Supplemental Table S.1: Candidate nephrotoxic drugs evaluated in DIRECT study.

Abacavir	Ciprofloxacin	Imipenem	Pantoprazole
Acyclovir	Cisplatin	Indomethacin	Penicillin
Allopurinol	Citalopram	Ipilimumab	Phenytoin
Amikacin	Clindamycin	Irbesartan	Piperacillin/tazobactam
Amoxicillin	Colistin	Ketoprofen	Polymyxin
Amphotericin	Cyclosporine	Ketorolac	Rifampin
Ampicillin	Daptomycin	Lansoprazole	Streptomycin
Atazanavir	Diclofenac	Levofloxacin	Sulfadiazine
Carbamazepine	Didanosine	Meropenem	Sulfamethoxazole/trimethoprim
Carboplatin	Doxycycline	Mesalamine	Sulfasalazine
Cefalexin	Esomeprazole	Metformin	Tacrolimus
Cefazolin	Etanercept	Methotrexate	Teicoplanin
Cefepime	Flucloxacillin	Nafcillin	Tenofovir
Ceftaroline	Foscarnet	Naproxen	Tobramycin
Ceftazidime	Fosfamide	Nitrofurantoin	Torsemide
Ceftriaxone	Furosemide	Omeprazole	Vancomycin
Celecoxib	Gemcitabine	Imipenem	
Cidofovir	Gentamicin	Oxacillin	

DIRECT = Drug-Induced Renal Injury Consortium.

Supplemental Table S.2: Timepoint-pairs referenced to calculate the relative change in Serum Creatinine.

Timepoint 1	Timepoint 2
Pre-Drug Exposure	Admission
Drug Exposure	Pre-Drug Exposure
AKI Onset	Admission
AKI Onset	Nadir SCr
AKI Onset	Drug Discontinuation
AKI Onset	Discharge
Drug Discontinuation	Nadir SCr or Resolution of Injury

AKI = acute kidney injury; SCr = serum creatinine.

Supplemental Table S.3: **Distribution of cases by country.**

Country, n (%)	Total	DI-AKI	Not DI-AKI
United States	214 (68)	181 (84.6)	33 (15.4)
India	31 (11)	30 (88.0)	4 (11.8)
United Kingdom	32 (10)	29 (93.5)	2 (6.5)
Brazil	13 (4.1)	12 (92.3)	1 (7.7)
Canada	9 (2.9)	9 (100)	0 (0)
Bolivia	6 (1.9)	4 (66.7)	2 (33.3)
Chile	2 (0.64)	1 (50)	1 (50)
China	2 (0.64)	2 (100)	0 (0)
Germany	2 (0.64)	2 (100)	0 (0)
South Korea	1 (0.32)	1 (100)	0 (0)

Supplemental Table S.4: Rationale for Not DI-AKI adjudication by tiebreaker adjudicator.

Case ID	Temporality in relationship to AKI onset	Drug exposure	Biopsy findings	Concomitant risk factors
1			X	
2				X
3	X	X		X
4	X			X
5	X			
6				X
7				X
8				X
9		X		X

Supplemental Table S.5: Incidence of AKI risk factors stratified by requiring a tiebreaker adjudicator.

AKI Risk Factor, n (%)	No tiebreaker (n = 229)	Tiebreaker (n = 85)	P-value
Hyperglycemia	107 (46.7)	37 (43.5)	0.70
Severe infection or sepsis	38 (16.6)	18 (21.2)	0.41
Extracellular fluid loss	31 (13.5)	10 (11.8)	0.85
Hypotension	31 (13.5)	8 (9.4)	0.44
Red blood cells transfusion	32 (14.0)	7 (8.2)	0.25
Intravascular fluid loss	32 (14.0)	5 (5.9)	0.05
Liver disease	22 (9.6)	8 (9.4)	1
Anesthetic agent	22 (9.6)	6 (7.1)	0.66
Other procedures	21 (9.2)	10 (11.8)	0.52
Cardiac failure	19 (8.3)	8 (9.4)	0.82
Increase vascular capacity	12 (5.2)	2 (2.4)	0.37
Cardiac surgery	4 (1.7)	3 (3.5)	< 0.40
Vascular surgery	2 (0.9)	2 (2.4)	0.30
Hepatorenal syndrome	1 (0.4)	2 (2.4)	0.18
Hemorrhage	2 (0.9)	0 (0)	1
Intravenous drug abuse	1 (0.4)	0 (0)	1

AKI = acute kidney injury; DI-AKI = drug-induced acute kidney injury.

AKI risk factors were present if they were recorded in the 72 hours preceding AKI onset. Increased vascular capacity was defined as clinical events leading to reduced blood perfusion (e.g., mean arterial pressure < 65 mm Hg, sepsis). Hyperglycemia was defined as blood sugar >110 mg/dL or the patient is on insulin.

Supplemental Table S.6: Kidney biopsy findings.

Biopsy	AIN	ATN	GN	TH	Other	Suspected drugs in order of contribution
1		X				abacavir, tenofovir
2	X					amoxicillin
3		X				amoxicillin
4	X					amoxicillin, diclofenac*
5	X					amoxicillin, flucloxacillin*
6	X					cefalexin, pantoprazole
7	X					diclofenac
8	X	X				flucloxacillin
9		X				gentamicin
10					X	gentamicin, vancomycin*
11	X					meropenem
12	X	X	X		X	piperacillin/tazobactam, vancomycin*
13	X					piperacillin/tazobactam, vancomycin**
14	X					piperacillin/tazobactam, vancomycin*
15		X				piperacillin/tazobactam, vancomycin**
16	X	X			X	piperacillin/tazobactam, vancomycin*
17	X				X	vancomycin
18	X				X	vancomycin
19	X	X				vancomycin
20	X	X				vancomycin
21					X	vancomycin
22		X				vancomycin
23		X				vancomycin
24	X					rifampin, teicoplanin**
25	X					rifampin, ibuprofen
26	X					ibuprofen
27	X					ibuprofen
28		X	X		X	Ibuprofen
29					X	Ibuprofen
30		X	X			naproxen, vancomycin*
31	X				X	lansoprazole
32	X	X				omeprazole
33	X	X				pantoprazole

AIN = acute interstitial nephritis; ATN = acute tubular necrosis; GN = glomerulonephritis; Thrombosis = TH.

*Causal drugs had equal rank order contribution to AKI in clinical adjudication.

**No consensus on rank order of causal drug contribution to AKI in clinical adjudication.

Supplemental Table S.7: List of candidate predictor variables with their domains, timepoints and summary statistics.

Domain	Label	Type	Value	Timepoints	Summary, n (%) or median (IQR)	Missing, n (%)
Biopsy	Kidney Biopsy Acute Interstitial Nephritis	Categorical	Present	Hospital Admission to Hospital Discharge	22 (7.01)	0 (0)
Biopsy	Kidney Biopsy Acute Tubular Necrosis	Categorical	Present	Hospital Admission to Hospital Discharge	15 (4.78)	0 (0)
Biopsy	Kidney Biopsy Glomerulonephritis	Categorical	Present	Hospital Admission to Hospital Discharge	3 (0.96)	0 (0)
Biopsy	Kidney Biopsy Other	Categorical	Present	Hospital Admission to Hospital Discharge	9 (2.87)	0 (0)

Contrast	Amount of contrast subject received, mL	Numeric	---	Hospital Admission to AKI Onset	0 (0)	0 (0)
Contrast	Difference in days between AKI Onset and exposure date to contrast medium	Numeric	---	Hospital Admission to AKI Onset	0 (0)	0 (0)
Contrast	Intraarterial Contrast	Categorical	Present	Hospital Admission to AKI Onset	1 (0.32)	0 (0)
Contrast	Intraarterial Contrast	Categorical	Present	Hospital Admission to AKI Onset	42 (13.38)	0 (0)
Contrast	Intravenous Contrast	Categorical	Present	Hospital Admission to AKI Onset	60 (19.11)	0 (0)
Demographics	Age	Numeric	---	Hospital Admission	55 (31)	0 (0)

Demographics	Gender	Categorical	Female	Hospital Admission	154 (49.04)	0 (0)
Demographics	Gender	Categorical	Male	Hospital Admission	160 (50.96)	0 (0)
Demographics	Patient age > 75 years	Categorical	Present	Hospital Admission	31 (9.87)	0 (0)
Demographics	Race	Categorical	White	Hospital Admission	174 (55.41)	0 (0)
Demographics	Race	Categorical	American Indian or Alaska Native	Hospital Admission	1 (0.32)	0 (0)
Demographics	Race	Categorical	Asian	Hospital Admission	42 (13.38)	0 (0)
Demographics	Race	Categorical	Black	Hospital Admission	29 (9.24)	0 (0)

Demographics	Race	Categorical	Native Hawaiian or Other Pacific Islander	Hospital Admission	2 (0.64)	0 (0)
Demographics	Race	Categorical	Hispanic or Latino	Hospital Admission	62 (19.75)	0 (0)
Demographics	Race	Categorical	Not Reported	Hospital Admission	4 (1.27)	0 (0)
Dialysis	KRT	Categorical	Present	Hospital Admission to Hospital Discharge	60 (19.11)	0 (0)
Dialysis	KRT	Categorical	Present	AKI Onset	7 (2.23)	0 (0)
Inpatient - ICU	Patient at ICU	Categorical	Present	AKI Onset	76 (24.2)	0 (0)

Inpatient AKI Risk Factors	Anesthetic Agent	Categorical	Present	72 hours prior to AKI Onset	28 (8.92)	0 (0)
Inpatient AKI Risk Factors	Cardiac Catheterization	Categorical	Present	72 hours prior to AKI Onset	4 (1.27)	0 (0)
Inpatient AKI Risk Factors	Cardiac Surgery	Categorical	Present	72 hours prior to AKI Onset	7 (2.23)	0 (0)
Inpatient AKI Risk Factors	Extracellular Fluid Loss	Categorical	Present	72 hours prior to AKI Onset	41 (13.06)	0 (0)
Inpatient AKI Risk Factors	Hemorrhage	Categorical	Present	72 hours prior to AKI Onset	2 (0.64)	0 (0)

Inpatient AKI Risk Factors	Hepatorenal Syndrome	Categorical	Present	72 hours prior to AKI Onset	3 (0.96)	0 (0)
Inpatient AKI Risk Factors	Hyperglycemia (glucose > 110 mg/dL or 6.1 mmol/L)	Categorical	Present	72 hours prior to AKI Onset	144 (45.86)	0 (0)
Inpatient AKI Risk Factors	Increased Vascular Capacity	Categorical	Present	72 hours prior to AKI Onset	14 (4.46)	0 (0)
Inpatient AKI Risk Factors	Intravascular Fluid Loss	Categorical	Present	72 hours prior to AKI Onset	37 (11.78)	0 (0)
Inpatient AKI Risk Factors	Liver Disease	Categorical	Present	72 hours prior to AKI Onset	30 (9.55)	0 (0)

Inpatient AKI Risk Factors	MAP < 65 mmHg for more than 60 minutes if monitored, or SBP < 90 mmHg if not monitored	Categorical	Present	72 hours prior to AKI Onset	39 (12.42)	0 (0)
Inpatient AKI Risk Factors	Other Procedures	Categorical	Present	72 hours prior to AKI Onset	27 (8.6)	0 (0)
Inpatient AKI Risk Factors	RBC Transfusion	Categorical	Present	72 hours prior to AKI Onset	39 (12.42)	0 (0)
Inpatient AKI Risk Factors	Severe infection (sepsis)	Categorical	Present	72 hours prior to AKI Onset	56 (17.83)	0 (0)

Inpatient AKI Risk Factors	Vascular Surgery	Categorical	Present	72 hours prior to AKI Onset	4 (1.27)	0 (0)
Inpatient Meds	Count of nephrotoxic drugs	Numeric	---	Hospital Admission to Hospital Discharge	1 (1)	0 (0)
Labs	Albumin	Numeric	---	AKI Onset	2.9 (1.1)	172 (54.78)
Labs	ALP	Numeric	---	AKI Onset	96 (81.5)	187 (59.55)
Labs	ALT	Numeric	---	AKI Onset	25 (45)	182 (57.96)
Labs	AST	Numeric	---	AKI Onset	35 (58)	195 (62.1)
Labs	Bands	Numeric	---	AKI Onset	0 (3)	233 (74.2)
Labs	Bicarbonate	Numeric	---	AKI Onset	23 (4.6)	92 (29.3)
Labs	Calcium	Numeric	---	AKI Onset	8.4 (1)	73 (23.25)
Labs	Chloride	Numeric	---	AKI Onset	103 (8)	57 (18.15)

Labs	Direct Bilirubin	Numeric	---	AKI Onset	0.7 (2.15)	251 (79.94)
Labs	Eosinophils	Numeric	---	AKI Onset	2 (2)	123 (39.17)
Labs	Fractional Excretion of Sodium	Numeric	---	AKI Onset	0.04 (0.08)	243 (77.39)
Labs	Glucose	Numeric	---	AKI Onset	112 (46)	57 (18.15)
Labs	HCT	Numeric	---	AKI Onset	29.4 (7.02)	86 (27.39)
Labs	Hemoglobin	Numeric	---	AKI Onset	9.7 (2.3)	37 (11.78)
Labs	INR	Numeric	---	AKI Onset	1.4 (0.92)	212 (67.52)
Labs	Ionized Calcium	Numeric	---	AKI Onset	4.32 (0.63)	292 (92.99)
Labs	Lactate	Numeric	---	AKI Onset	7.4 (12.6)	273 (86.94)

Labs	Magnesium	Numeric	---	AKI Onset	2.07 (0.42)	168 (53.5)
Labs	Phosphate	Numeric	---	AKI Onset	4.5 (1.88)	164 (52.23)
Labs	Platelets	Numeric	---	AKI Onset	211 (209)	61 (19.43)
Labs	Potassium	Numeric	---	AKI Onset	4.2 (1)	16 (5.1)
Labs	PT	Numeric	---	AKI Onset	15.3 (8.1)	223 (71.02)
Labs	PTT	Numeric	---	AKI Onset	37.1 (15.95)	259 (82.48)
Labs	SCr	Numeric	---	Hospital Admission	1.1 (1.45)	12 (3.82)
Labs	SCr	Numeric	---	Hospital Discharge	1.8 (1.58)	51 (16.24)
Labs	SCr	Numeric	---	Follow up	1.27 (0.85)	142 (45.22)
Labs	SCr	Numeric	---	AKI Onset	2.34 (2.06)	1 (0.32)
Labs	Sodium	Numeric	---	AKI Onset	137 (7)	16 (5.1)

Labs	Total Bilirubin	Numeric	---	AKI Onset	0.8 (2.14)	187 (59.55)
Labs	Urea Nitrogen	Numeric	---	AKI Onset	28.01 (30.5)	34 (10.83)
Labs	WBC	Numeric	---	AKI Onset	9.9 (6.77)	52 (16.56)
Past Medical History	Allergic Disease	Categorical	Present	Hospital Admission	30 (9.55)	0 (0)
Past Medical History	Autoimmune Disease	Categorical	Present	Hospital Admission	18 (5.73)	0 (0)
Past Medical History	Cardiac - Congestive Heart Failure	Categorical	Present	Hospital Admission	36 (11.46)	0 (0)
Past Medical History	Cardiac - Coronary Artery Disease	Categorical	Present	Hospital Admission	36 (11.46)	0 (0)

Past Medical History	Chronic Obstructive Pulmonary Disease	Categorical	Present	Hospital Admission	32 (10.19)	0 (0)
Past Medical History	Diabetes Mellitus	Categorical	Present	Hospital Admission	96 (30.57)	0 (0)
Past Medical History	Heart Transplant	Categorical	Present	Hospital Admission	2 (0.64)	0 (0)
Past Medical History	Historical evidence of CKD based on standard criteria: proteinuria, biopsy, ultrasound. size	Categorical	Present	Hospital Admission	61 (19.43)	0 (0)

Past Medical History	Hypertension	Categorical	Present	Hospital Admission	140 (44.59)	0 (0)
Past Medical History	Immunocompromised - AIDS	Categorical	Present	Hospital Admission	4 (1.27)	0 (0)
Past Medical History	Immunocompromised - HIV Positive/ARC	Categorical	Present	Hospital Admission	6 (1.91)	0 (0)
Past Medical History	Immunocompromised - Non-Renal Organ Transplant	Categorical	Present	Hospital Admission	8 (2.55)	0 (0)
Past Medical History	Leukemia or Lymphoma	Categorical	Present	Hospital Admission	19 (6.05)	0 (0)

Past Medical History	Liver Disease - Cirrhosis of Liver	Categorical	Present	Hospital Admission	26 (8.28)	0 (0)
Past Medical History	Liver Disease - Hepatic Failure with Encephalopathy or Coma	Categorical	Present	Hospital Admission	16 (5.1)	0 (0)
Past Medical History	Liver Disease - Other Liver Disease	Categorical	Present	Hospital Admission	8 (2.55)	0 (0)
Past Medical History	Liver Transplant	Categorical	Present	Hospital Admission	4 (1.27)	0 (0)

Past Medical History	Lung Transplant	Categorical	Present	Hospital Admission	2 (0.64)	0 (0)
Past Medical History	Malignancy - Chemotherapy	Categorical	Present	Hospital Admission	27 (8.6)	0 (0)
Past Medical History	Malignancy - Other Cancer Therapy	Categorical	Present	Hospital Admission	15 (4.78)	0 (0)
Past Medical History	Malignancy - Other Cancers	Categorical	Present	Hospital Admission	32 (10.19)	0 (0)
Past Medical History	Malignancy - Radiation Therapy	Categorical	Present	Hospital Admission	7 (2.23)	0 (0)

Past Medical History	Malignancy - Solid Tumor with Metastasis	Categorical	Present	Hospital Admission	12 (3.82)	0 (0)
Past Medical History	Patient given any blood products in the last four weeks	Categorical	Present	Hospital Admission	24 (7.64)	0 (0)
Past Medical History	Patient undergone any procedures requiring radio contrast in the last four weeks	Categorical	Present	Hospital Admission	52 (16.56)	0 (0)
Past Medical History	Peripheral Vascular Disease	Categorical	Present	Hospital Admission	19 (6.05)	0 (0)

Past Medical History	Primary Kidney Disease	Categorical	Present	Hospital Admission	51 (16.24)	0 (0)
Past Medical History	Procedure in last 4 weeks - Cardiac Catheterization	Categorical	Present	Hospital Admission	7 (2.23)	0 (0)
Past Medical History	Procedure in last 4 weeks - Other Major Surgery/Trauma	Categorical	Present	Hospital Admission	24 (7.64)	0 (0)
Past Medical History	Procedure in last 4 weeks: Cardiac Surgery	Categorical	Present	Hospital Admission	10 (3.18)	0 (0)
Physical Exam	Ascites	Categorical	Present	AKI Onset	18 (5.73)	0 (0)

Physical Exam	Edema	Categorical	Present	AKI Onset	111 (35.35)	0 (0)
Physical Exam	Fluid Overload	Categorical	Present	AKI Onset	27 (8.6)	0 (0)
Physical Exam	Foley Catheter	Categorical	Present	AKI Onset	94 (29.94)	0 (0)
Physical Exam	Heart Failure	Categorical	Present	AKI Onset	35 (11.15)	0 (0)
Physical Exam	Confirmed Infection	Categorical	Present	AKI Onset	203 (64.65)	0 (0)
Physical Exam	Confirmed Infection - Cerebrospinal Fluid	Categorical	Present	AKI Onset	4 (1.27)	0 (0)
Physical Exam	Confirmed Infection - Blood	Categorical	Present	AKI Onset	42 (13.38)	0 (0)

Physical Exam	Confirmed Infection - Gastrointestinal Tract	Categorical	Present	AKI Onset	15 (4.78)	0 (0)
Physical Exam	Confirmed Infection - Joint	Categorical	Present	AKI Onset	10 (3.18)	0 (0)
Physical Exam	Confirmed Infection - Lung	Categorical	Present	AKI Onset	57 (18.15)	0 (0)
Physical Exam	Confirmed Infection - Other	Categorical	Present	AKI Onset	58 (18.47)	0 (0)
Physical Exam	Confirmed Infection - Skin	Categorical	Present	AKI Onset	22 (7.01)	0 (0)
Physical Exam	Confirmed Infection - Urinary Tract	Categorical	Present	AKI Onset	47 (14.97)	0 (0)

Physical Exam	Jaundice	Categorical	Present	AKI Onset	15 (4.78)	0 (0)
Physical Exam	Lung Rales	Categorical	Present	AKI Onset	33 (10.51)	0 (0)
Physical Exam	Surgical Status	Categorical	Present	AKI Onset	28 (8.92)	0 (0)
Pre-admission Meds	ACEi/ARBs in last 4 weeks	Categorical	Present	Hospital Admission	57 (18.15)	0 (0)
Pre-admission Meds	Antibiotics in last 4 weeks	Categorical	Present	Hospital Admission	100 (31.85)	0 (0)
Pre-admission Meds	Diuretics in last 4 weeks	Categorical	Present	Hospital Admission	56 (17.83)	0 (0)

Pre-admission Meds	Medication in last 4 weeks-NSAIDs (excluding aspirin)	Categorical	Present	Hospital Admission	42 (13.38)	0 (0)
Pre-admission Meds	Past Medical History: Currently Taking Oral Contraceptives	Categorical	Present	Hospital Admission	2 (0.64)	0 (0)
Pre-admission Meds	Procedure in last 4 weeks - Nephrotoxic Insult	Categorical	Present	Hospital Admission	8 (2.55)	0 (0)
Pre-admission Meds	Recreational drugs in last 4 weeks	Categorical	Present	Hospital Admission	6 (1.91)	0 (0)
Psychosocial	Intravenous Drug Abuse	Categorical	Present	AKI Onset	4 (1.27)	0 (0)

Psychoso cial	Past Medical History: Smoking Status	Categorical	Present	Hospital Admission	45 (14.33)	0 (0)
Psychoso cial	Past Medical History: Smoking Status	Categorical	4	Hospital Admission	51 (16.24)	0 (0)
Trends - Labs	ALP Diff.	Numeric	---	AKI Onset, Drug Exposure	-9.5 (39.25)	244 (77.71)
Trends - Labs	ALT Diff.	Numeric	---	AKI Onset, Drug Exposure	-3 (16.25)	244 (77.71)
Trends - Labs	AST Diff.	Numeric	---	AKI Onset, Drug Exposure	-1 (28.75)	246 (78.34)
Trends - Labs	Bands Diff.	Numeric	---	AKI Onset, Drug Exposure	0 (0.6)	251 (79.94)
Trends - Labs	Bicarbonate Diff.	Numeric	---	AKI Onset, Drug Exposure	-1 (5.88)	138 (43.95)

Trends - Labs	Blood Albumin Diff.	Numeric	---	AKI Onset, Drug Exposure	-0.1 (0.6)	230 (73.25)
Trends - Labs	Calcium Diff.	Numeric	---	AKI Onset, Drug Exposure	-0.2 (0.81)	118 (37.58)
Trends - Labs	Chloride Diff.	Numeric	---	AKI Onset, Drug Exposure	2 (7.75)	116 (36.94)
Trends - Labs	Direct Bilirubin Diff.	Numeric	---	AKI Onset, Drug Exposure	0 (1.2)	283 (90.13)
Trends - Labs	Eosinophils Diff.	Numeric	---	AKI Onset, Drug Exposure	0 (1.6)	176 (56.05)
Trends - Labs	Glucose Diff.	Numeric	---	AKI Onset, Drug Exposure	-7 (52)	117 (37.26)
Trends - Labs	HCT Diff.	Numeric	---	AKI Onset, Drug Exposure	-2.9 (5)	123 (39.17)
Trends - Labs	Hemoglobin Diff.	Numeric	---	AKI Onset, Drug Exposure	-0.9 (1.8)	107 (34.08)

Trends - Labs	INR Diff.	Numeric	---	AKI Onset, Drug Exposure	0.09 (0.42)	256 (81.53)
Trends - Labs	Ionized Calcium Diff.	Numeric	---	AKI Onset, Drug Exposure	0.13 (0.46)	308 (98.09)
Trends - Labs	Lactate Diff.	Numeric	---	AKI Onset, Drug Exposure	-0.9 (1.5)	301 (95.86)
Trends - Labs	Magnesium Diff.	Numeric	---	AKI Onset, Drug Exposure	0.1 (0.45)	235 (74.84)
Trends - Labs	Phosphate Diff.	Numeric	---	AKI Onset, Drug Exposure	1.15 (1.5)	246 (78.34)
Trends - Labs	Platelets Diff.	Numeric	---	AKI Onset, Drug Exposure	-4 (85)	113 (35.99)
Trends - Labs	Potassium Diff.	Numeric	---	AKI Onset, Drug Exposure	0.1 (0.88)	84 (26.75)
Trends - Labs	PT Diff.	Numeric	---	AKI Onset, Drug Exposure	0.2 (4)	261 (83.12)

Trends - Labs	PTT Diff.	Numeric	---	AKI Onset, Drug Exposure	3.2 (9.5)	283 (90.13)
Trends - Labs	Relative SCr Diff.	Numeric	---	Hospital Admission, AKI Onset	0.5 (0.54)	13 (4.14)
Trends - Labs	Relative SCr Diff.	Numeric	---	AKI Onset, Drug Discontinuation	0 (0.28)	21 (6.69)
Trends - Labs	Relative SCr Diff.	Numeric	---	Hospital Discharge, AKI Onset	0.27 (0.53)	51 (16.24)
Trends - Labs	Relative SCr Diff.	Numeric	---	AKI Onset, Nadir Serum Creatinine	0.34 (0.49)	70 (22.29)
Trends - Labs	Relative SCr Diff.	Numeric	---	Drug Discontinuation, Nadir Serum Creatinine	0.37 (1.29)	85 (27.07)
Trends - Labs	Relative SCr Diff.	Numeric	---	Pre-Drug Exposure, Drug Exposure	0 (0)	80 (25.48)
Trends - Labs	Relative SCr Diff.	Numeric	---	Hospital Admission, Pre-Drug Exposure	0 (0.59)	42 (13.38)

Trends - Labs	Relative SCr Diff.	Numeric	---	Hospital Admission, AKI Onset	1.2 (1.35)	74 (23.57)
Trends - Labs	Sodium Diff.	Numeric	---	AKI Onset, Drug Exposure	1 (6)	85 (27.07)
Trends - Labs	Total Bilirubin Diff.	Numeric	---	AKI Onset, Drug Exposure	-0.1 (0.73)	250 (79.62)
Trends - Labs	WBC Diff.	Numeric	---	AKI Onset, Drug Exposure	-0.2 (6.8)	109 (34.71)
Trends - Vitals	Diastolic Blood Pressure Diff.	Numeric	---	AKI Onset, Drug Exposure	-2 (18)	75 (23.89)
Trends - Vitals	Heart Rate Diff.	Numeric	---	AKI Onset, Drug Exposure	-3 (24)	71 (22.61)
Trends - Vitals	MAP Diff.	Numeric	---	AKI Onset, Drug Exposure	-3 (19)	76 (24.2)
Trends - Vitals	Respiratory Rate Diff.	Numeric	---	AKI Onset, Drug Exposure	0 (4)	93 (29.62)

Trends - Vitals	Systolic Blood Pressure Diff.	Numeric	---	AKI Onset, Drug Exposure	-4.5 (25)	74 (23.57)
Trends - Vitals	Temperature Diff.	Numeric	---	AKI Onset, Drug Exposure	-0.06 (0.89)	80 (25.48)
Trends - Vitals	Weight Diff.	Numeric	---	AKI Onset, Drug Exposure	0 (3.75)	208 (66.24)
Urinalysis	Urinary Sediments	Categorical	Present	Hospital Admission to Hospital Discharge	85 (27.1)	0 (0)
Urinalysis	Eosinophils	Categorical	Present	Hospital Admission to Hospital Discharge	42 (13.38)	0 (0)
Urinalysis	Eosinophils	Categorical	Present	AKI Onset	23 (7.32)	0 (0)
Urinalysis	Glucose	Categorical	Minimal	AKI Onset	303 (96.5)	5 (1.59)
Urinalysis	Glucose	Categorical	Moderate	AKI Onset	10 (3.18)	
Urinalysis	Glucose	Categorical	Heavy	AKI Onset	1 (0.32)	
Urinalysis	Max Glucose	Categorical	Minimal	Hospital Admission to Hospital Discharge	270 (85.99)	1 (0.32)

Urinalysis	Max Glucose	Categorical	Moderate	Hospital Admission to Hospital Discharge	28 (8.92)	
Urinalysis	Max Glucose	Categorical	Heavy	Hospital Admission to Hospital Discharge	16 (5.1)	
Urinalysis	Max pH	Numeric	---	Hospital Admission to Hospital Discharge	6 (1)	59 (18.79)
Urinalysis	Max Protein	Categorical	Minimal	Hospital Admission to Hospital Discharge	166 (52.87)	7 (2.23)
Urinalysis	Max Protein	Categorical	Moderate	Hospital Admission to Hospital Discharge	106 (33.76)	
Urinalysis	Max Protein	Categorical	Heavy	Hospital Admission to Hospital Discharge	42 (13.38)	
Urinalysis	Max RBC	Categorical	Minimal	Hospital Admission to Hospital Discharge	192 (61.15)	25 (7.96)
Urinalysis	Max RBC	Categorical	Moderate	Hospital Admission to Hospital Discharge	54 (17.2)	

Urinalysis	Max RBC	Categorical	Heavy	Hospital Admission to Hospital Discharge	68 (21.66)	
Urinalysis	Max Specific Gravity	Numeric	---	Hospital Admission to Hospital Discharge	1.02 (0.01)	67 (21.34)
Urinalysis	Max WBC	Categorical	Minimal	Hospital Admission to Hospital Discharge	184 (58.6)	21 (6.69)
Urinalysis	Max WBC	Categorical	Moderate	Hospital Admission to Hospital Discharge	71 (22.61)	
Urinalysis	Max WBC	Categorical	Heavy	Hospital Admission to Hospital Discharge	59 (18.79)	
Urinalysis	Mean pH	Numeric	---	Hospital Admission to Hospital Discharge	6 (0.67)	59 (18.79)
Urinalysis	Mean Specific Gravity	Numeric	---	Hospital Admission to Hospital Discharge	1.01 (0.01)	67 (21.34)
Urinalysis	Min pH	Numeric	---	Hospital Admission to Hospital Discharge	5.5 (1)	59 (18.79)

Urinalysis	Min Specific Gravity	Numeric	---	Hospital Admission to Hospital Discharge	1.01 (0.01)	67 (21.34)
Urinalysis	pH	Numeric	---	AKI Onset	6 (1)	176 (56.05)
Urinalysis	Protein	Categorical	Minimal	AKI Onset	237 (75.48)	13 (4.14)
Urinalysis	Protein	Categorical	Moderate	AKI Onset	66 (21.02)	
Urinalysis	Protein	Categorical	Heavy	AKI Onset	11 (3.5)	
Urinalysis	RBC	Categorical	Minimal	AKI Onset	261 (83.12)	27 (8.60)
Urinalysis	RBC	Categorical	Moderate	AKI Onset	27 (8.6)	
Urinalysis	RBC	Categorical	Heavy	AKI Onset	26 (8.28)	
Urinalysis	Specific Gravity	Numeric	---	AKI Onset	1.01 (0.01)	182 (57.96)
Urinalysis	WBC	Categorical	Minimal	AKI Onset	263 (83.76)	21 (6.69)
Urinalysis	WBC	Categorical	Moderate	AKI Onset	29 (9.24)	
Urinalysis	WBC	Categorical	Heavy	AKI Onset	22 (7.01)	

Urine Chemistry	Albumin	Numeric	---	AKI Onset	1.6 (0)	313 (99.68)
Urine Chemistry	Calcium	Numeric	---	AKI Onset	NA (NA)	314 (100)
Urine Chemistry	Chloride	Numeric	---	AKI Onset	33 (41.5)	271 (86.31)
Urine Chemistry	Creatinine	Numeric	---	AKI Onset	70 (68)	229 (72.93)
Urine Chemistry	Max Albumin	Numeric	---	Admission Day to Hospital Discharge	7.05 (19.38)	306 (97.45)
Urine Chemistry	Max Calcium	Numeric	---	Admission Day to Hospital Discharge	4.2 (5.55)	311 (99.04)
Urine Chemistry	Max Chloride	Numeric	---	Admission Day to Hospital Discharge	42 (48.5)	239 (76.11)
Urine Chemistry	Max Creatinine	Numeric	---	Admission Day to Hospital Discharge	62 (78.2)	160 (50.96)

Urine Chemistry	Max Osmolarity	Numeric	---	Admission Day to Hospital Discharge	325.5 (155)	274 (87.26)
Urine Chemistry	Max Phosphate	Numeric	---	Admission Day to Hospital Discharge	31 (21)	312 (99.36)
Urine Chemistry	Max Potassium	Numeric	---	Admission Day to Hospital Discharge	30 (33.5)	235 (74.84)
Urine Chemistry	Max Protein	Numeric	---	Admission Day to Hospital Discharge	39.5 (72.2)	254 (80.89)
Urine Chemistry	Max Sodium	Numeric	---	Admission Day to Hospital Discharge	47 (47)	176 (56.05)
Urine Chemistry	Max Urea Nitrogen	Numeric	---	Admission Day to Hospital Discharge	248 (295)	253 (80.57)
Urine Chemistry	Mean Albumin	Numeric	---	Admission Day to Hospital Discharge	7.05 (19.4)	306 (97.45)
Urine Chemistry	Mean Calcium	Numeric	---	Admission Day to Hospital Discharge	4.2 (5.55)	311 (99.04)

Urine Chemistry	Mean Chloride	Numeric	---	Admission Day to Hospital Discharge	39 (50)	239 (76.11)
Urine Chemistry	Mean Creatinine	Numeric	---	Admission Day to Hospital Discharge	57.13 (58)	160 (50.96)
Urine Chemistry	Mean Osmolarity	Numeric	---	Admission Day to Hospital Discharge	325.5 (151)	274 (87.26)
Urine Chemistry	Mean Phosphate	Numeric	---	Admission Day to Hospital Discharge	31 (21)	312 (99.36)
Urine Chemistry	Mean Potassium	Numeric	---	Admission Day to Hospital Discharge	30 (30.5)	235 (74.84)
Urine Chemistry	Mean Protein	Numeric	---	Admission Day to Hospital Discharge	38.5 (71.1)	254 (80.89)
Urine Chemistry	Mean Sodium	Numeric	---	Admission Day to Hospital Discharge	41.25 (45.8)	176 (56.05)
Urine Chemistry	Mean Urea Nitrogen	Numeric	---	Admission Day to Hospital Discharge	228 (278)	253 (80.57)

Urine Chemistry	Min Albumin	Numeric	---	Admission Day to Hospital Discharge	7.05 (19.38)	306 (97.45)
Urine Chemistry	Min Calcium	Numeric	---	Admission Day to Hospital Discharge	4.2 (5.55)	311 (99.04)
Urine Chemistry	Min Chloride	Numeric	---	Admission Day to Hospital Discharge	38 (48.5)	239 (76.11)
Urine Chemistry	Min Creatinine	Numeric	---	Admission Day to Hospital Discharge	53.5 (58.8)	160 (50.96)
Urine Chemistry	Min Osmolarity	Numeric	---	Admission Day to Hospital Discharge	306.5 (148.5)	274 (87.26)
Urine Chemistry	Min Phosphate	Numeric	---	Admission Day to Hospital Discharge	31 (21)	312 (99.36)
Urine Chemistry	Min Potassium	Numeric	---	Admission Day to Hospital Discharge	29 (27)	235 (74.84)
Urine Chemistry	Min Protein	Numeric	---	Admission Day to Hospital Discharge	33 (63)	254 (80.89)

Urine Chemistry	Min Sodium	Numeric	---	Admission Day to Hospital Discharge	38.5 (44)	176 (56.05)
Urine Chemistry	Min Urea Nitrogen	Numeric	---	Admission Day to Hospital Discharge	209 (277)	253 (80.57)
Urine Chemistry	Osmolarity	Numeric	---	AKI Onset	345 (136.5)	298 (94.9)
Urine Chemistry	Phosphate	Numeric	---	AKI Onset	NA (NA)	314 (100)
Urine Chemistry	Potassium	Numeric	---	AKI Onset	30 (36)	269 (85.67)
Urine Chemistry	Protein	Numeric	---	AKI Onset	39 (70)	283 (90.13)
Urine Chemistry	Sodium	Numeric	---	AKI Onset	34.5 (39.8)	234 (74.52)
Urine Chemistry	Urea Nitrogen	Numeric	---	AKI Onset	224.5 (340.8)	282 (89.81)

Vitals	Body Surface Area	Numeric	---	AKI Onset	1.91 (0.41)	69 (21.97)
Vitals	Diastolic Blood Pressure	Numeric	---	AKI Onset	70 (19)	19 (6.05)
Vitals	Heart Rate	Numeric	---	AKI Onset	88 (23.5)	19 (6.05)
Vitals	Height	Numeric	---	AKI Onset	167.64 (16.6)	47 (14.97)
Vitals	MAP	Numeric	---	AKI Onset	86 (20.7)	19 (6.05)
Vitals	Respiratory Rate	Numeric	---	AKI Onset	19 (4)	33 (10.51)
Vitals	Systolic Blood Pressure	Numeric	---	AKI Onset	119 (28.5)	19 (6.05)
Vitals	Temperature	Numeric	---	AKI Onset	36.83 (0.54)	23 (7.32)
Vitals	Weight	Numeric	---	AKI Onset	79.8 (25.2)	167 (53.18)
Vitals	Weight	Numeric	---	AKI Onset	77.6 (28.8)	51 (16.24)

AKI = acute kidney injury; ACE = angiotensin-converting enzyme Inhibitor; AIDS = acquired immune deficiency syndrome; ALT = alanine transaminase; ARB = angiotensin II receptor blocker; AST = aspartate transaminase; CKD = chronic kidney disease; DI-AKI = drug-induced acute kidney injury; DM = diabetes mellitus; HIV = human immunodeficiency virus; HCT = hematocrit; ICU = intensive care unit; INR = international normalized ratio; MAP = mean arterial pressure; NSAIDs =

nonsteroidal anti-inflammatory drugs; RBC = red blood cells count; KRT = kidney replacement therapy; SCr = serum creatinine; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cells count.

Supplemental Table S.8: DI-AKI predictors from multivariable logistic regression analysis.

Variable	Odds ratio (95% CI)	*P*-Value
Intercept	1.05 (0.03-33.7)	0.97
Demographics		
Age, 10 years	0.66 (0.54 – 0.90)	0.01
Intensive care unit		
Intensive care units stay at AKI Onset	0.33 (0.1– 1.09)	0.07
Past Medical History		
Cardiac catheterization in the last 4 weeks	0.33 (0.02-6.22)	0.50
Receiving blood product in the last 4 weeks	0.58 (0.13 – 2.64)	0.48
Procedures requiring contrast in the last 4 weeks	1.13 (0.27 – 4.70)	0.86
Cardiac surgery in the last 4 weeks	0.83 (0.09 –7.74)	0.87
Diabetes mellitus	1.01 (0.31 – 3.29)	0.98
AKI Risk Factors		
Increased vascular capacity	0.07 (0.01 – 0.55)	0.01

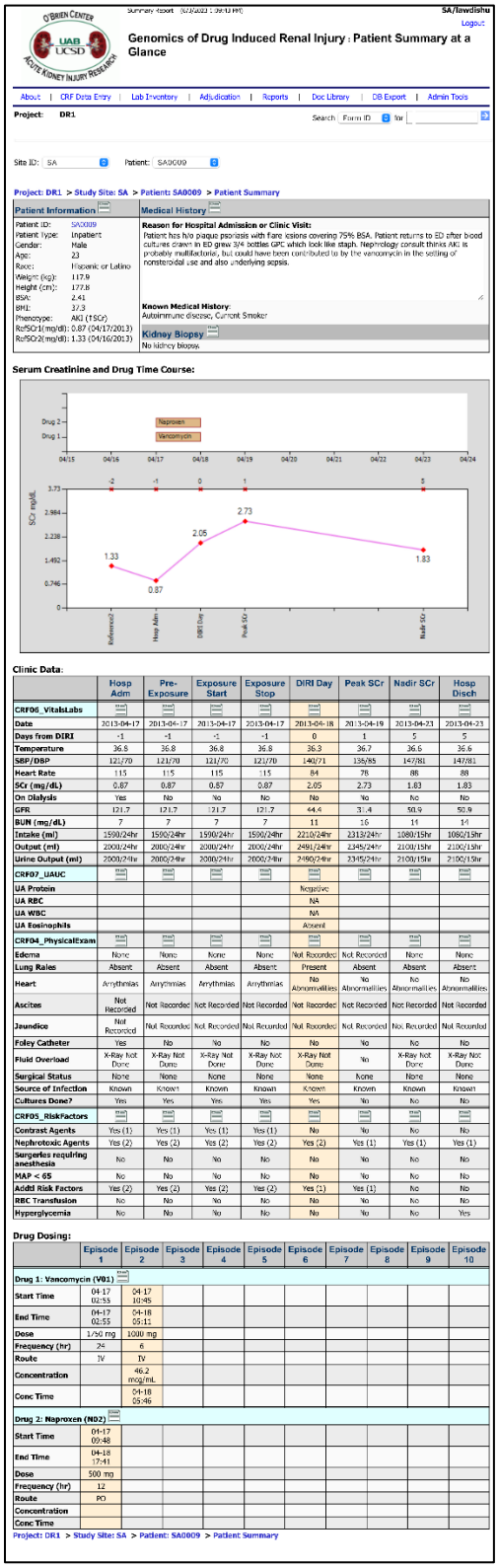
Red blood cells transfusion	0.18 (0.01 – 0.65)	< 0.01
Hyperglycemia	3.72 (1.21-11.4)	0.02
Cardiac surgery	0.8 (0.05 – 14.1)	0.87
Contrast Exposure		
Days between AKI Onset and contrast exposure, days	1.08 (1.01 – 1.15)	0.02
Physical Exam		
Confirmed Infection	3.84 (1.3 – 11.3)	0.01
Ascites	0.17 (0.04 – 0.74)	0.02
Edema	0.37 (0.14 – 1.02)	0.05
Surgical procedure	0.54 (0.11 – 2.79)	0.46
Foley catheter	1.42 (0.46 – 4.38)	0.54
Labs		
Glucose, mg/dL, AKI onset	1.02 (1.0 –1.03)	0.08
Eosinophils, mg/dL, AKI onset	1.34 (0.9 – 2.0)	0.15
Vitals		

Respiratory rate, bpm, AKI onset	1.09 (0.98-1.21)	0.11
Trends – Labs		
Relative SCr Diff. (Drug Exposure, Pre-Drug Exposure)	0.03 (0.00 – 0.08)	< 0.01
Relative SCr Diff. (Pre-Drug Exposure, Hospital Admission)	0.65 (0.42 – 1.01)	0.05
Relative SCr Diff. (AKI Onset, Drug Discontinuation)	0.46 (0.13 – 1.62)	0.22
Platelets Diff. (AKI Onset, Drug Exposure), 100 x 10^9/L	0.40 (0.21 – 0.73)	< 0.01
WBC Diff. (AKI Onset, Drug Exposure), 5 x 10^9/L	0.64 (0.41 – 0.98)	0.04
Trends – Vitals		
Heart rate Diff. (AKI Onset, Drug Exposure), bpm	0.99 (0.97 – 1.02)	0.72
Urinalysis		
WBC – Heavy, AKI Onset	0.16 (0.03 – 0.85)	0.03
WBC – Moderate, AKI Onset	5.5 (0.68 – 44.7)	0.11
WBC – Heavy, Max	0.37 (0.1 – 1.37)	0.13
WBC – Moderate, Max	2.2 (0.64 – 7.52)	0.21

AKI = acute kidney injury; CI =confidence internal; ICU = intensive care unit; SCr = serum creatinine; WBC = white blood cells.

Increased vascular capacity was defined as clinical events leading to reduced blood perfusion to the kidney (e.g., mean arterial pressure < 65, sepsis). Hyperglycemia was defined as blood sugar >110 mg/dL or 6.05 mmol/L, or patient is on insulin. Hospital Admission time point was defined as the day of hospital admission. Pre-Drug Exposure time point was defined as the day prior to treatment with candidate nephrotoxic drug. Drug Exposure time point was defined as the first day of treatment with a candidate nephrotoxic drug. AKI Onset time point was defined as the first day of AKI meeting the 2012 Kidney Disease Improving Global Outcomes (KDIGO) AKI stage 2 criteria. Relative SCr Diff. (Drug Exposure, Pre-Drug Exposure) was defined as the relative change in SCr between Drug Exposure and Pre-Drug Exposure time points. Relative SCr Diff. (Pre-Drug Exposure, Hospital Admission) was defined as the relative change in SCr between Pre-Drug Exposure and Admission time points. Protein urinalysis was defined as minimal (< 1+), moderate (1+ to 2+), and heavy (> 2+). WBC urinalysis was defined as minimal (< 6), moderate (6-20), and heavy (> 21).

Supplemental Figure S.1: Patient summary as presented in the DIRECT study web platform.



Genomics of Drug Induced Renal Injury : Patient Summary at a Glance

About | CRF Data Entry | Lab Inventory | Adjudication | Reports | Doc Library | DB Export | Admin Tools

Project: DR1

Site ID: SA Patient: SA0009

Project: DR1 > Study Site: SA > Patient: SA0009 > Patient Summary

Patient Information

Patient ID: SA0009
Patient Type: Inpatient
Gender: Male
Age: 23
Race: Hispanic or Latino
Weight (kg): 117.9
Height (cm): 177.8
BSA: 2.41
BMI: 37.3
Phenotype: AKI (TSCr)
RefSCr1(mg/dl): 0.87 (04/17/2013)
RefSCr2(mg/dl): 1.33 (04/16/2013)

Medical History

Reason for Hospital Admission or Clinic Visit:
Patient has h/o plaque psoriasis with flare lesions covering 75% BSA. Patient returns to ED after blood cultures drawn in ED grew 3/4 bottles GPC which look like staph. Nephrology consult thinks AKI is probably multifactorial, but could have been contributed to by the vancomycin in the setting of nonsteroidal use and also underlying sepsis.

Known Medical History:
Autoimmune disease, Current Smoker

Kidney Biopsy
No kidney biopsy.

Serum Creatinine and Drug Time Course:

Clinic Data:

	Hosp Adm	Pre-Exposure	Exposure Start	Exposure Stop	DIRI Day	Peak SCr	Nadir SCr	Hosp Disch
CRF06_VitalsLabs								
Date	2013-04-17	2013-04-17	2013-04-17	2013-04-17	2013-04-18	2013-04-19	2013-04-23	2013-04-23
Days from DIRI	-1	-1	-1	-1	0	1	5	5
Temperature	36.8	36.8	36.8	36.8	36.3	36.7	36.6	36.6
SBP/DBP	121/70	121/70	121/70	121/70	140/71	136/85	147/81	147/81
Heart Rate	115	115	115	115	84	78	88	88
SCr (mg/dL)	0.87	0.87	0.87	0.87	2.05	2.73	1.83	1.83
On Dialysis	Yes	No	No	No	No	No	No	No
GFR	121.7	121.7	121.7	121.7	44.4	31.4	50.9	50.9
BUN (mg/dL)	7	7	7	7	11	16	14	14
Intake (ml)	1590/24hr	1590/24hr	1590/24hr	1590/24hr	2210/24hr	2313/24hr	1080/15hr	1080/15hr
Output (ml)	2000/24hr	2000/24hr	2000/24hr	2000/24hr	2491/24hr	2345/24hr	2100/15hr	2100/15hr
Urine Output (ml)	2000/24hr	2000/24hr	2000/24hr	2000/24hr	2490/24hr	2345/24hr	2100/15hr	2100/15hr
CRF07_UAUC								
UA Protein					Negative			
UA RBC					NA			
UA WBC					NA			
UA Eosinophils					Absent			
CRF04_PhysicalExam								
Edema	None	None	None	None	Not Recorded	Not Recorded	None	None
Lung Rales	Absent	Absent	Absent	Absent	Present	Absent	Absent	Absent
Heart	Arrythmias	Arrythmias	Arrythmias	Arrythmias	No Abnormalities	Yes Abnormalities	No Abnormalities	No Abnormalities
Ascites	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded
Jaundice	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded	Not Recorded
Foley Catheter	Yes	No	No	No	No	No	No	No
Fluid Overload	X-Ray Not Done	X-Ray Not Done	X-Ray Not Done	X-Ray Not Done	X-Ray Not Done	No	X-Ray Not Done	X-Ray Not Done
Surgical Status	None	None	None	None	None	None	None	None
Source of Infection	Known	Known	Known	Known	Known	Known	Known	Known
Cultures Done?	Yes	Yes	Yes	Yes	Yes	No	No	No
CRF05_RiskFactors								
Contrast Agents	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No	No	No	No
Nephrotoxic Agents	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (1)	Yes (1)	Yes (1)
Surgeries requiring anesthesia	No	No	No	No	No	No	No	No
MAP < 65	No	No	No	No	No	No	No	No
Addtl Risk Factors	Yes (2)	Yes (2)	Yes (2)	Yes (2)	Yes (1)	Yes (1)	No	No
RBC Transfusion	No	No	No	No	No	No	No	No
Hyperglycemia	No	No	No	No	No	No	No	Yes

Drug Dosing:

	Episode 1	Episode 2	Episode 3	Episode 4	Episode 5	Episode 6	Episode 7	Episode 8	Episode 9	Episode 10
Drug 1: Vancomycin (V01)										
Start Time	04-17 02:55	04-17 10:45								
End Time	04-17 02:55	04-18 05:11								
Dose	1/50 mg	1000 mg								
Frequency (hr)	24	6								
Route	IV	IV								
Concentration		46.2 mcg/mL								
Conc Time		04-18 05:46								
Drug 2: Naproxen (N02)										
Start Time	04-17 09:48									
End Time	04-18 17:41									
Dose	500 mg									
Frequency (hr)	12									
Route	PO									
Concentration										
Conc Time										

Project: DR1 > Study Site: SA > Patient: SA0009 > Patient Summary

Supplemental Figure S.2: Naranjo causality assessment scale.

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Genomics of Drug Induced Renal Injury (DIRI): Adjudication Report

DR1 - CRF 15

Patient ID: ☐☐☐☐☐☐

Form ID: ☐☐☐☐☐ - ☐☐☐☐☐

1. Adjudicator ID: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

2. Date of Review: ☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy)

3. a. Phenotype and DIRI criteria that was used to determine patient's eligibility for enrollment with this study:

- ○ AKI phenotype with AKIN stage 2 criteria based on rising serum creatinine
- ○ AKI phenotype with AKIN stage 2 criteria based on declining serum creatinine

(based on time course and magnitude of creatinine change)

- ○ Glomerular disorder phenotype *(based on biopsy)*

b. Study Drugs:

	NA	Drug ID	Drug Name	Met DIRI Criteria
Drug 1	☐	___		○ Y ○ N
Drug 2	☐	___		○ Y ○ N
Drug 3	☐	___		○ Y ○ N

4. Assessment Tools

a. Naranjo Scores (*Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. 1981;30:239-245.*)

Naranjo scores of 9 - 10 indicate that event was "definitely" an ADR; scores of 5 - 8 rate the likelihood as "probable"; scores of 1 - 4 are "possible"; and scores of less than 1 are "doubtful".

To assess the adverse drug reaction, please answer the following questions and give pertinent subscores for each drug.	Question Points			Subscores		
	Yes	No	DoNot Know	Drug 1	Drug 2	Drug 3
(1) Are there previous conclusive reports on this reaction?	+1	0	0	___	___	___
(2) Did the adverse event appear after the suspected drug was administered?	+2	-1	0	___	___	___
(3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	___	___	___
(4) Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	___	___	___
(5) Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	___	___	___
(6) Did the reaction reappear when a placebo was given?	-1	+1	0	___	___	___
(7) Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	___	___	___
(8) Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	___	___	___
(9) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	___	___	___
(10) Was the adverse event confirmed by any objective evidence?	+1	0	0	___	___	___
Add subscores from each column to calculate the Naranjo score for respective drug: (Score 0: Unlikely, Score 1-4: Possible, Score 5-8: Probable, Score 9-10: Definite)				___	___	___

(DR1-15-AdjudicationRpt.v2_101-140613

Page 1 of 4

Supplemental Figure S.3: Liverpool causality assessment scale.

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Genomics of Drug Induced Renal Injury (DIRI): Adjudication Report

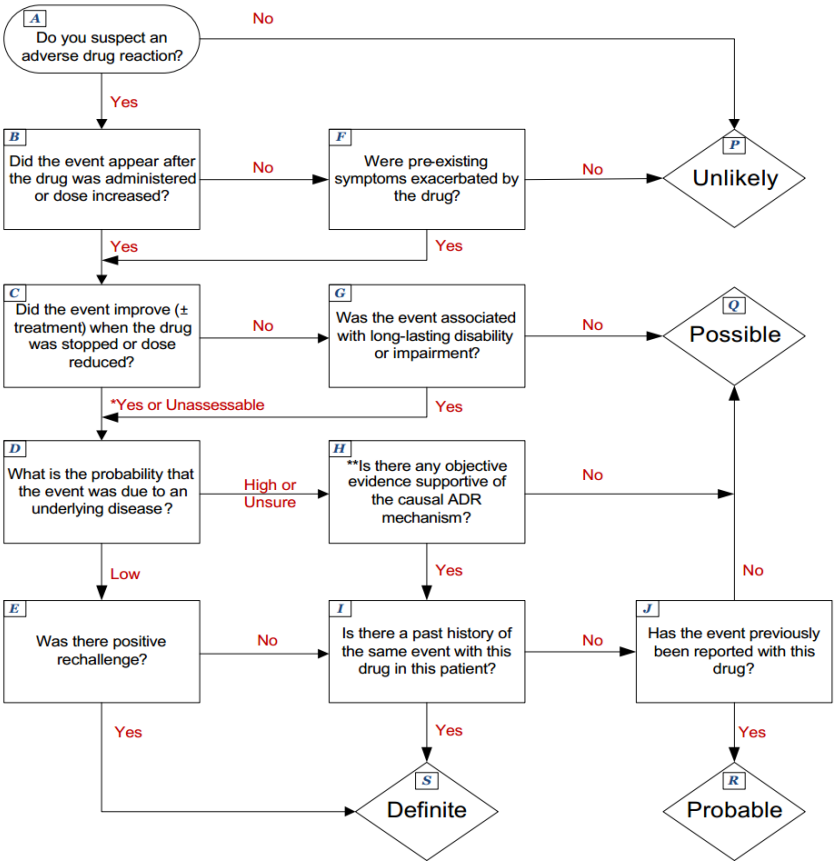
DR1 - CRF 15

Patient ID: ☐☐☐☐☐☐

Form ID: ☐☐☐☐☐ - ☐☐☐☐☐

4. Assessment Tools *(--- continued from Page 1 ---)*

b. Liverpool Adverse Drug Reaction Causality Assessment Tool *(DOI: 10.1371/journal.pone.0028096)*



Apply the Liverpool ADR assessment tool to construct the decision paths and determine the likelyhood of ADR associated with the drugs. Decision path is a sequence of tag letters (at the upper left corner of each question box) which represents an unbroken chain of path from box A to one of the final assessment results.

	Decision Path	Result
Drug 1	☐☐☐☐☐☐☐☐☐☐	○ Unlikely ○ Possible ○ Probable ○ Definite
Drug 2	☐☐☐☐☐☐☐☐☐☐	○ Unlikely ○ Possible ○ Probable ○ Definite
Drug 3	☐☐☐☐☐☐☐☐☐☐	○ Unlikely ○ Possible ○ Probable ○ Definite

Supplemental Figure S.4: Clinical adjudication form of DIRECT study

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Genomics of Drug Induced Renal Injury (DIRI): Adjudication Report

DR1 - CRF 15

Patient ID: ☐☐☐☐☐☐

Form ID: ☐☐☐☐☐ - ☐☐☐☐☐

5. Event attributable to drug and if so what level of certainty (use Naranjo scores and Liverpool assessment tool in #4):

Assessment	Drug 1	Drug 2	Drug 3	Underlying and Concomitant Risk Factors
Likely Cause to ADR	O Unlikely O Possible O Probable O Definite	O Unlikely O Possible O Probable O Definite	O Unlikely O Possible O Probable O Definite	O Unlikely O Possible O Probable O Definite
Percent Contribution (add to 100%) **Total =** ☐☐☐ %	☐☐☐ %	☐☐☐ %	☐☐☐ %	☐☐☐ %
Type of Event **A: Drug Toxicity** **B: Hypersensitivity**	O Drug Toxicity O Hypersensitivity	O Drug Toxicity O Hypersensitivity	O Drug Toxicity O Hypersensitivity	

6. Relative contribution of various categories of risk factors (reported in CRF05) in relation to drug exposure:

Risk Factors	Percent contribution of individual risk factor category to overall risk (total among risk factors should be 100%)
a. Procedures requiring intravascular contrast agents	☐☐☐ %
b. Nephrotoxic agents	☐☐☐ %
c. Surgical procedures requiring general anethesia	☐☐☐ %
d. MAP < 65 mmHg for more than 60 minutes if monitored, or SBP < 90 mmHg if not monitored	☐☐☐ %
e. Additional risk factors for AKI (intravascular fluid loss, increased vascular capacity,cardiac failure, liver diseases, ECF losses, other procedures)	☐☐☐ %
f. RBC transfusion	☐☐☐ %
g. Hyperglycemia	☐☐☐ %
Total =	☐☐☐ %