Supplementary Table S1 Summary of studies that have evaluated potential strategies for prevention of VIKI

	Study[ref]	Animals included/cell line	Comparators	Main outcome
	Antioxidants			
1	Nishino et al. 2003[78]	Wistar rats	Vancomycin was administered 200 mg/kg, i.p. twice a day for 7 days. At the same time, AH-SOD 5 mg/kg/day 5 min before vancomycin, or saline, was administered sc before vancomycin was injected.	Vancomycin caused destruction of glomeruli and necrosis of proximal tubules which was prevented by AH-SOD.
2	Oktem et al. 2005[122]	22 Wistar albino rats	Rats were divided into three groups: (i) control; (ii) vancomycin (200 mg/kg, twice daily for 7 days, i.p.); (iii) vancomycin plus erdosteine (10 mg/kg, orally, once daily). Erdosteine was started 24 h before vancomycin.	Erdosteine pretreatment showed a marked reduction in tubular damage.
3	Celik et al. 2005[131]	30 female Sprague Dawley rats	Rats were divided into six groups. A saline-treated group served as control. The other five groups were treated for 7 days with vancomycin alone or in combination with either α-lipoic acid, ginkgo biloba extract, melatonin, or amrinone.	The antioxidants and amrinone treatments significantly improved the renal pathology and histology compared to rats treated with vancomycin alone. Amrinone, the phosphodiesterase type III inhibitor, was the most effective.
4	Cetin et al. 2007[121]	24 Wistar albino rats	Rats were divided into three groups: (i) control; (ii) vancomycin (200 mg/kg, i.p.); (iii) vancomycin plus erythropoietin (150 IU/kg, i.p.). Vancomycin was administered to Groups 2 and 3 for 7 days. Erythropoietin was started 24 h before vancomycin and lasted for 7 days.	Histopathological changes were significantly improved after erythropoietin administration.
5	Ocak et al. 2007[120]	30 Wistar albino rats	Rats were divided into six groups: (i) control; (ii) vancomycin (200 mg/kg, ip); (iii) vancomycin plus 10 μmol/kg CAPE; (iv) vancomycin plus vitamin C – vancomycin, i.p. with 200 mg/dl vitamin C in drinking water; (v)	Vitamin E was the most effective agent in prevention of vancomycin-induced tubular damage, followed by vitamin C, N-acetylcysteine, and CAPE.

			vancomycin plus 1000 mg/kg vitamin E, i.m.; and (vi) vancomycin plus 10 mg/kg N-acetylcysteine, i.p.. Vancomycin administration was started 1 day after the first treatments of the antioxidants and continued for 7 days.	
6	Naghibi et al. 2007[80]	Wistar albino rats	2,3-Dihydrobenzoic acid (DHB) at doses of 50 and 100 mg/kg and tempol at doses of 7.5, 15, and 30 mg/kg were administered s.c to rats, 30 min prior to 200 mg/kg vancomycin i.p.	Both doses of DHB ameliorated the rise in serum urea ($P<0.001$) and creatinine [($P<0.01$ for dose of 50 mg/kg and $P<0.001$) for dose of 100 mg/kg] concentrations. Tempol in any doses could not prevent the tissue injury.
7	Ahmida MH 2010[139]	32 Sprague–Dawley rats (divided in 4 groups)	The first group was considered as the control, the second, third, and fourth groups were treated orally with curcumin (200 mg/kg/day), vancomycin (200 mg/kg/day i.p.), and vancomycin plus curcumin. Curcumin was started 2 weeks earlier and continued for 1 week simultaneously with vancomycin.	Treatment of rats with curcumin before and simultaneously with vancomycin alleviated its nephrotoxic effects.
8	Dalaklioglu et al. 2010[84]	Male Wistar rats (4 groups)	Rats were divided into four groups: (i) control; (ii) vancomycin (200 mg/kg, i.p. twice daily for 7 days); (iii) vancomycin plus 1,5-isoquinolinediol (ISO) (3 mg/kg/day, i.p.); (iv) ISO-treated. Vancomycin was administered to Groups 2 and 3 for 7 days. ISO was started 24 h before vancomycin and lasted for 8 days.	ISO prevented VIKI as measured by serum BUN and creatinine monitoring, urinary N-acetyl-beta-D-glucosaminidase excretion, and renal histology.
9	Basarslan et al. 2012[140]	28 Wistar albino rats (divided in 4 groups)	The study groups received normal saline (control group), vancomycin 200 mg/kg, i.p. for 7 days, vancomycin plus thymoquinone 10 mg/kg i.p. for 8 days, and thymoquinone	The serum concentrations of BUN, creatinine and kidney tissue malondialdehyde which were increased in the vancomycin group were ameliorated significantly by thymoquinone.

10	Panonnummal et al. 2013[119]	24 Albino Wistar rats (4 groups)	Animals received atorvastatin (5, 10, 20 mg/kg, orally) for 5 days followed by vancomycin (200 mg/kg, ip twice daily) + atorvastatin (5, 10, 20 mg/kg, orally) for 7 days, followed by atorvastatin (5, 10, 20 mg/kg, orally) for 5 days. The control group received carboxy methyl cellulose (CMC) 0.5% orally for 5 days followed by vancomycin + CMC for 7 days, followed by CMC orally for 5 days.	Higher doses of atorvastatin exhibited considerable degree of antioxidant activity and atorvastatin at 10 mg/kg provided significant degree of protection under histological examination. The 5 mg/kg low dose of atorvastatin was insufficient to provide a protective effect due to inability to restore the altered antioxidant status. Atorvastatin at 20 mg/kg showed effective antioxidant action but it failed to provide a protective effect in renal damage, may be due to its direct toxic effect on rat kidney.
11	Bayomy et al. 2016[112]	49 Wistar albino rats	Rats were divided into 7 groups: (i) Control (saline, i.p.), (ii) spirulina (1000 mg/kg per day, gastric gavage), (iii) pycnogenol (200 mg/kg per day, gastric gavage), (iv) vancomycin (200 mg/kg per day every 12 h, i.p.), (v) spirulina + vancomycin, (vi) pycnogenol + vancomycin, and (vii) spirulina + pycnogenol + vancomycin groups. All treatments were administered for 7 days.	The combination therapy of spirulina + pycnogenol showed better protective effects than the corresponding monotherapy.
12	Sakamoto et al. 2017[141]	Porcine proximal tubular epithelial LLC-PK1 cell line	Vancomycin, vitamin E, mitoTEMPO (mitochondria-targeted antioxidant), vitamin C, N-acetylcysteine, glutathione	Vancomycin induces reactive oxygen species-dependent apoptosis via mitochondrial cardiolipin peroxidation in renal tubular epithelial cells. Vitamin E and a mitochondria-targeted antioxidant, mitoTEMPO, significantly suppressed vancomycin-induced depolarization of mitochondrial membrane and apoptosis. In this study vitamin C, n-acetylcysteine, or glutathione did not provide significant protection.

13	Uckun et al. 2018[113]	56 Wistar albino rats	Rats were divided into 7 groups: (i) Control (saline, i.p.), (ii) carboxymethyl cellulose (0.5% CMC, orally), (iii) vancomycin (400 mg/kg, i.p.), (iv) NAR100 (naringenin 100 mg/kg, orally), (v) vancomycin + NAR25 (25 mg/kg, orally), (vi) vancomycin + NAR50 (50 mg/kg, orally), and (vii) vancomycin + NAR100 (100 mg/kg, orally) groups. Vancomycin administration was started 1 day after the first treatment of NAR and continued for 7 days.	NAR 25 and 50 mg have more potent protective effects on vancomycin-induced nephrotoxicity compared to NAR 100 mg as measured by apoptotic and oxidative stress markers and histopathology.
14	Kandemir et al. 2018[114]	42 Sprague Dawley rats	Rats were divided into 6 groups: (i) Control (saline, i.p.), (ii) zingerone (25 mg/kg, orally), (iii) zingerone (50 mg/kg, orally), (iv) vancomycin (200 mg/kg, i.p.), (v) vancomycin + zingerone (25 mg/kg, orally), and (vi) vancomycin + zingerone (50 mg/kg, orally) groups. All treatments were administered for 7 days.	This study reported a novel finding that vancomycin caused a decrease in aquaporin (AQP1) protein level compared to the control group which may account for vancomycin-induced water retention in the kidneys. Aquaporins are a water-channel membrane protein that allow water to move rapidly through permeable membranes of the tubular epithelial cells and maintain osmotic pressure of the cells by restricting cation and proton flow. Zingerone at both doses attenuated vancomycin-induced oxidative stress, inflammation, and apoptosis and increased aquaporin protein 1 level.
15	Shi et al. 2018[116]	85 Balb/c mice (17/group)	Mice were divided into 5 groups: normal group, vancomycin (400 mg/kg, i.p.); phosphatidylcholine group; DHA (docosahexaenoic acid group, 300 mg/kg/day); DHA-PC (DHA-enriched phosphatidylcholine, 300 mg/kg/day) group. All antioxidants were administered by gavage before injection of	DHA-PC significantly extended the survival time of mice, compared to DHA and PC alone. The protective effect of DHA-PC on VIKI was mediated through inhibition of oxidative stress and apoptosis.

			vancomycin. All treatments were administered for 4 days.	
16	Qu et al. 2019[117]	40 Wistar rats	Rats were divided into 4 groups: (i) Control (saline, i.p. 1 ml/kg), (ii) rutin (150 mg/kg, p.o.), (iii) vancomycin (200 mg/kg, i.p., twice daily), (iv) rutin + vancomycin groups. Rutin was administered 2 h before vancomycin. All treatments were administered for 7 days.	Rutin exerts a protective effect against vancomycin-induced nephrotoxicity by increasing mRNA levels of the transcription factor Nrf2 and its downstream target gene the antioxidant enzyme heme oxygenase-1 (HO-1) and suppressed oxidative stress, apoptosis, and downregulated the inflammatory response.
17	Guzel et al. 2019[118]	49 Wistar albino rats	Rats were divided into 7 groups: (i) Control (saline, i.p., 2 ml), (ii) DMSO (i.p., 0.5 ml), (iii) vancomycin (400 mg/kg, i.p. 7 days), (iv) silymarin (100 mg/kg/day, i.p.), (v) vancomycin + silymarin 50 mg/kg/day, (vi) vancomycin + silymarin 100 mg/kg/day, and (vii) vancomycin + silymarin 200 mg/kg/day groups. Silymarin was administered 1 h before vancomycin and continued once daily for 8 days. Vancomycin administration was started 1 day after the first treatment of silymarin and continued for 7 days.	Pretreatment with silymarin at high doses was nephroprotective against vancomycin-induced toxicity as measured by oxidative stress, apoptotic, inflammatory markers, and histopathology.

18	Caglayan et al. 2019[115]	42 Sprague Dawley rats	Rats were divided into 6 groups: (i) Control (saline, i.p.), (ii) zingerone (25 mg/kg, orally), (iii) zingerone (50 mg/kg, orally), (iv) vancomycin (200 mg/kg, i.p.), (v) vancomycin + zingerone (25 mg/kg, orally), and (vi) vancomycin + zingerone (50 mg/kg, orally) groups. The animals received zingerone orally 30 min after the vancomycin injection. All treatments were administered for 7 days.	Coadministration of zingerone regulated α-glycosidase, butyrylcholinesterase, aldose reductase, acetylcholinesterase, paraoxonase-1, and carbonic anhydrase metabolic enzyme activities in lung, liver, kidney, and testis tissues of rats that were significantly increased or decreased with vancomycin compared to the control ($p<0.5$). They concluded that this regulation of metabolic enzymes may account for the protective effective of zingerone in various tissues.
	Transport inhibitors			
1	Toyoguchi et al. 1996[142]	Rabbits	Animals received vancomycin (300 mg/kg, i.v.), imipenem-cilastatin, flomoxef sodium, fosfomycin sodium, ceftazidime, cefpimizole sodium, cefoperazone sodium alone or in combination with vancomycin.	Renal concentrations of vancomycin in the groups administered vancomycin plus imipenem-cilastatin, flomoxef sodium, fosfomycin sodium were lower than the control group. Imipenem-cilastatin, flomoxef sodium, fosfomycin sodium may decrease the nephrotoxicity of vancomycin by inhibiting its uptake into the kidney.
2	Toyoguchi et al. 1997[123]	Male Japanese white rabbits (5/group)	Animals were divided into 5 groups: vancomycin (300 mg/kg, i.v.), cilastatin (75, 150 or 300 mg/kg, i.v.) plus vancomycin, cilastatin alone (300 mg/kg, i.v.)	Cilastatin reduced or eliminated the nephrotoxic effects of vancomycin in a dose-dependent manner.
3	Hori et al. 2017[60]	kidney-specific megalin KO mice (apoE cre, megalin lox/lox)	Intraperitoneal injection of vancomycin (400 mg/kg body wt) once daily for 4 days	In kidney-specific megalin knockout mice treated with vancomycin, the megalin-replete proximal tubule epithelial cells exhibited signs of injury, whereas the

				megalin-deficient cells did not.
4	Im et al. 2017[61]	C57BL/6J mice	Seven groups of mice: control, cilastatin 150 mg/kg/day, cilastatin 300 mg/kg/day, vancomycin 400 mg/kg/day + cilastatin 150 mg/kg/day, vancomycin 400 mg/kg/day + cilastatin 300 mg/kg/day, vancomycin 600 mg/kg/day + cilastatin 150 mg/kg/day, vancomycin 600 mg/kg/day + cilastatin 300 mg/kg/day. vancomycin and cilastatin were given i.p. for 7 days.	Mechanism of vancomycin nephrotoxicity may involve suppressing P-gp function, and cilastatin attenuated VIKI.
5	Wen et al. 2018[125]	30 Wistar rats	Animals were divided into 5 groups: saline (i.p., twice daily, 7 days); JBP485 (50 mg/kg, i.p., twice daily, 7 days); vancomycin (400 mg/kg, i.v. twice daily, 7 days), JBP485 (25 mg/kg) plus vancomycin; JBP485 (50 mg/kg) plus vancomycin.	Vancomycin decreased expression of transporters. JBP485 could reverse these effects without affecting plasma concentrations of vancomycin.
	Formulations			
1	Greenwald et al. 2003[143]	Bacterial efficacy studies	Polyethylene glycol (PEG)-vancomycin conjugates	Significant increases in the AUC were observed for all PEG-vancomycin conjugate, making them potential single dose therapies.
2	Hodoshima et al. 2004[132]	Sprague Dawley rats	A generic form of vancomycin with 2 inactive ingredients, D-mannitol and Macrogol400 (PEG400), referred to as MEEK was compared with the branded form at two doses 40 mg/kg and 400 mg/kg.	At the clinical dose of 40 mg/kg there was no difference in the pharmacokinetics of MEEK vs the brand. At the nephrotoxic dose of 400 mg/kg, the branded product caused impairment of renal function and kidney damage and decreased renal clearance. In contrast, MEEK had no effect on renal function, kidneys, and did

				not cause a marked change in renal clearance.
3	Hodoshima et al. 2007[149]	Sprague Dawley rats	MEEK was compared with the branded form at two doses 40 mg/kg and 80 mg/kg, in nephrectomized rats.	MEEK decreased renal accumulation and toxicity of vancomycin in rats with chronic renal failure compared to standard vancomycin.
4	Chakraborty et al. 2011[138]	Swiss mice	Vancomycin and nanoconjugated vancomycin were administered to normal mice, vancomycin susceptible (VSSA-) and vancomycin resistant staphylococcus aureus VRSA-infected mice at doses of 100 mg/kg/day and 500 mg/kg/day, for 10 days.	VSSA and VRSA infection significantly increases oxidative stress markers as compared to control group. These markers were near normal in nanoconjugated vancomycin-treated group.
5	Muppidi et al. 2011[134]	42 CF-1 mice	Vancomycin (5 mg/kg) in the form of a standard solution or conventional or PEGylated liposomes.	PEGylated liposomal vancomycin, compared to standard and non-PEGylated formulations, significantly prolonged blood circulation time and increased deposition in lung, liver, and spleen and yet reduced accumulation in kidney tissue
6	Sande et al. 2012[144]	CD-1 mice	50 mg/kg of free vancomycin or 50 mg/kg of dicetylphosphate (DCP) liposomal vancomycin	Liposomal vancomycin improved kidney clearance of a USA300 strain by 1 log compared with an injection of free vancomycin.
7	Liu et al. 2015[145]	Kunming mice	Vancomycin hydrochloride solution and liposomal formulation	Vancomycin liposomes decreased accumulation of vancomycin hydrochloride in the kidney.

8	Kalhapure et al. 2017[137]	Mice	Vancomycin loaded pH-responsive chitosan nanoparticles containing anionic gemini surfactant (DL_CSSNPs) vs vancomycin.	The MRSA burden in mice treated with DL_CSSNPs was reduced by almost 8-fold compared to those treated with pure vancomycin.
9	Guan et al. 2018[146]	Human renal proximal tubule epithelial cells (HK-2) , human liver cell line (HL-7702)	Vancomycin analog compounds were compared with vancomycin and telavancin in a cytotoxicity assay.	On HK-2 cells, compounds 16 and 46 produced a similar effect on cell viability as telavancin and slightly reduced toxicity compared to vancomycin. In HL-7702 cells, these compounds had significantly lower toxicity compared with vancomycin and telavancin.
10	Pawar et al. 2019[136]	Bacterial inhibition assay	Blank, vancomycin (CH-VAN), ciprofloxacin (CH-CIP), and cefuroxime (CH-CEF) loaded chitosan sponges.	Due to the highly hydrophilic properties of vancomycin, the CH-VAN sponge showed the highest swelling and fastest degradation profile. The CH-VAN sponge demonstrated the short-term release in contrast with the CH-CEF and CH-CIP sponges, which showed sustained release along with sustainable antibacterial activity.
11	Hassan et al. 2019[147]	Adenocarcinoma human alveolar basal epithelial cells (A549), embryonic kidney cells (HEK-293), and liver hepatocellular carcinoma (Hep G2) cell lines	Vancomycin and the optimized vancomycin-dextran sulfate sodium nanoplexes	In *in vitro* cytotoxicity studies the nanoplexes were found to be nontoxic against different mammalian cell lines tested.

12	Makhathini et al. 2019[135]	Balb/c mice	Saline, VAN alone, and pH-responsive liposomal formulations DOAPA-VAN-Lipo, and DLAPA-VAN-Lipo	Reduced MRSA were recovered from mice receiving the liposomal formulations compared to vancomycin alone.
13	Kaur et al. 2019[148]	Bacterial efficacy studies	vancomycin loaded silver nanoparticles	The well diffusion test showed synergetic rather than the additive effect in antibacterial activity against both gram-positive and gram-negative bacteria.
	Others			
1	Marre et al. 1984[36]	Female albino Wistar rats (10/group)	Vancomycin (25 mg/kg daily, i.v.) or vancomycin combined with potassium salt of D-glucaro-1.5-lactam (a β-glucuronidase inhibitor, 25 mg/kg daily, i.m.) in 7 single doses twice a day for 4 days.	A reduction in the nephrotoxic effect was observed when vancomycin was combined with D-glucaro-1.5-lactam.
2	Marre et al. 1985[126]	Female albino Wistar rats (10/group)	Vancomycin (50 mg/kg), fosfomycin (50 and 250 mg/kg), and tobramycin (2.5 mg/kg) were dissolved in distilled water or saline and administered i.p., i.v., or i.m. twice a day for 5 days (nine doses in total). Drugs were given alone or in combination with vancomycin. Controls received saline.	Fosfomycin protected against nephrotoxicity caused by vancomycin whereas tobramycin increased vancomycin nephrotoxicity. The novel finding in this study was that repeated dosing of vancomycin 50 mg/kg dissolved in distilled water led to renal accumulation; when combined with fosfomycin 250 mg/kg renal vancomycin concentrations were lower, but similar to that when vancomycin was dissolved in saline. Since the sodium load due to fosfomycin was less than with vancomycin in saline, they concluded that the protection afforded by fosfomycin was significantly better than that of sodium alone indicating that fosfomycin molecule itself interacts with vancomycin

				nephrotoxicity.
3	Nakamura et al. 1998[127]	35 Wistar albino rats	Fosfomycin (300 mg/kg) or imipenem/cilastatin (150/150 mg/kg) was administered intravenously with 300 and 500 mg/kg of vancomycin i.v. Normal healthy rats served as controls.	The accumulation of vancomycin was not significantly changed by cotreatment with fosfomycin or imipenem/cilastatin. However, both drugs decreased the excretion ratio of vancomycin in the perfused kidney indicating that the drugs inhibited the tubular transport of vancomycin, though on which membrane side fosfomycin and imipenem/cilastatin inhibited vancomycin transport could not be determined.
4	Nakamura et al. 1999[150]	Wistar albino rats (4-6/group)	Fosfomycin (300 mg/kg, i.v.) or imipenem/cilastatin (150/150 mg/kg, i.v.) was administered just before administration of vancomycin (500, 700, and 1000 mg/kg, i.v.) or cisplatin (5 or 10 mg/kg, i.v.). Normal healthy rats injected with saline served as controls.	Their results suggested that the effect of vancomycin nephrotoxicity is to reduce glomerular filtration of vancomycin more markedly than renal tubular secretion. Fosfomycin and imipenem-cilastatin protect both renal functions against vancomycin-induced nephrotoxicity.
5	Yoshiyama et al. 2001[128]	Wistar rats (5/group)	Fosfomycin (0.25 and 0.5 g/kg, i.p.), teicoplanin (50 mg/kg, i.p.), vancomycin (200 mg/kg, i.p.), fosfomycin plus vancomycin or fosfomycin plus teicoplanin were administered once daily for 3 days. Fosfomycin was injected	Fosfomycin significantly decreased renal accumulation of vancomycin and teicoplanin and reduced the glycopeptide antibiotic-induced nephrotoxicity in a dose-dependent manner.

			first followed by vancomycin or teicoplanin after a 30 min interval. Gentamicin (80 mg/kg, s.c. was coadministered to induce nephrotoxicity in each group).	
6	Bayram et al. 2019[130]	32 female albino Wistar rats	Rats were divided into 4 groups: Control (saline, i.p.), vancomycin (200 mg/kg, i.p.), dexmedetomidine (5 µg/kg, i.p.), dexmedetomidine plus vancomycin. Vancomycin was administered 20 min following dexmedetomidine. All treatments were administered twice per day for 7 days.	Dexmedetomidine can reduce the extent of renal damage by preventing the elevation of vasoconstrictor agent endothelin-1.
7	Xu et al. 2019[92]	Proximal tubule Atg7 wild type and deficient mice	Mice were treated with vancomycin (600 mg/kg/d, i.p.) alone or in combination with chloroquine (50 mg/kg/d) or rapamycin for 7 days.	Vancomycin suppresses the ERK1/2 and mTOR signaling pathway to increase autophagy. Rapamycin an mTOR inhibitor plus vancomycin increased VIKI. Inhibition of autophagy by chloroquine ameliorated VIKI. Atg7 may directly interact with PKC-δ to induce renal cell apoptosis during vancomycin treatment.

Abbreviations: AH-SOD, hexamethylenediamine-conjugated superoxide dismutase; Atg, Autophagy related gene; AUC, area under the concentration time curve; BUN, blood urea nitrogen; CAPE, caffeic acid phenyl ester; CMC, carboxy methyl cellulose; DCP, Dicetylphosphate; DL_CSSNPs, vancomycin loaded pH-responsive chitosan nanoparticles containing anionic gemini surfactant; DMSO, dimethylsulfoxide; DHA-PC, Docosahexaenoic acid-enriched phosphatidylcholine; DHB, 2,3-dihydrobenzoic acid; ERK, extracellular signal related kinase; i.m., intramuscular; i.p., intraperitoneal; ISO, isoquinolinediol; mTOR, mammalian target of rapamycin; NAR, naringenin; PEG, polyethylene glycol; PKCδ, protein kinase C delta; s.c., subcutaneously; VIKI, vancomycin-induced kidney injury; VRSA, vancomycin resistant staphylococcus aureus; VSSA, vancomycin susceptible staphylococcus aureus.