarcillin/clavulanic acid
Cidofovir[a]	Iohexol[a]	Tobramycin
Cisplatin	Iopamidol[a]	Topiramate
Colistimethate	Ioversol[a]	Valacyclovir
Cyclosporine	Ketorolac	Valganciclovir
Dapsone	Lisinopril	Vancomycin
Enalapril	Lithium	Zonisamide

[a] Medications counted for 7 days after administration toward exposure.

AKI Definition

TABLE 2 pRIFLE SCr-Based AKI Criteria

	eCCl[a]
Risk	eCCl decrease by 25%
Injury	eCCl decrease by 50%
Failure	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2
Loss	Persistent failure >4 wk
End stage	End-stage renal disease (persistent failure >3 mo)

eCCl, estimated creatinine clearance.

[a] eCCl derived for the Schwartz equation as previously described.[13]

Outcome Measures

TABLE 3 Outcome Measures and Definitions

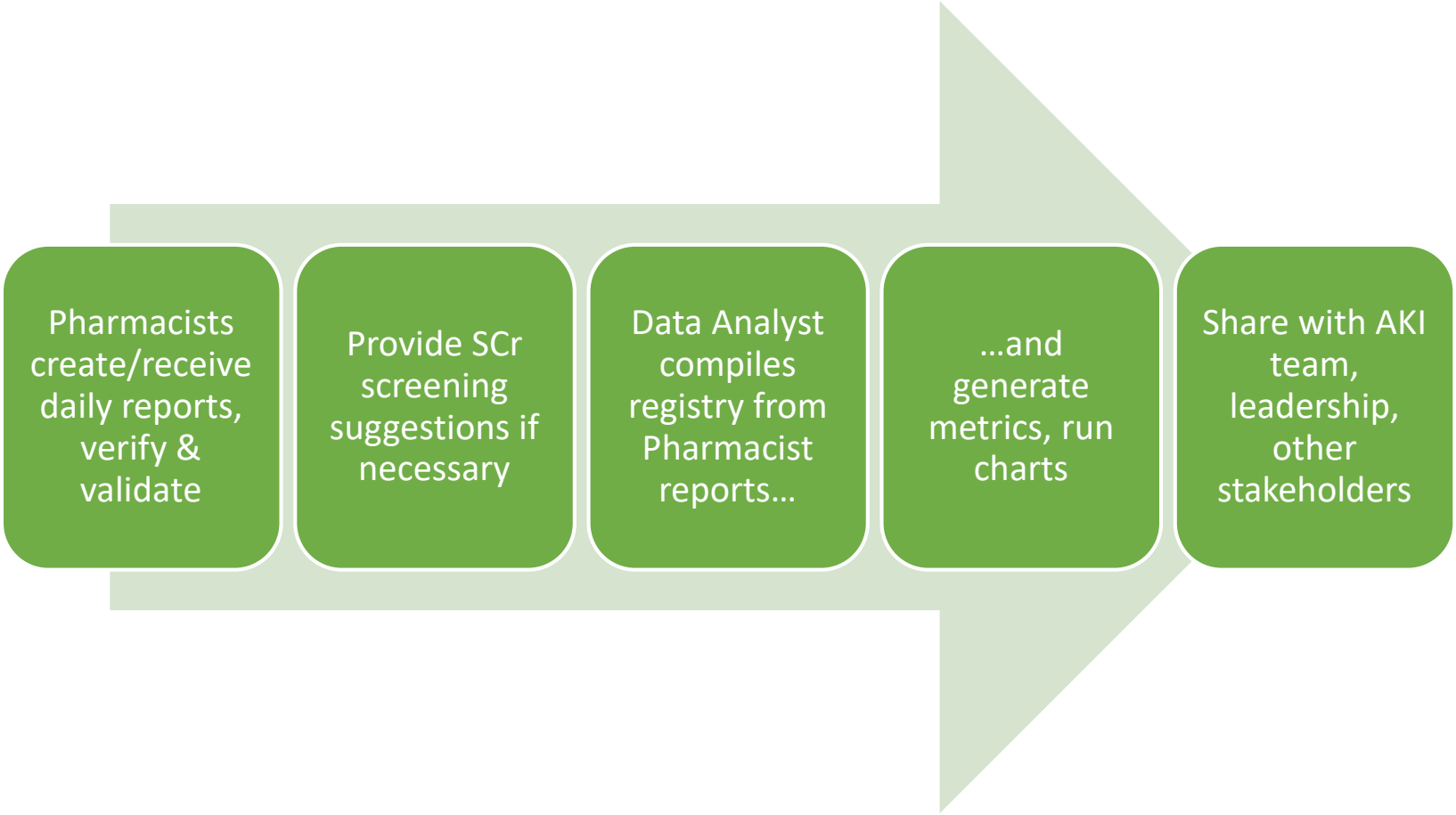
Measure Name	Numerator	Denominator	Clinical Meaning
High NTMx exposure prevalence rate (per 1000 patient-days)	Number of new patients with high NTMx exposure in the calendar week of study	The total number of noncritically ill patient hospital days standardized per 1000 patient days in the calendar week of study	This measure generates a normalized rate of high NTMx exposure cases per study week.
AKI prevalence rate (per 1000 patient-days)	Number of patients with high NTMx exposure who developed AKI in the calendar week of study	The total number of noncritically ill patient hospital days standardized per 1000 patient days in the calendar week of study	This measure generates a normalized rate of AKI cases per study week.
Rate of patients with high NTMx exposure who develop AKI (%)	Number of patients who develop AKI[a]	Number of new patients with high NTMx exposure in the calendar week of study	This measure generates the fraction of patients with high NTMx exposure who develop AKI.
AKI intensity rate (per 100 susceptible patient days)	Number of days patients have AKI	The total number of susceptible patient days standardized per 100 susceptible-days	This measure depicts a normalized duration of AKI per susceptible days.

NTMx, nephrotoxic medication.

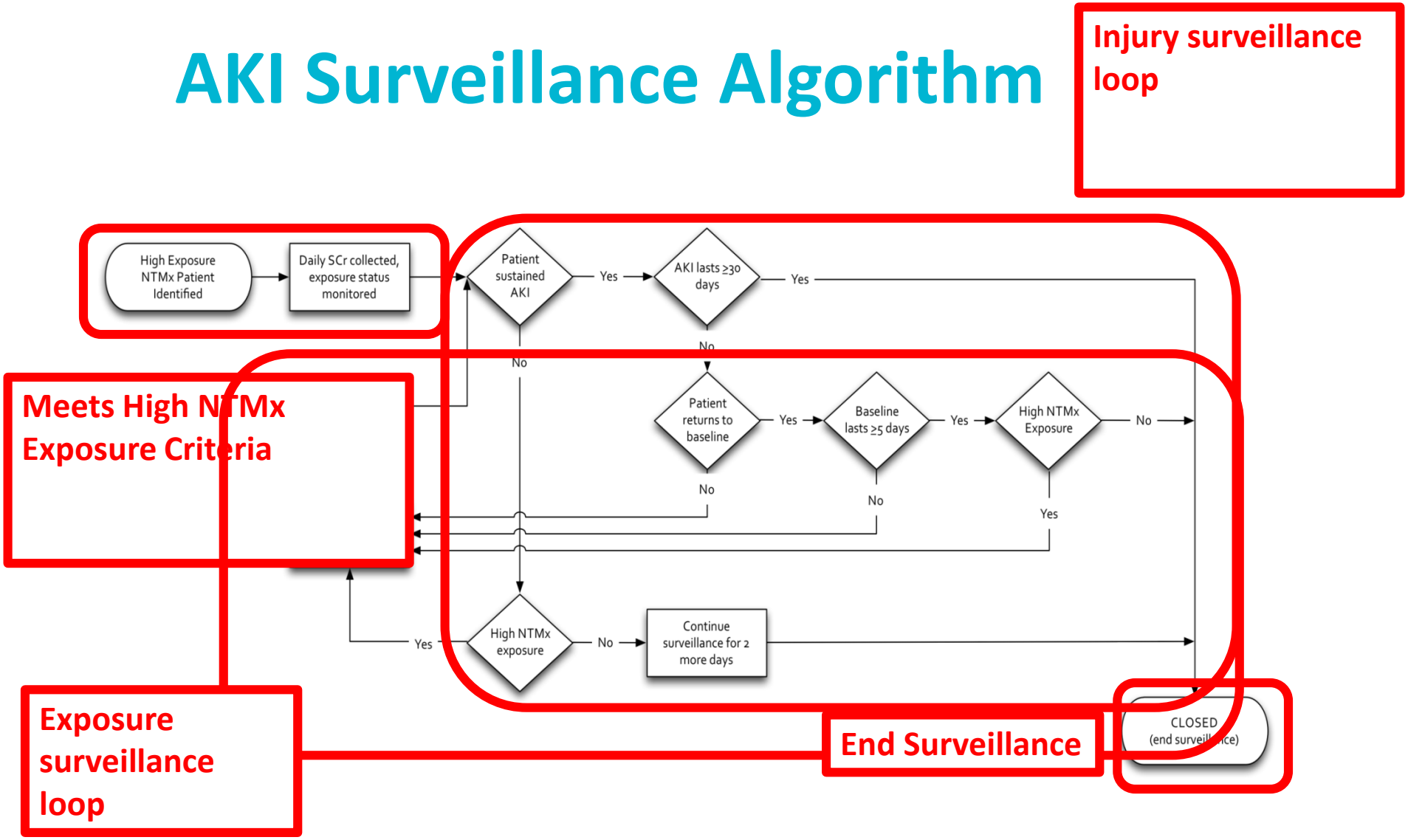
[a] AKI development factors into the numerator of the week that the patient became susceptible if AKI develops in a different calendar week than when a patient became susceptible.

Pediatrics 2013;132:e756–e767

The Process


Pharmacists create/receive daily reports, verify & validate
Provide SCr screening suggestions if necessary
Data Analyst compiles registry from Pharmacist reports…
…and generate metrics, run charts
Share with AKI team, leadership, other stakeholders

AKI Surveillance Algorithm



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RESULTS

PEDIATRICS®
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Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury

Stuart L. Goldstein, Eric Kirkendall, Hovi Nguyen, Joshua K. Schaffzin, John Bucuvalas, Tracey Bracke, Michael Seid, Marshall Ashby, Natalie Foertmeyer, Lori Brunner, Anne Lesko, Cynthia Barclay, Carole Lannon and Stephen Muething

Pediatrics; originally published online August 12, 2013;
DOI: 10.1542/peds.2013-0794

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Inclusion Flowchart

Data span June 2, 2011 – June 4, 2012

Pediatrics 2013;132:e756–e767

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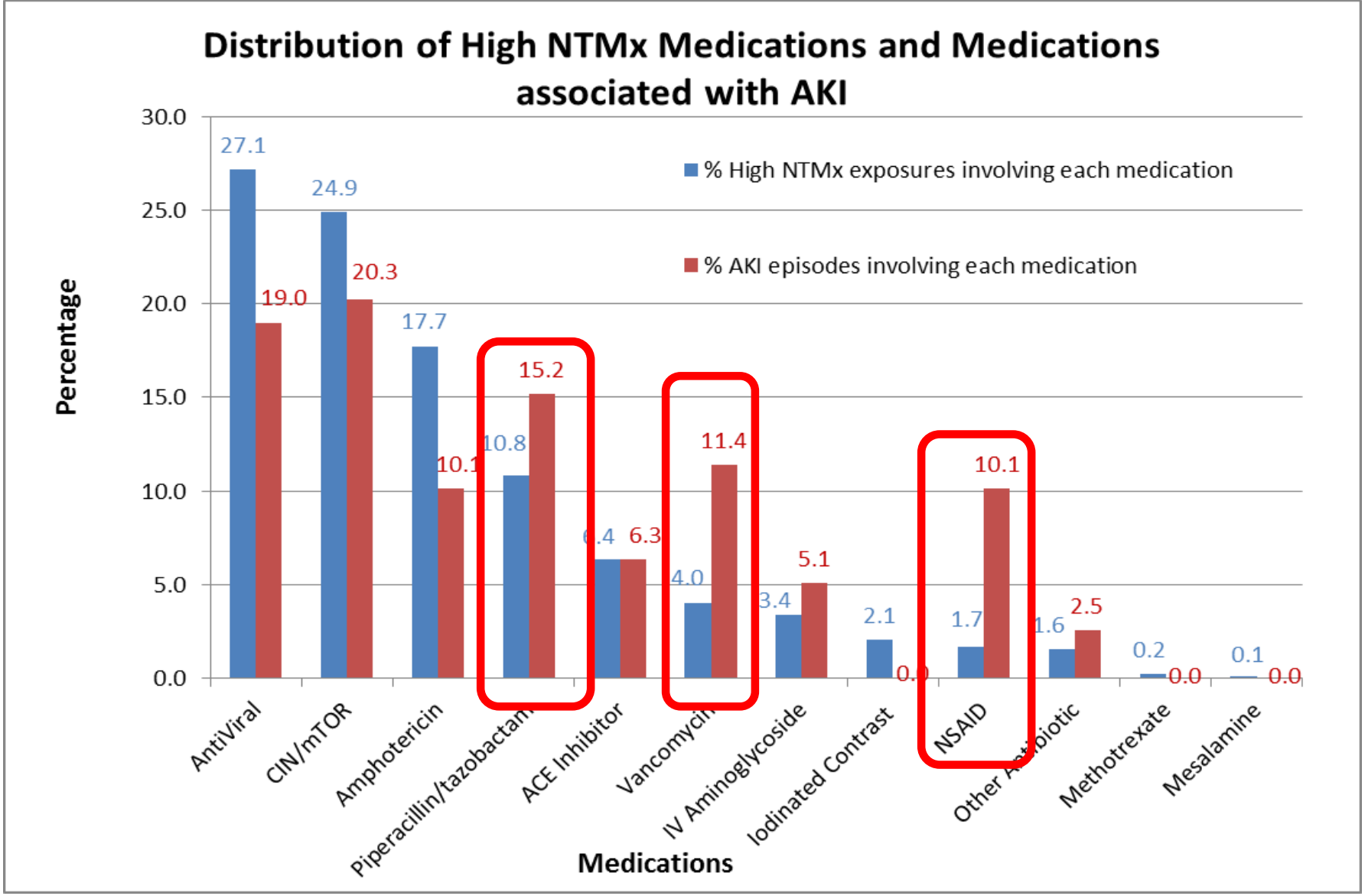

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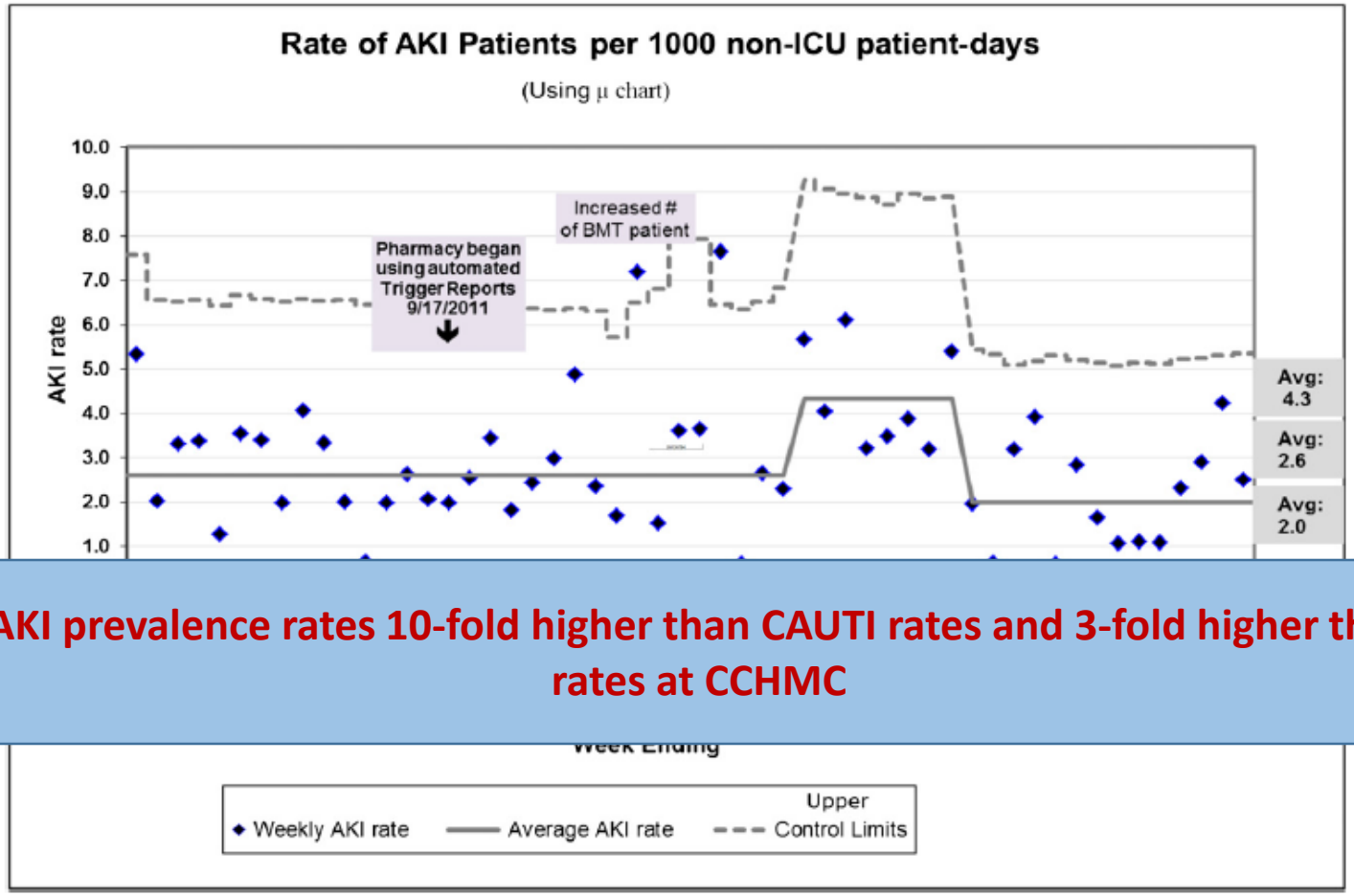

Initial AKI prevalence rates 10-fold higher than CAUTI rates and 3-fold higher than CLBSI rates at CCHMC

FIGURE 5
Weekly average AKI development rates as measured by patient number with AKI per 1000 noncritically ill patient hospital days. The AKI rates initially increased above, and then decreased below, the baseline rate. Each data point represents 1 week beginning from Monday to the following Sunday. BMT, bone marrow transplantation.

Pediatrics 2013;132:e756–e767

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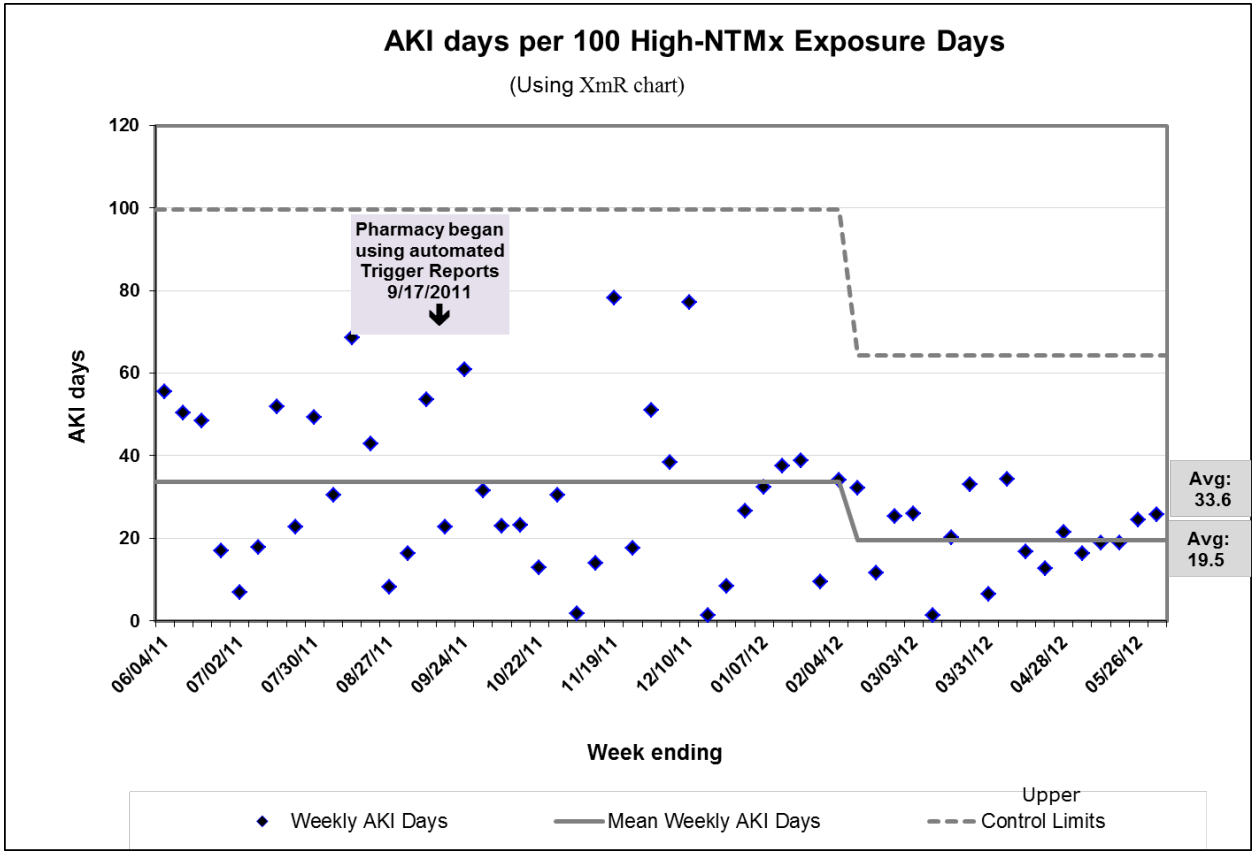
AKI intensity decreases in Year 1 of the project by 42%



Pediatrics 2013;132:e756–e767

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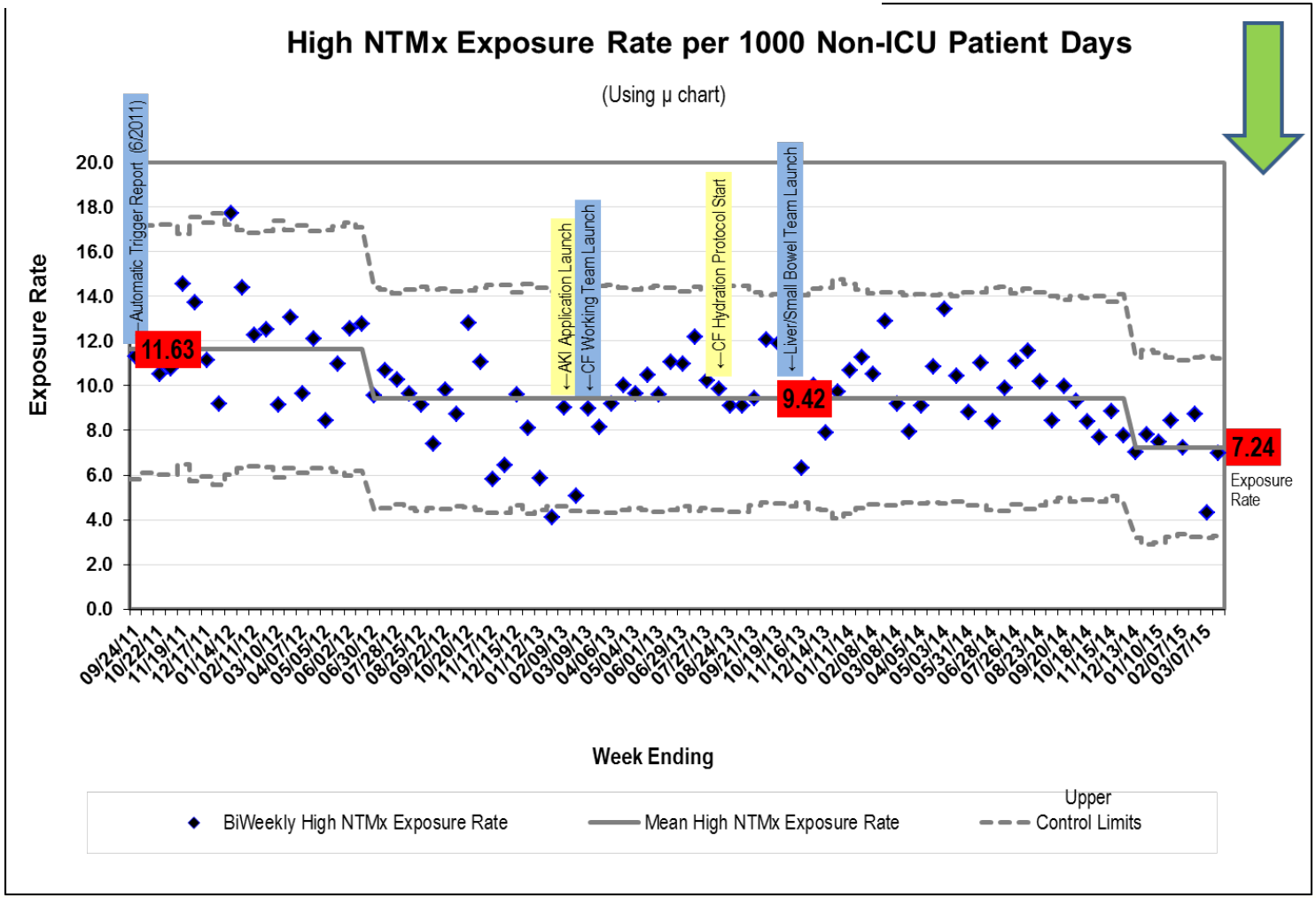
A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury

Stuart L. Goldstein[1], Theresa Mottes[1], Kendria Simpson[1], Cynthia Barclay[2], Stephen Muething[3], David B. Haslam[4] and Eric S. Kirkendall[5]



Kidney International (2016) **90,** 212–221;

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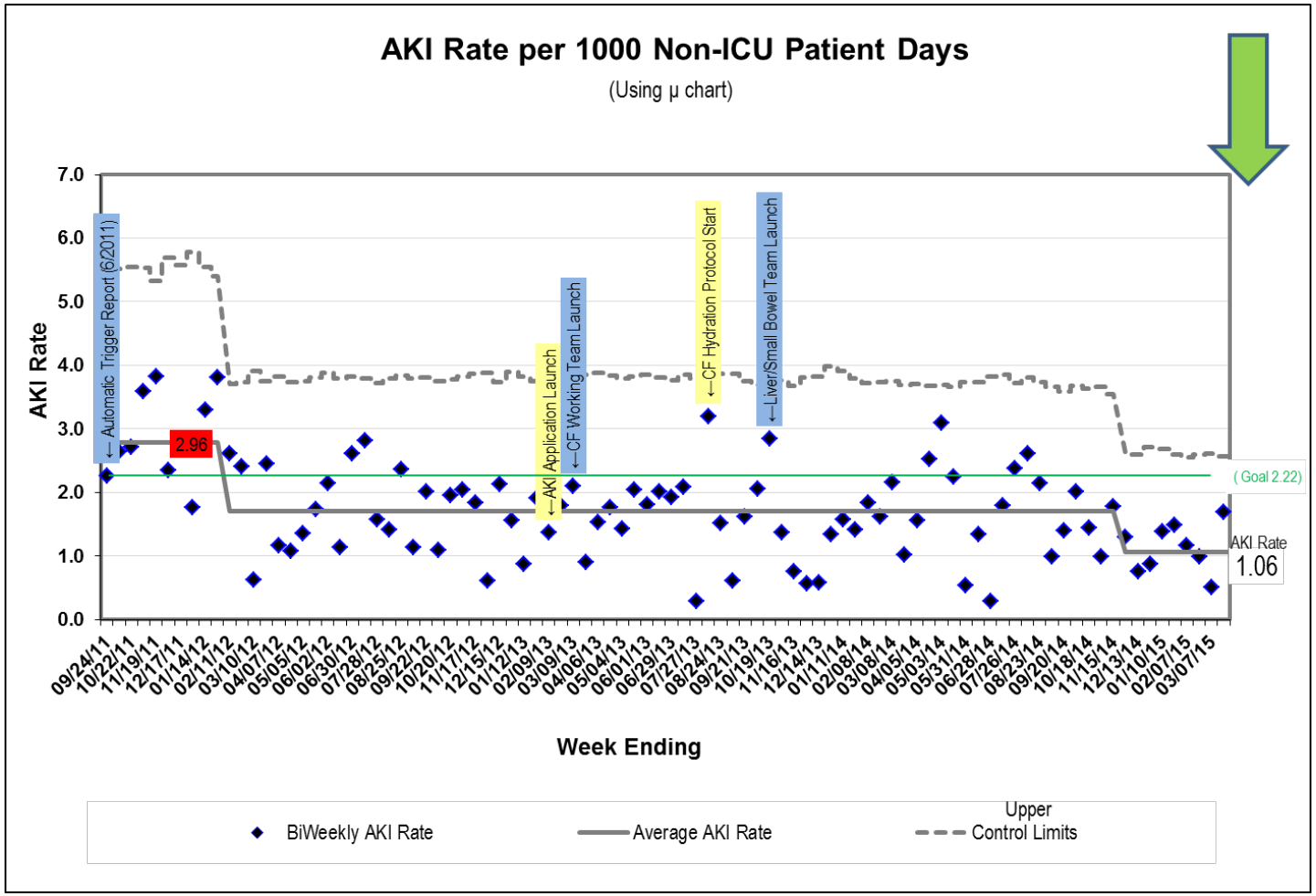

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Adverse Events Avoided

Measure	2011*	2012	2013	2014	2015*	Aggregate
Annualized Non-Critically Ill Patient Days (Actual Count)	97,065 (26,133)	91,363	90,627	99,076	109,968 (27,492)	334,691 Census Days
Annualized Number Of Patient Exposures (Actual Count)	1,129 (304)	969	837	960	692 (173)	3,243 Patient Exposures
Annualized Number Of Patients With AKI (Actual Count)	271 (73)	168	141	159	116 (29)	575 Patients With AKI
Patient Exposures Avoided	**N/A**	**108**	**200**	**219**	**106**	**633 Avoided Exposures**
Patients With AKI Avoided	**N/A**	**105**	**113**	**134**	**46**	**398 Avoided AKI Events**

**Data presented for partial year. Annualized values represent if data were extrapolated to full time period. Study period in 2011 (Sept – Dec), in 2015 (January – March). All aggregate data are actual count.*

Kidney International (2016) **90,** 212–221;

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Cost Implications – A Theoretical Model

- Costs incurred
  - Daily creatinine
  - Prolonged hospital admission for AKI detection
  - Follow up clinic and labs since AKI detected
  - Medications to slow CKD progression
- Potential cost savings (earlier detection)
  - AKI avoided
  - CKD avoided
  - ESRD avoided

University of Michigan
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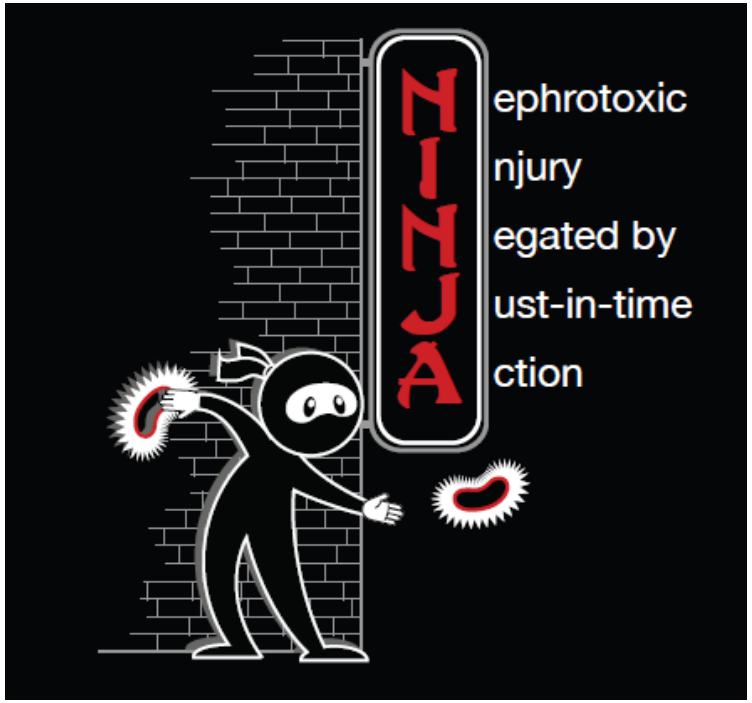
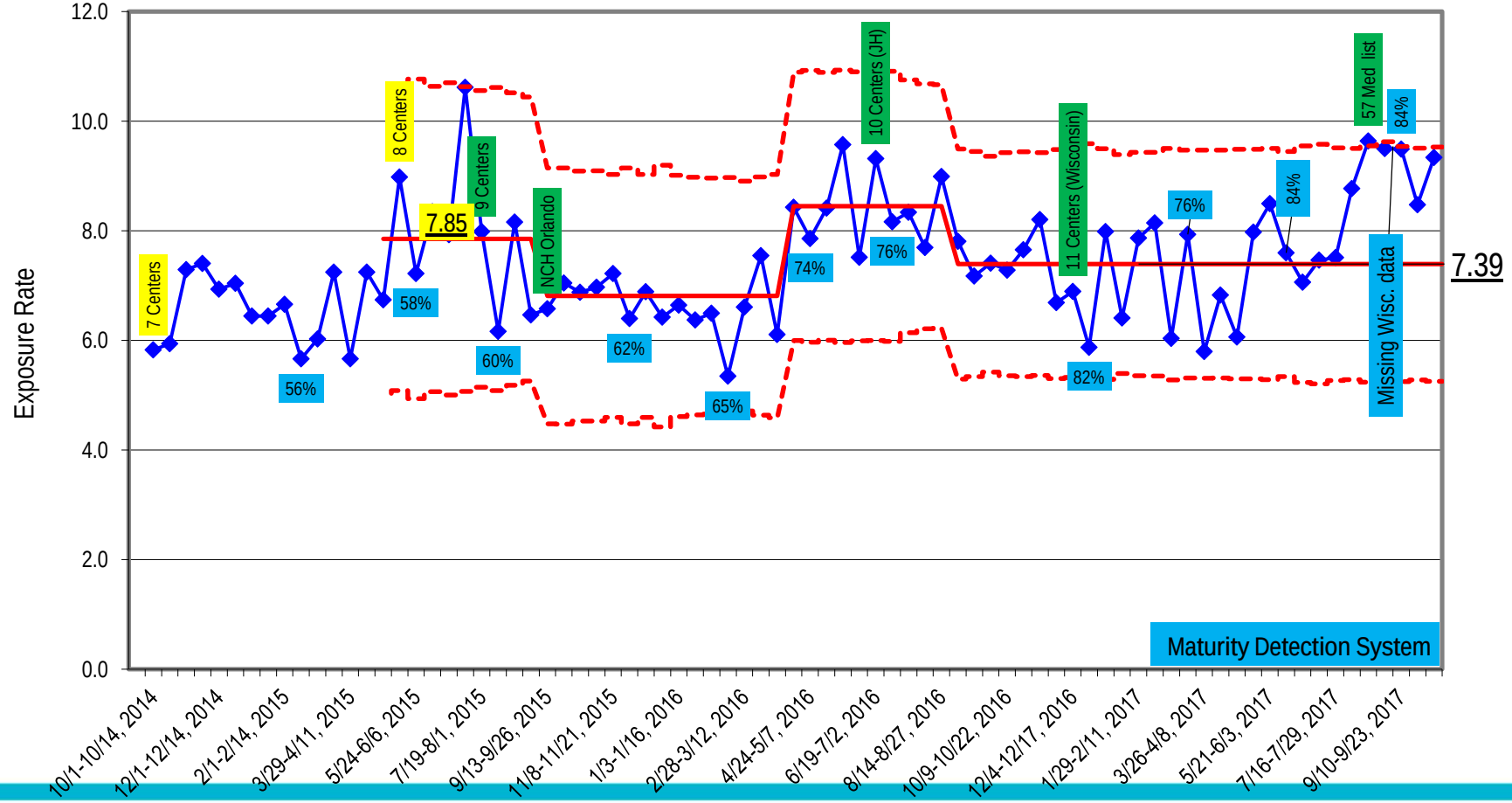


The Rate of Patients with Nephrotoxic Medication (NTMx) Exposure per 1000 Non-ICU Patient Days

All Centers



High NTMx Exposure Rate — Average High NTMx Exposure Rate — Control Limits

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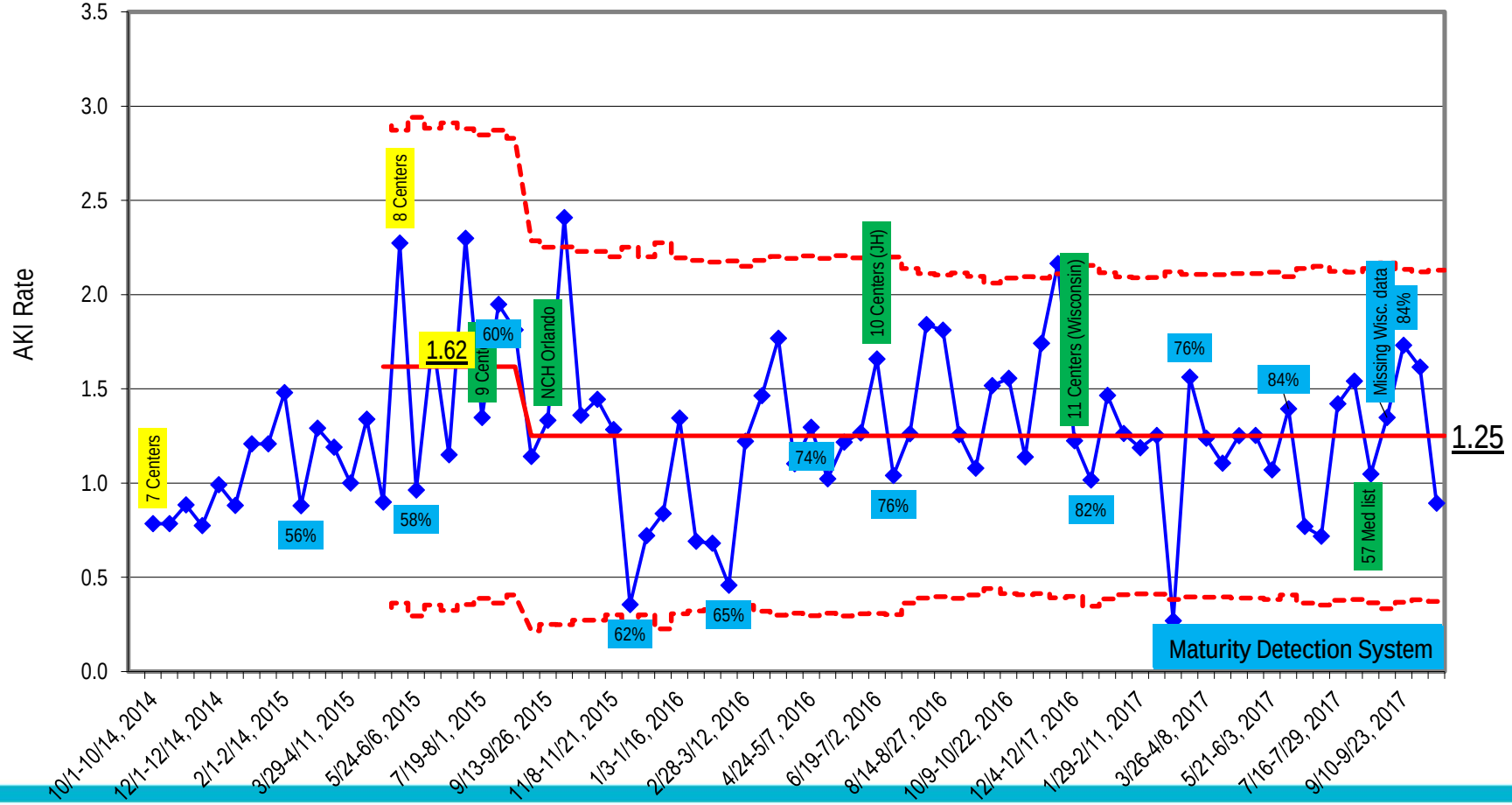
Rate of Nephrotoxic Medication (NTMx) associated Acute Kidney Injury (AKI) per 1000 Non-ICU Patient Days

All Centers



AKI Rate — Average AKI Rate — Control Limits

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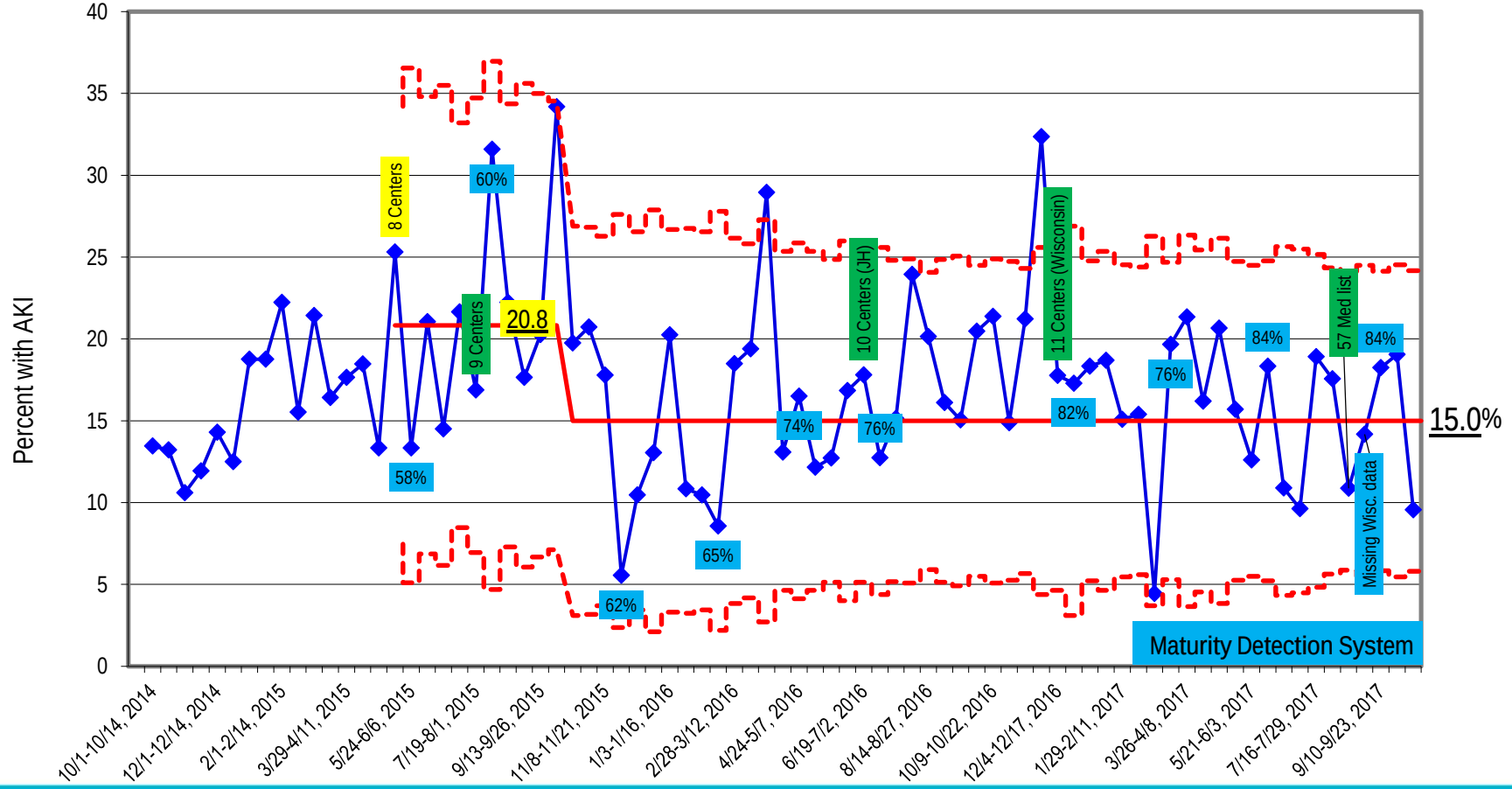
Percent of patients with Nephrotoxic Medication (NTMx) Exposure who develop Acute Kidney Injury (AKI)

All Centers



BiMonthly Percent with AKI — Average Percent of Patients with AKI — Control Limits

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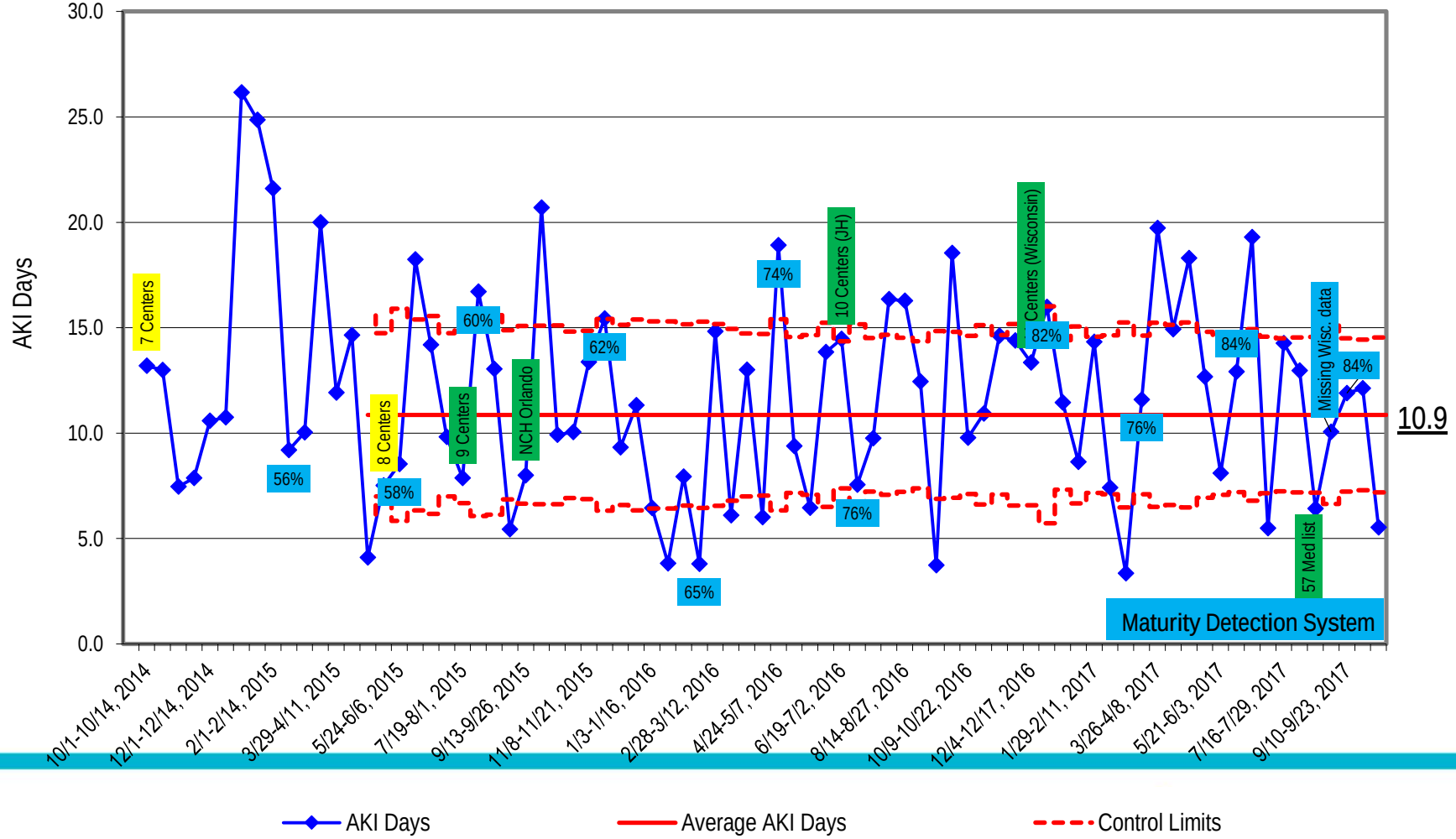
Acute Kidney Injury (AKI) Days per 100 High NTMx Exposure Days

All Centers



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Children's Hospitals'
Solutions for
Patient Safety
Every patient. Every day.

NINJA has been accepted as the next Hospital Acquired Condition to be spread across the Solutions for Patient Safety

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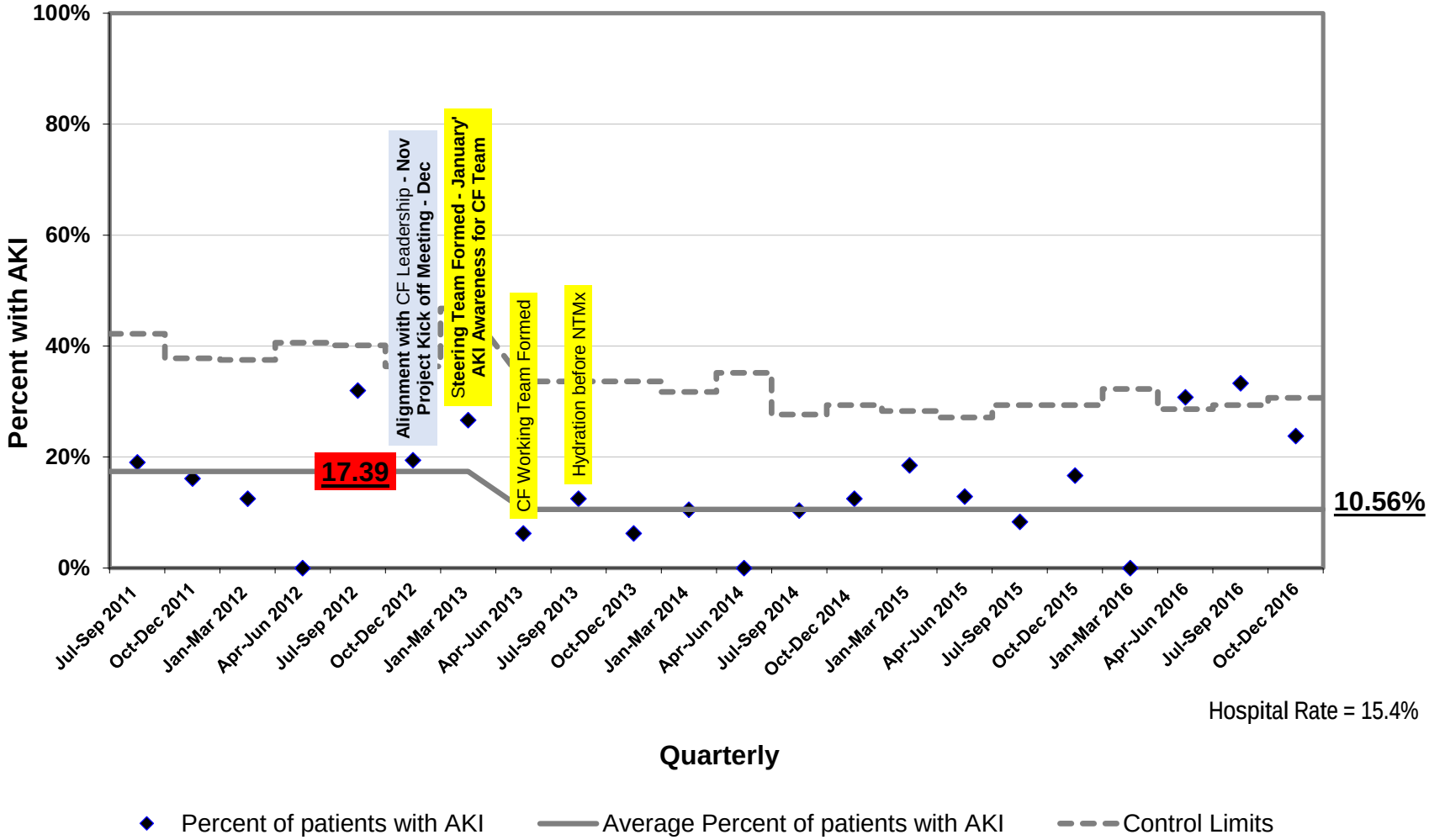
Vision for NINJA

- Develop reliable AKI detection and mitigation across the collaborative
- Once the clinical NINJA engine is in place, this reliable NTMx-AKI phenotype will allow for:
  - Disease specific epidemiology and AKI reduction strategies
  - Development of translational research initiatives
    - Pharmacogenomics
    - AKI biomarker validation
    - Personalized AKI detection and reduction strategies

Percent of CF Patient with High NTMx exposure devloping AKI

(Using p chart)



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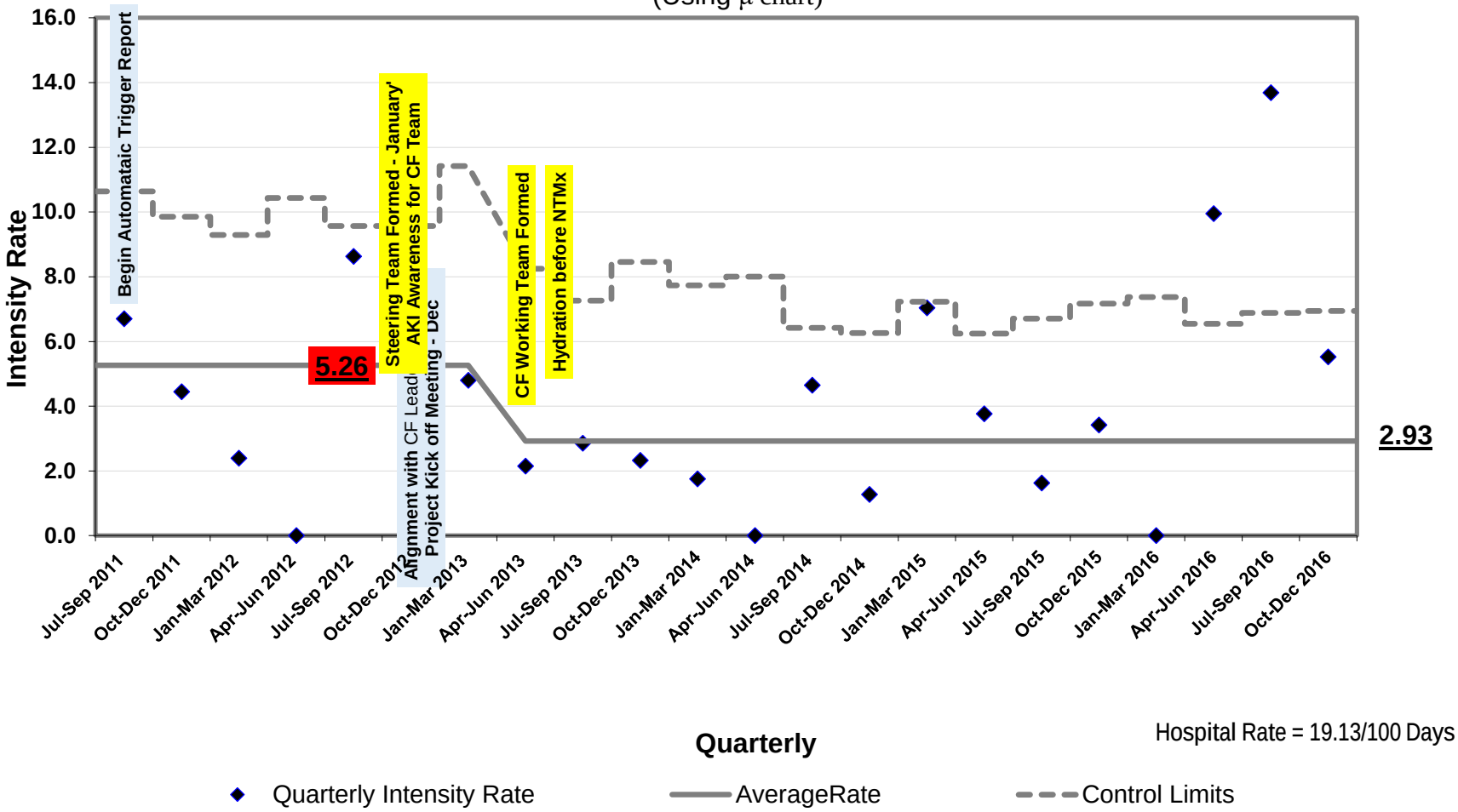
AKI Days per 100 High-NTMx Exposure Days in CF Patients (Intensity)

(Using μ chart)



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Next for NINJA

- Accepted by the Solutions for Patient Safety as the next Hospital Acquired Condition
- Use NINJA as the foundation for more translational work
  - Risk stratification
  - Biomarker integration
  - Sub-population assessment

Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: a population pharmacokinetic analysis

Kevin J. Downes[1,2]*, Min Dong[2], Tsuyoshi Fukuda[2,3], John P. Clancy[3,4], Christopher Haffner[5], Michael R. Bennett[5], Alexander A. Vinks[2,3] and Stuart L. Goldstein[3,5]

[1]Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [2]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [3]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [4]Division of Pulmonology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [5]Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

J Antimicrob Chemother 2017; **72**: 254–260

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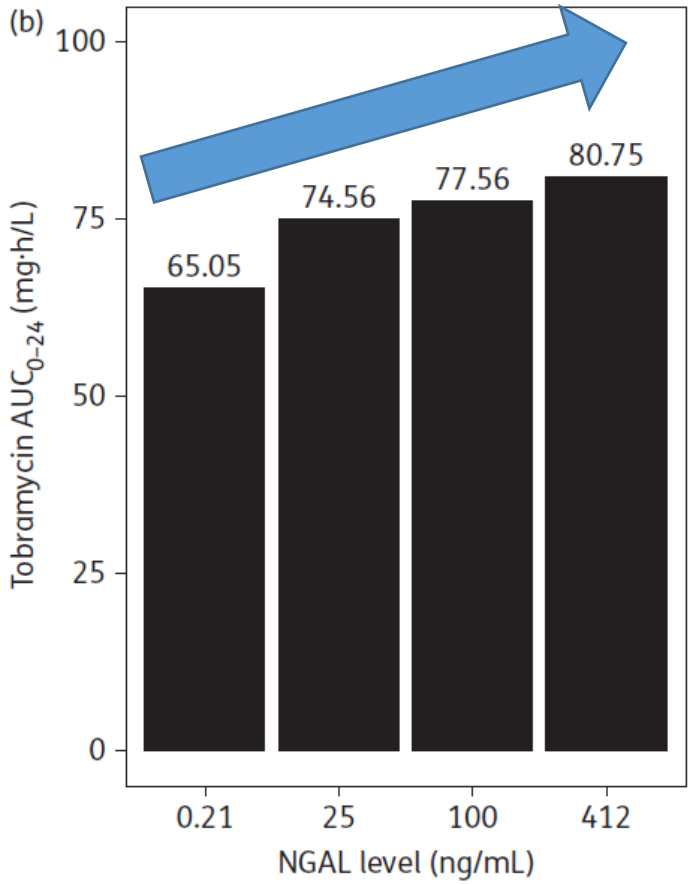

Table 2. Between-subject correlations of weighted average biomarker concentrations and individual PK parameter estimates[a]

	C_{max}		AUC_{0-24}	
Biomarker[b]	regression coefficient	*P* value	regression coefficient	*P* value
NGAL	0.07	0.57	0.46	<0.001
NGAL/UCr	0.19	0.15	0.33	0.009
RBP	−0.19	0.16	0.15	0.25
RBP/UCr	−0.15	0.26	0.03	0.80
KIM-1	0.19	0.14	0.13	0.32
KIM-1/UCr	0.29	0.02	−0.08	0.53

[a]Analyses performed using 186 PK estimates and biomarker pairs, accounting for repeated measurements during 60 tobramycin courses.
[b]Biomarkers log-transformed for comparisons.

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JAMA Pediatrics | Original Investigation

Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children

Kevin J. Downes, MD; Carter Cowden, MPH; Benjamin L. Laskin, MD, MS; Yuan-Shung Huang, MS; Wu Gong, MS, MPH; Matthew Bryan, PhD; Brian T. Fisher, DO, MPH, MSCE; Stuart L. Goldstein, MD; Theoklis E. Zaoutis, MD, MSCE

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Table 2. Unadjusted Frequency of AA-AKI Among Patients Who Received Combination Therapy on at Least Hospital Days 1 and 2

β-Lactam Antibiotic	Patients, No. (%)		% Increase in SCr Level Among Those With AA-AKI, Median (IQR)
	Courses of Treatment (n = 1915)	Cumulative Incidence of AA-AKI (n = 157)	
Piperacillin sodium/tazobactam sodium	1009	117 (11.7)	67 (67-120)
Ceftazidime sodium	295	17 (5.8)	75 (55-200)
Cefepime hydrochloride	422	17 (4.0)	67 (60-120)
Meropenem/imipenem	189	6 (3.2)	69 (43-133)

Abbreviations: AA-AKI, antibiotic-associated acute kidney injury; IQR, interquartile range; SCr, serum creatinine.

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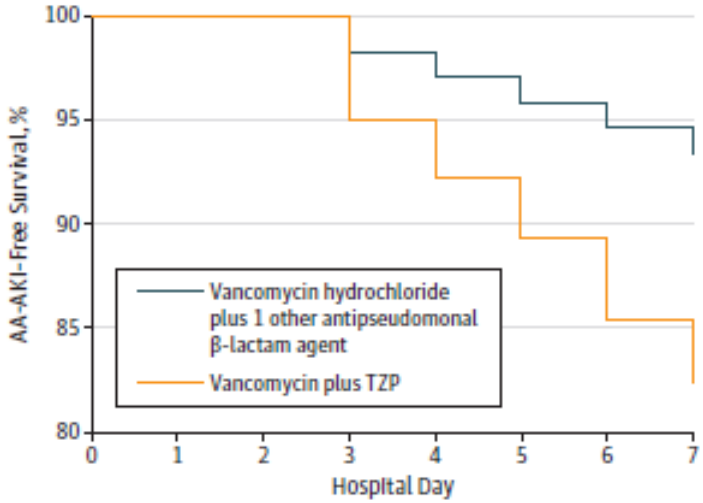
Figure. Kaplan-Meier Curves for Antibiotic-Associated Acute Kidney Injury (AA-AKI)–Free Survival in Hospitalized Children



No. at risk								
Other agents	906	906	906	906	825	536	328	219
TZP	1009	1009	1009	1009	883	570	342	226

Combination therapy was administered to children during the first week of hospitalization. TZP indicates piperacillin sodium/tazobactam sodium.

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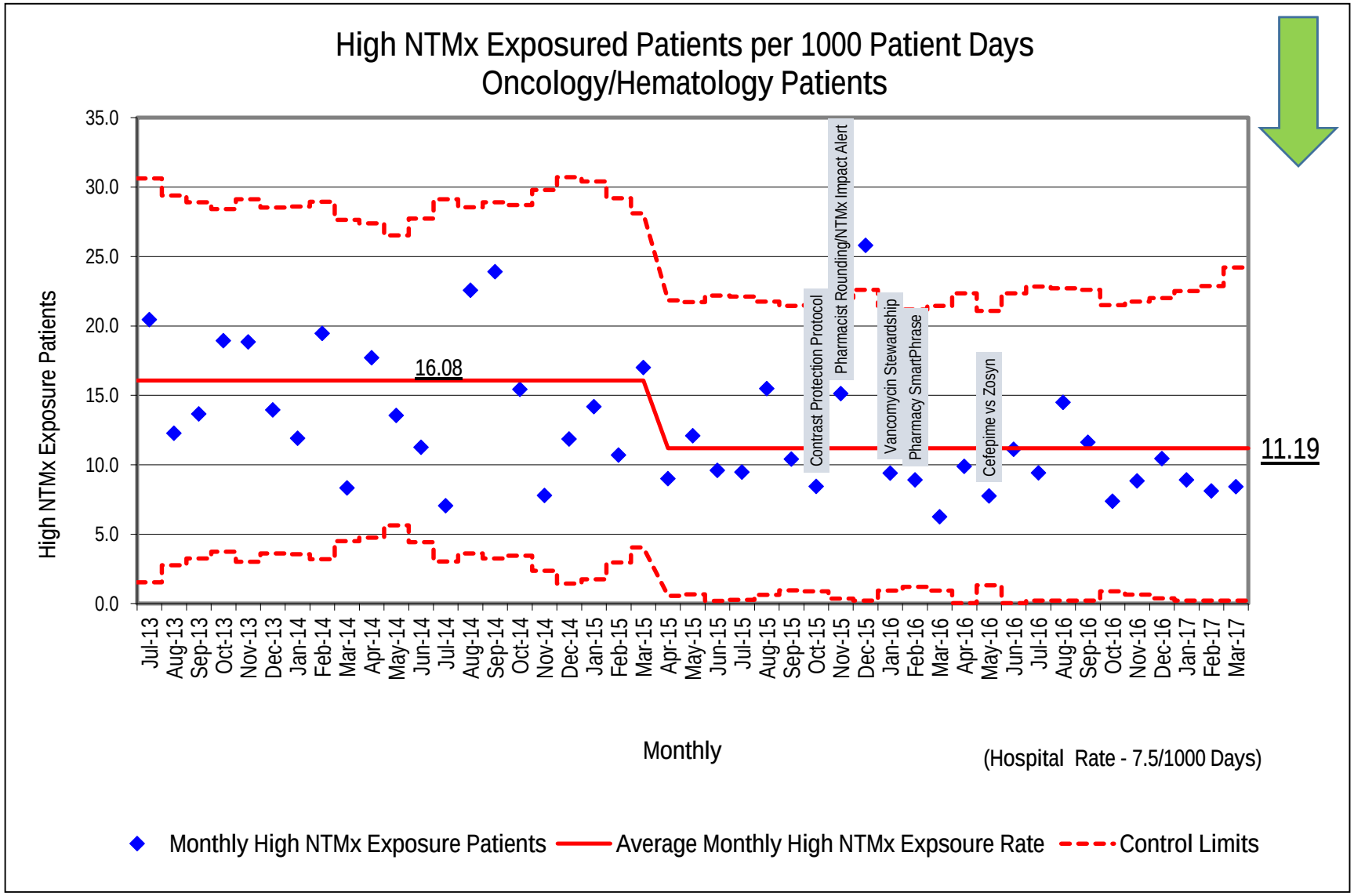
Table 4. Discrete-Time Failure Models of AA-AKI in Patients Who Received IV Vancomycin Hydrochloride Plus 1 Antipseudomonal β-Lactam Antibiotic

Covariate	OR (95% CI)[a]	aOR (95% CI)[b]
Vancomycin plus		
1 other antipseudomonal β-lactam agent	1 [Reference]	1 [Reference]
Piperacillin sodium/tazobactam sodium	2.64 (1.83-3.79)	3.40 (2.26-5.14)
Female sex	1.06 (0.77-1.46)	
Race		
Other, mixed race, or unknown	1 [Reference]	
White	1.06 (0.76-1.49)	
Black	1.13 (0.60-2.13)	
Hispanic or Latino ethnicity	0.77 (0.39-1.53)	
Age in years	1.14 (1.12-1.17)	1.15 (1.12-1.18)
Presence of ≥2 complex or chronic conditions	1.16 (0.83-1.60)	
Receipt of ≥2 concomitant nephrotoxins on hospital days 0-2	1.17 (0.81-1.70)	
Receipt of ≥2 concomitant nephrotoxins on the preceding hospital day	1.12 (0.73-1.73)	
Receipt of ≥2 nephrotoxins for >2 consecutive days	1.36 (0.80-2.31)	1.50 (0.87-2.16)
Receipt of IV contrast on hospital days 0-2	1.32 (0.85-2.06)	
Receipt of IV contrast on the preceding hospital day	0.49 (0.12-2.00)	
Requirement of ICU level of care on hospital days 0-2	1.31 (0.95-1.80)	
Requirement of ICU level of care on a given day	1.42 (1.01-2.00)	1.46 (0.99-2.16)
Receipt of mechanical ventilation on a given day	1.22 (0.85-1.76)	
Receipt of vasopressors on a given day	1.68 (0.98-2.88)	



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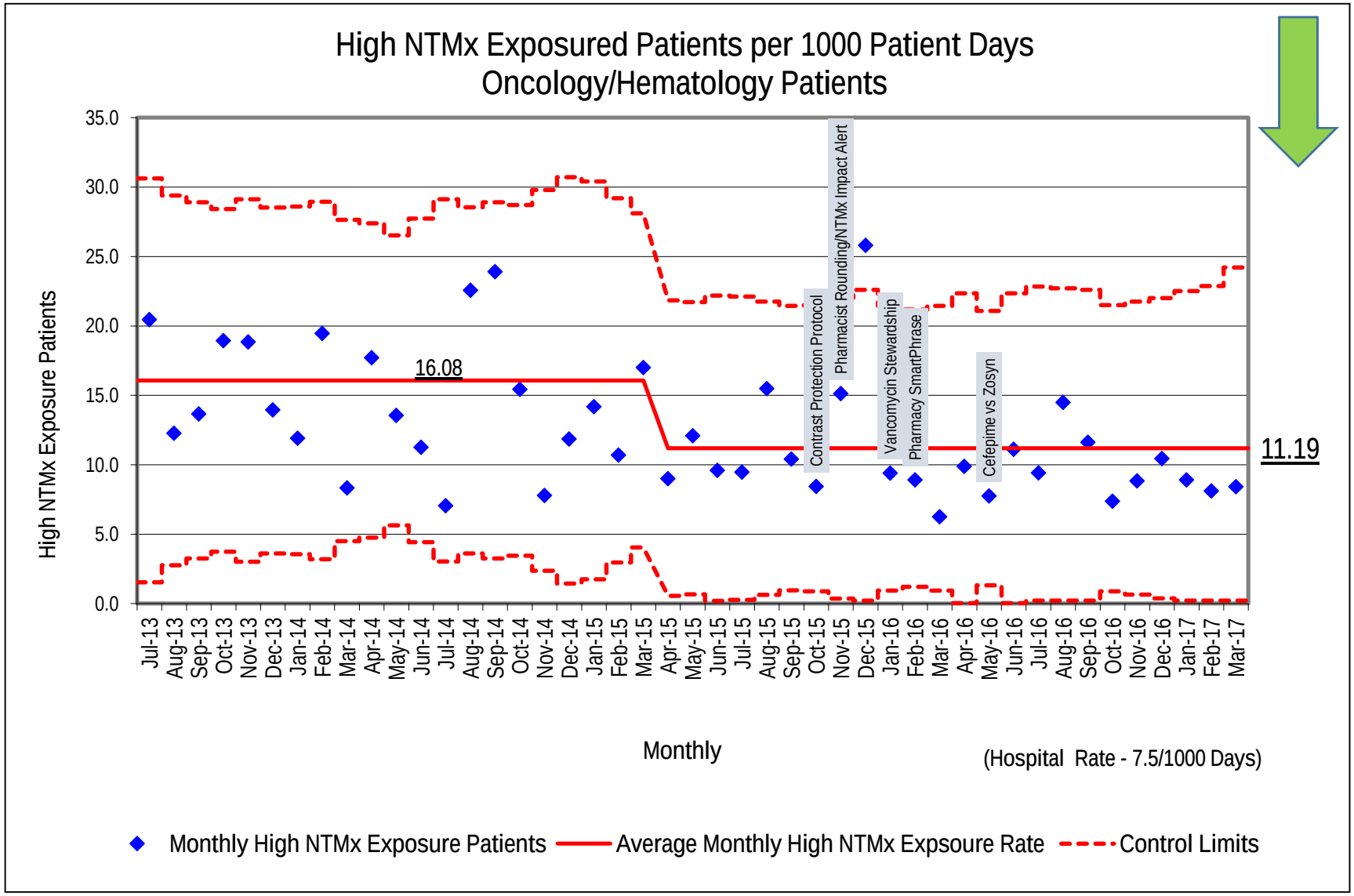

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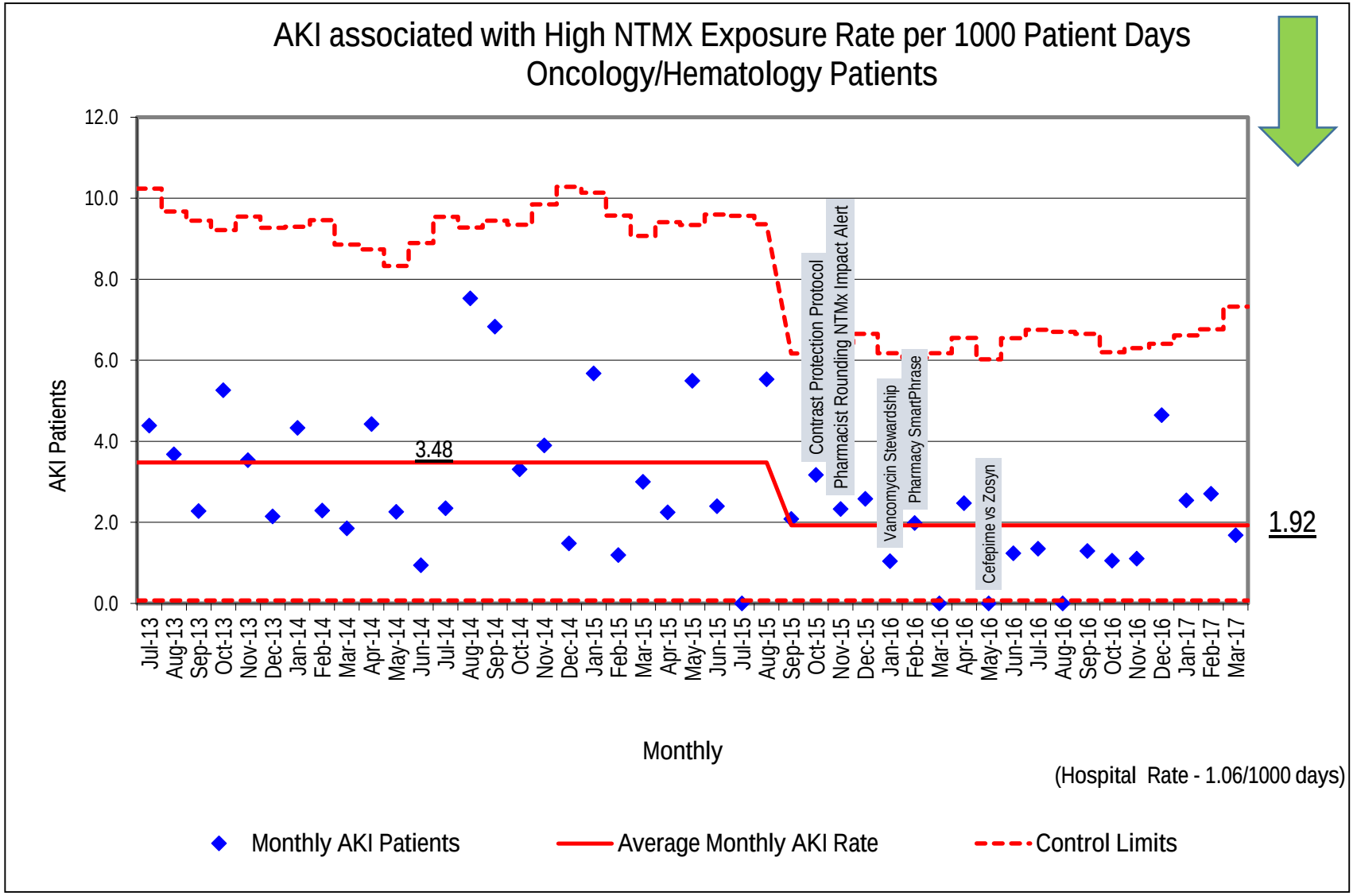

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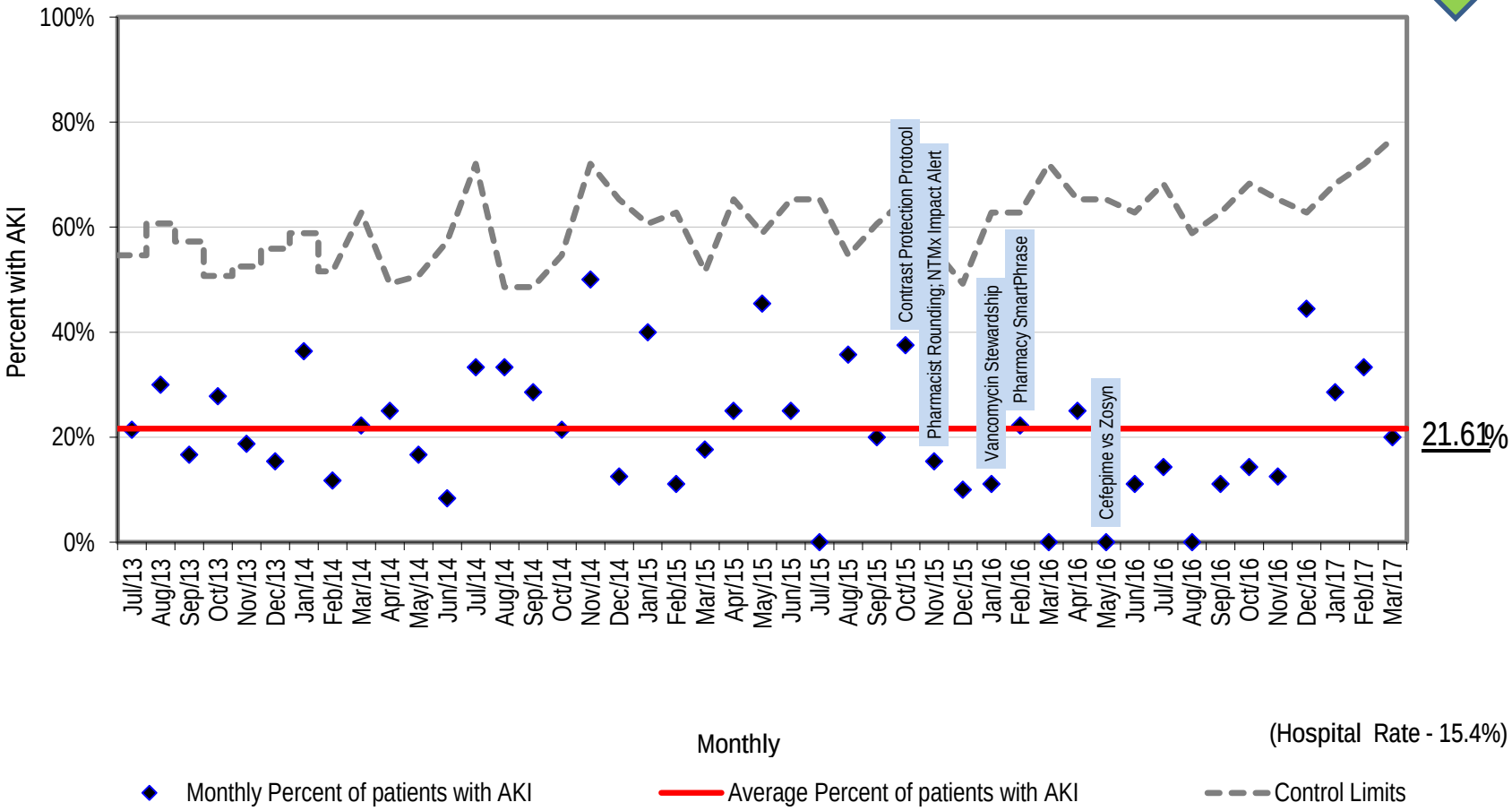
Percent of High NTMx Exposed Patients with AKI
Oncology/Hematology Patients

(Using P chart)



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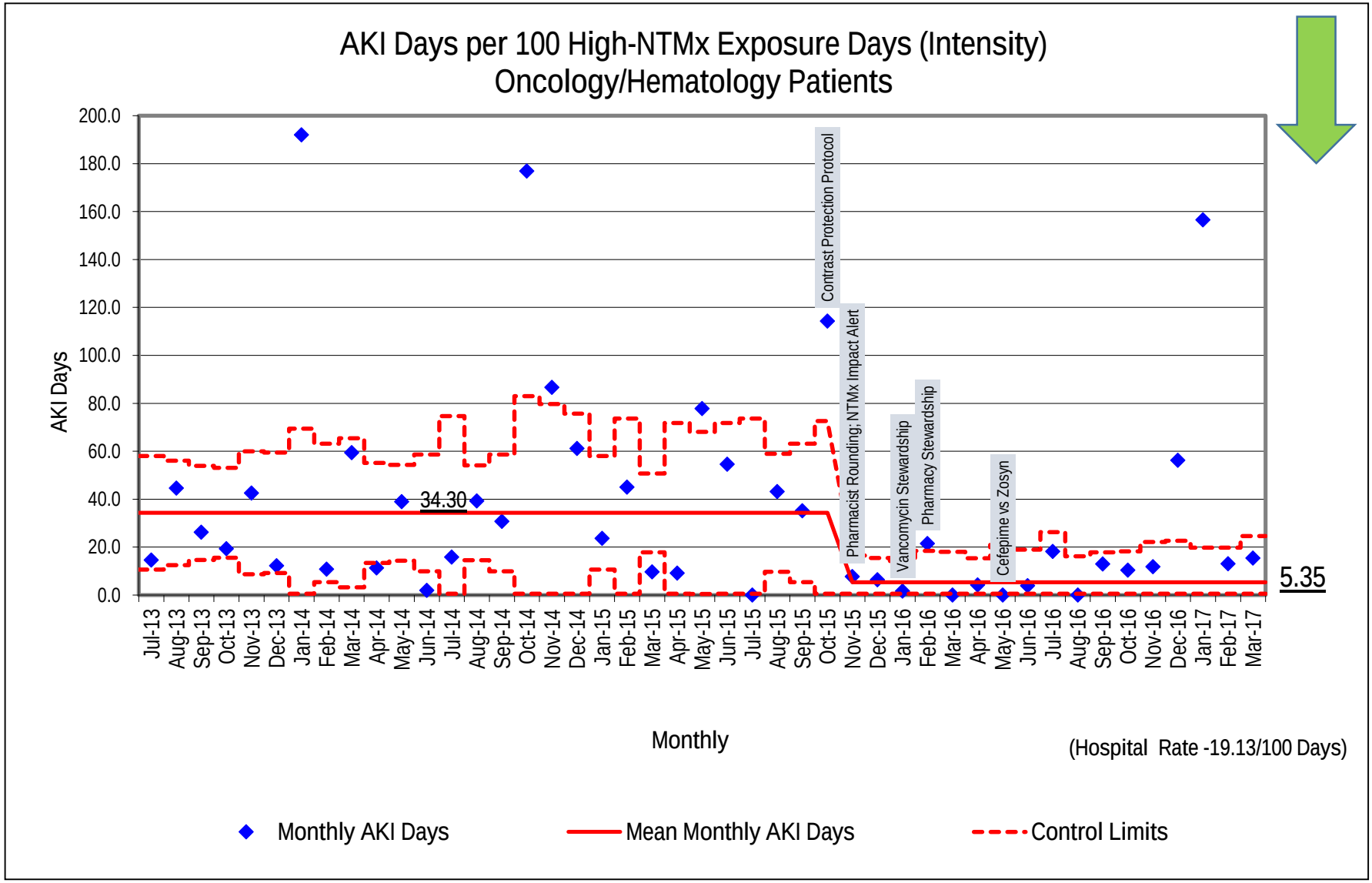

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Can NINJA work in the ICU?

- NO!
  - NINJA raised awareness of NTMx-AKI by increasing surveillance in at-risk non-ICU patients
    - AKI risk is already high in the ICU
    - Aren’t we already monitoring for AKI daily anyway in the ICU?
    - Don’t all ICU patients get at least 3 NTMx the femptosecond they roll in the door?
- MAYBE!
  - Are pharmacists in the ICU armed and supported to
    - Make medication recommendations/dosing adjustments based on risk?
    - Highlight the need to minimize “unnecessary” NTMx?
    - Look up organism antimicrobial susceptibility?

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NINJA COLLABORATIVE: LEARNING SESSION: FEB. 2018

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