JPPT | Review

Clinical Review of Risk of Nephrotoxicity with Acyclovir Use for Treatment of Herpes Simplex Virus Infections in Neonates and Children

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OBJECTIVE This study aims to clarify the risk of nephrotoxicity with intravenous use of acyclovir (ACV) for the treatment of neonates (ages <3 months) and children (ages ≥3 months to <12 years) with herpes simplex virus (HSV) infections and to identify gaps in knowledge that could be further investigated.

METHODS Multiple databases were searched to identify studies on risk of nephrotoxicity with ACV use for treatment of invasive HSV infections, defined as any neonatal infection or HSV encephalitis (HSE) in children.

RESULTS There were 5 and 14 studies that evaluated the risk of ACV-associated nephrotoxicity in neonates and children, respectively. The US Food and Drug Administration (FDA) delayed the approval of high (HD; 60 mg/kg/day) ACV in neonates secondary to risk of toxicity. Based on our review, the risk of ACV-associated nephrotoxicity was lower in the neonatal compared with the pediatric population. Acyclovir dose >1500 mg/m^2, older age, and concomitant use of nephrotoxic drugs were identified as variables that increased the risk of ACV nephrotoxicity in children. Although the FDA has approved the use of HD ACV for the treatment of HSE in children, the American Academy of Pediatrics recommends a lower dose to minimize the risk of toxicity. The efficacy and safety of high vs lower doses of ACV for the management of HSE in children has yet to be evaluated.

CONCLUSIONS The risk of ACV-associated nephrotoxicity was lower among neonates compared with older children. Future studies are needed to identify the optimal dosage that minimizes toxicities and maximizes the efficacy of ACV in children with HSE.

ABBREVIATIONS AAP, American Academy of Pediatrics; ACV, acyclovir; AKI, acute kidney injury; CNS, central nervous system; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; HD, high dose; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; ID, intermediate dosage; IV, intravenous; KDIGO, Kidney Diseases: Improving Global Outcomes; LD, low dose; pRIFLE, Pediatric Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; RCT, randomized controlled trial; SCr, serum creatinine; SD, standard dosage; SEM, skin, eye, and/or mouth

KEYWORDS acute kidney injury; acyclovir; encephalitis; herpes simplex; nephrotoxic

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Introduction

In 1977, acyclovir (ACV), ((9-[(2-hydroxyethoxy) methyl] guanine), Zovirax), was identified as a selective and a specific inhibitor of the replication of herpes simplex virus (HSV), *in vitro*.[1] Since then, extensive work has been conducted to establish its *in vivo* efficacy and effectiveness against the herpes group of viruses and to assess its potential toxicity.[2] ACV became the drug of choice to treat neonates and children with suspected or proven HSV infections.[3,4] Most ACV is cleared intact through the kidney.[5,6] Therefore, one of the major concerns with ACV administration is the impairment of renal function.[5,6] The mechanism of ACV nephrotoxicity is mostly attributed to the deposition of crystals in the lower nephron, causing obstructive nephropathy.[5–7] Acyclovir crystallization is most pronounced when the drug concentration in the kidney exceeds its solubility threshold. This can be prevented by slow intravenous infusion of the drug, adequate fluid hydration, and dosage reduction in patients with renal insufficiency.[6] However, there have been several documented cases of ACV-induced nephrotoxicity in the absence of crystalluria.[8,9] Renal biopsies in these patients showed flattened, vacuolated, bulging epithelial cells or tubulointerstitial nephritis with intratubular casts and no evidence of crystals.[8,9] Thus, other proposed etiologies

for ACV nephrotoxicity include microangiopathy, interstitial nephritis, and direct injury to renal tubular cells.[6,10]

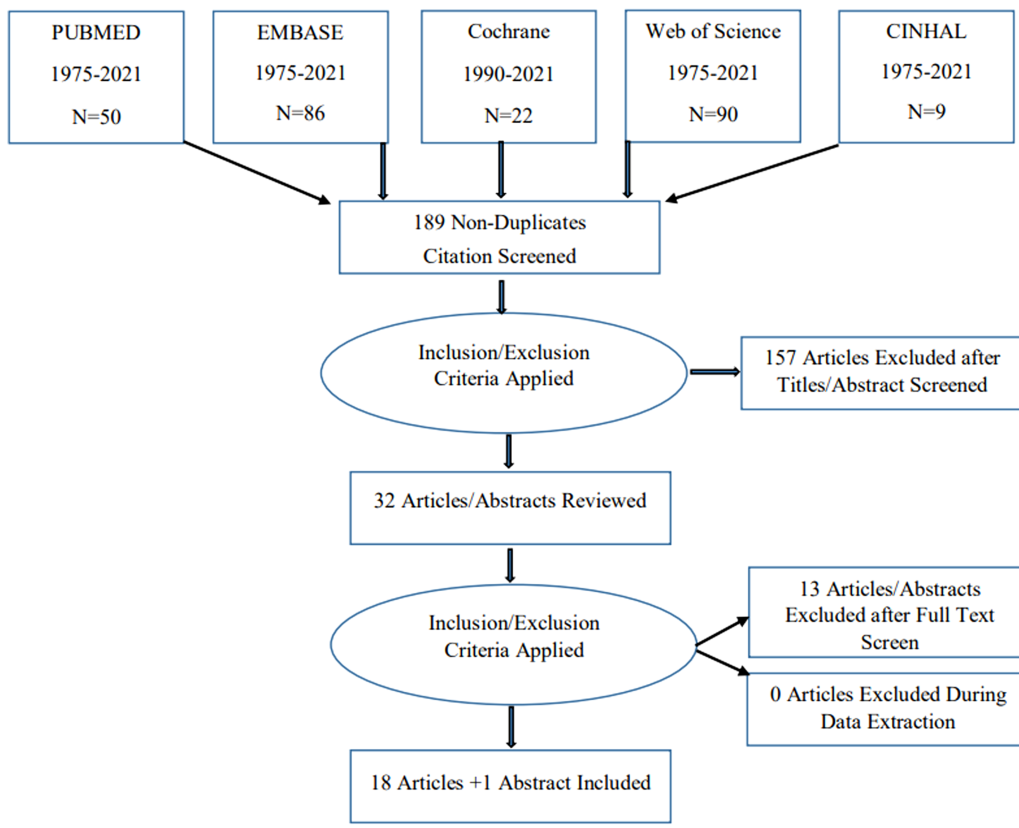
Neonatal HSV type 1 and 2 infections occur in the United States at an estimated incidence of 8.4 to 60 cases per 100,000 births and are associated with substantial morbidity and mortality even with appropriate treatment.[11–15] Likewise, HSV type 1 and 2 infections in children are associated with long-term adverse neurologic outcomes despite proper antiviral therapy.[16] The potentially devastating outcomes of these diseases are lessened with earlier initiation of ACV.[3,17] Thus, ACV is administered presumptively to both neonates and children with suspected HSV infections.[3,17] As a result, there is a need to balance the potential risk of these diseases with the possible side effects of ACV exposure, such as nephrotoxicity. We conducted an extensive search of the literature to assess the rates of kidney injury and identify risk factors for nephrotoxicity in neonates (ages <3 months) and children (ages ≥3 months to <12 years) receiving intravenous (IV) ACV for the management of invasive HSV type 1 and 2 infections (any neonatal infection or HSV encephalitis [HSE] in children). Our goals were first to clarify the risk of nephrotoxicity with IV use of ACV for the aforementioned indications and then identify gaps in current knowledge on ACV-associated nephrotoxicity in this patient population that could be further investigated.

Methods

Literature Search. Comprehensive literature searches were conducted (January 1, 1975–November 1, 2021) in PubMed, Embase, Web of Science, Cochrane Library, and CINAHL databases. We used the following search strategy ("acute kidney failure" OR "nephrotoxicity" OR "acute kidney injury" OR "kidney injury" OR "renal failure" OR "renal injury" OR "AKI") AND ("acyclovir" OR "acyclovir" OR "Zovirax"). We then supplemented our search using references from included articles and relevant reviews.

Articles were included if they were written in English and evaluated ACV-associated nephrotoxicity in our patient population. They were excluded if they focused on the oral use of ACV, only evaluated its use for indications other than neonatal or pediatric invasive HSV type 1 and 2 infections, or examined the dosing of IV ACV in patients receiving continuous renal replacement therapy or extracorporeal membrane oxygenation therapy; they were also excluded if the study mainly described ACV pharmacokinetic properties or summarized the adverse events drug reports of various nephrotoxic drugs (Figure 1).

Figure. Flow diagram of the literature search.



Earlier studies on ACV use included study cohorts that ranged from the neonatal age group through adult life. Thus, the summary of our search was divided into a list of studies that only assessed IV ACV use in neonates and another list that evaluated its use in children including some neonates.

Definition of Acute Kidney Injury. Acute kidney injury (AKI) is described as an acute decline in kidney function leading to disturbances in fluid balance, electrolytes, and wastes.[18] Multiple studies have described an increased risk of chronic kidney disease in children[19,20] or neonates[21,22] who survived 1 episode of AKI. Unfortunately, studies that evaluated the risk of nephrotoxicity with IV ACV use adapted various definitions of AKI. The serum creatinine (SCr) concentration, a metabolic byproduct of muscle metabolism, is the most common biomarker used to diagnose AKI.[23] On the first day of life, SCr values reflect maternal levels. Subsequently, these values decrease over days to weeks such that neonatal concentrations average 0.1 to 0.3 mg/dL,[24] then progressively increase through childhood such that levels in older children average 0.4 to 0.8 mg/dL.[24] Serum creatinine can be used to calculate estimated glomerular filtration rate (eGFR), the combined total filtration rate of the functioning nephron units, using equations such as the modified Schwartz.[25–28] Acute kidney injury represents an abrupt decline in kidney function (eGFR), reflected as an increase in SCr from baseline. Multiple classifications of AKI have been published to stage the severity of AKI in adults, and these classifications have been further modified to account for the developmental changes in renal physiology between infants, children, and adults.[18,29–31] Although a detailed discussion of the differences between the various designations of AKI is beyond the scope of this manuscript, a summary of the definitions used in this review is listed in Table 1.

Table 1. Summary of Different Classifications of Acute Kidney Injury (AKI)*

Neonatal AKI KDIGO Classification[18,29]			RIFLE[30]		pRIFLE[31]	
Stage	**SCr**	**Urine Output**	**Classification**	**Rise in Creatinine, %**	**Classification**	**Criteria**
0	No change in SCr or rise <0.3 mg/dL	≥0.5 mL/kg/hr	Risk	>150 to <200	Risk	eGFR decrease of 25%–49%
1	SCr rise ≥0.3 mg/dL within 48 hr or SCr rise ≥1.5 to 1.9 × reference SCr† within 7 days	<0.5 mL/kg/hr for 6–12 hr	Injury	≥200 to <300	Renal injury	eGFR decrease of 50%–74% from baseline or urine output <0.3 mL/kg/hr for 16 hr
2	SCr rise ≥2.0 to 2.9 × reference SCr	<0.5 mL/kg/hr for >12 hr	Failure	≥300	Failure	eGFR decrease of 75% from baseline or eGRF<35 mL/min/1.73 m^2 or urine output <0.3 mL/kg/hr for 24 hr or anuric for 12 hr
3	SCr rise ≥3 × reference SCr or SCr ≥2.5 mg/dL‡ or receipt of dialysis	<0.5 mL/kg/hr for ≥24 hr or anuria for ≥12 hr	Loss	Failure >4 wk	Loss	Failure >4 wk
			End-stage renal disease	Failure >3 mo	End-stage renal disease	Failure >3 mo

eGFR, estimated glomerular filtration rate; KDIGO, Kidney Diseases: Improving Global Outcomes; pRIFLE, Pediatric Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; SCr, serum creatinine

*Only the classifications of AKI used in this review are listed in this table.

†,‡ Differences between the neonatal and the pediatric KDIGO AKI definition: † Reference SCr was defined as the lowest previous SCr compared with baseline SCr and ‡ SCr value was set at 2.5 mg/dL compared with 4 mg/dL when defining the neonatal vs pediatric KDIGO criteria.

Studies and Discussion

ACV-Associated Nephrotoxicity in Neonates. Neonatal HSV type 1 and 2 infections manifest as 1) skin, eye, and/or mouth (SEM) disease; 2) encephalitis with or without skin involvement (central nervous system [CNS]) disease; or 3) disseminated infections.[32] SEM is treated with a shorter course of ACV and has less morbidity than CNS or disseminated disease. Historically, the mortality of infants with disseminated HSV exceeded 50%, and more than 70% of surviving infants with neonatal HSV CNS disease had developmental impairment.[32] With the use of high dose (HD) ACV (60 mg/kg/day divided in 3 doses for 21 days), 1-year mortality has been reduced to approximately 30% in patients with disseminated disease.[4] With the additional use of oral suppressive ACV therapy for 6 months, 69% of infants with neonatal HSV CNS disease had normal Bayley Mental Development Scales at 12 months.[33] Recently, the overall US national mortality rate of infants receiving a diagnosis of any category of HSV infection between 2003 and 2014 was estimated at 7.9%.[14]

Vidarabine was the first antiviral agent used to treat HSV infections.[34] In 1991, Whitley et al[35] conducted a randomized controlled trial (RCT) comparing 10 days' therapy of vidarabine (30 mg/kg continuous IV infusion during 12 hours) vs ACV (30 mg/kg/day given parenterally every 8 hours) for the management of neonatal herpes (Table 2). The authors did not detect differences in mortality or morbidity between the 2 groups. There were no significant renal adverse effects reported with either drug. Because of its ease of administration, ACV supplanted vidarabine as the drug of choice for treatment of HSV and became licensed by the US Food and Drug Administration (FDA) for this indication in 1998.[36] Because the mortality and morbidity with neonatal HSV disease remained significantly elevated on standard dosage (SD; 30 mg/kg/day) of ACV, additional studies focused on the effect of higher dosing and longer duration of this drug. In 2001, Kimberlin et al[4] evaluated the outcomes of 88 neonates primarily with CNS or disseminated HSV disease who received intermediate dosage (ID; 45 mg/kg/day) or HD (60 mg/dose/day) of ACV for 21 days and compared their outcomes to a historical cohort of infants who received SD[35] and duration (10 days)[35] of ACV. The authors determined that the mortality rates were significantly lower in patients who received HD vs SD of ACV.[4] After controlling for confounding variables, the HD ACV group was also noted to have had a borderline improvement in their development outcomes at 12 months, compared with the SD ACV group.[4] Approximately 17% and 6% of patients receiving ID and HD ACV, respectively, developed elevated SCr during ACV therapy, although the authors could not confirm the cause of renal insufficiency. In 2012, Vanderpluym et al[37] evaluated the renal adverse effects among 118 neonates who received IV ACV for empiric management of HSV. Only 3 infants had ACV-associated nephrotoxicity. The authors attributed this low rate to the diminished renal concentrating ability in neonates that can protect them from intratubular crystallization.

Although the American Academy of Pediatrics (AAP) recommended HD ACV for the treatment of neonatal HSV disease in 2015, the FDA did not approve HD ACV for this indication at that time.[38] Thus, in 2017, Ericson et al[39] evaluated the adverse effects of ACV therapy among 89 neonates ages ≤120 days who received ≥14 days of therapy or died while receiving ACV. Prolonged ACV therapy (≥14 days) was used as a proxy measure for clinical or confirmed diagnosis of HSV disease. A total of 89% of the study cohort received HD ACV. Nonetheless, elevated SCr (>1.7 mg/dL) was only detected in 2% of infants. Based on their results, the authors recommended that all neonates with HSV disease should receive HD ACV. In 2019, the FDA finally approved HD ACV for the treatment of neonatal HSV. A year later, Downes et al[40] published a retrospective cohort study that used the modified neonatal Kidney Diseases Improving Global Outcomes (KDIGO) criteria (Table 1)[18,29] to examine the risk of AKI among 1017 infants who were treated with ≥1 dose of IV ACV. Only 31 of 1017 patients had confirmed HSV disease. A total of 6% of the overall study population developed AKI during therapy or within 48 hours of ACV completion. Interestingly, nearly one-quarter of infants with confirmed disease who received ACV for ≥14 days developed AKI. Multivariate analysis identified confirmed HSV disease, receipt of mechanical ventilation, admission to intensive care unit, and receipt of ≥2 concomitant nephrotoxic medications on preceding day of AKI diagnosis as risk factors for AKI. The authors recommended close monitoring of kidney function during ACV therapy in neonates.

ACV-Associated Nephrotoxicity for Treatment of HSE in Children. Between 2000 through 2010, the US rates of HSE hospitalizations in nonfederal acute care hospitals were estimated at 5.76 ± 0.76, 0.34 ± 0.05, and 0.21 ± 0.02 per 100,000 for children ages <1, 1 to 4, and 5 to 19 years, respectively.[41] Among childhood encephalitis, HSE still accounts for the highest rate of long-term sequelae (64%).[16] Acyclovir is the current treatment of choice for HSE,[3] although the risk of associated nephrotoxicity remains one of the main concern with its use.

In 1979, Selby et al[7] were the first authors to report a transient impairment in renal function among 2 adult patients who received ACV for disseminated zoster. In 1982, Brigden et al[5] reported reversible renal dysfunction among 58 of 354 pediatric and adult patients who received IV ACV for various indications (Table 3). That same year, Keeney et al[42] described a transient increase in SCr among 12% of 85 children who received "bolus" injections of ACV, whereas no adverse renal effects were observed among 42 children who

Table 2. Summary of Studies on Intravenous Acyclovir (ACV)–Associated Nephrotoxicity in Neonates*

Author Study Type	Sample Size	Study Setting	Patient Population	Outcomes	Limitations
Whitley[35] Blinded RCT	210	27 US pediatric hospitals	Newborns ages <1 mo with virologically confirmed HSV disease were enrolled from February 1981 through January 1988. 8 infants had disease at birth and were excluded from efficacy study. 95 and 107 patients were randomized to receive IV vidarabine (30 mg/kg/dose/day as a continuous infusion during 12 hr) × 10 days vs ACV (30 mg/kg/day q8 hr during the course of 1 hr) × 10 days, respectively. Renal adverse effect was defined as SCr >2.99 mg/dL.	No significant difference between the vidarabine vs ACV groups in rate of mortality for the first 12 mo after enrollment (p = 0.27) or normal development at 1 year of life (p = 0.83), after adjusting for the extent of HSV disease between the 2 therapeutic arms. Higher laboratory aberration in the vidarabine vs ACV groups, although none were associated with clinical complications.	No specific rate of renal adverse effects was provided for the vidarabine vs ACV groups.
Kimberlin[4] Open-label Phase 2 trial	88	14 US pediatric	Neonates (age ≤28 days, weight ≥1200 g, and gestational age >32 wk) were enrolled between 1989 and 1997. Only 10 patients had SEM disease with the rest of study cohort with either CNS (n = 28) or disseminated (n = 41) HSV disease; 9 patients whose clinical picture was suggestive of HSV but who did not have virologic confirmation of the disease were also enrolled. 79 patients with virologically confirmed HSV were included in the efficacy study; all 88 patients were enrolled in safety analyses. 16 patients, enrolled between 1989 and 1990, received ID (45 mg/kg/day divided q8 hr) ACV, whereas 72 patients, enrolled between 1990 and 1997, received HD (60 mg/kg/day divided q8 hr) ACV. All patients received ACV therapy × 21 days and were compared to 107 historical controls[35] who received SD (30 mg/kg/day divided q8 hr × 10 days) of ACV.	The differences in mortality for each of these disease categories were weighted to allow for statistical comparison of the treatment groups (HD, ID, and SD therapy); survival rate for patients treated with HD ACV was significantly higher than historical controls who received SD ACV (OR, 3.3; 95% CI, 1.5–7.3). After controlling for confounding variables, patients who received HD vs SD ACV had a borderline improvement in their development outcomes at 12 mo (p = 0.051). Renal toxicity assessment was quantitated using the Division of AIDS Toxicity Tables (grade 1, 1.1–1.3 upper limit of normal; grade 2, >1.3 to 1.8 upper limit of normal or increase to 1.3 to <1.5 × participant's baseline; grade 3, >1.8 to < 3.5 upper limit of normal or increase to 1.5 to <2.0 × participant's baseline; grade 4, ≥3.5 upper limit of normal or increase of ≥2.0 × participant's baseline).[54] Grade 3 or 4 elevation in SCr occurred only in patients with disseminated HSV disease and was noted in 2 of 12 patients (17%) and 4 of 64 patients (6%) in ID and HD groups, respectively. The laboratory abnormality in SCr seen in the ID and HD groups was similar and was not statistically significant.	Difficulty in determining if elevated SCr was secondary to underlying HSV disease or ACV toxicity or a combination of both.

Table 2. Summary of Studies on Intravenous Acyclovir (ACV)–Associated Nephrotoxicity in Neonates* *(cont.)*

Author Study Type	Sample Size	Study Setting	Patient Population	Outcomes	Limitations
Vanderpluym[37] Retrospective chart review	118	University of Alberta, Royal Alexandra, Misericordia, Grey Nuns, and Alberta Children's Hospitals in Canada	118 neonates aged up to 43 days, treated with IV ACV for presumed HSV between January 2001 and February 2007, were included in the study. Patients were excluded if the indication for ACV was unrelated to HSV. Only 7.6% (9 of 118) of patients had proven HSV infection and received >7 days of ACV. 2 patients with SEM HSV were treated with 30 mg/kg/day ACV, whereas the rest of patients with disseminated or CNS HSV received 60 mg/kg/day ACV. SCr values at the onset of ACV treatment and at the highest level while on ACV therapy were recorded. Patients were allocated into 3 groups based on duration of ACV exposure (≤3, 4–7, and >7 days).	ACV-associated nephrotoxicity was defined as a 20% increase in median SCr in each group during ACV exposure compared with baseline. Duration of ACV did not increase the median peak of SCr; none of the 64 and 10 infants treated with ACV <3 and >7 days, respectively, had elevation in SCr during ACV therapy; among patients who received ACV for 4–7 days, 3 had an ACV-associated nephrotoxicity that resolved after ACV was stopped.	<8% of study cohort received ACV >7 days. ACV-associated nephrotoxicity in 1 of 3 patients was confounded by concomitant bacteremia. Many infants had no SCr measured during ACV exposure.
Ericson[39] Retrospective chart review	89	42 US NICUs managed by the Pediatrix Medical Group from 2002 to 2012	Neonates who were age ≤120 days and treated with ≥14 days of IV ACV or died while on ACV therapy were included in the study.	Elevated SCr, defined as >1.7 mg/dL, occurred only in 2% (2 of 89) of infants and 0.2% of infant-days, and no infants developed renal failure requiring dialysis.	No detailed report of infusion rate of ACV or hydration status.
Downes[40] Retrospective chart review	1017	4 US hospitals: Children's Hospital of Philadelphia; Children's Hospital of Los Angeles; Inova Children's Hospital, and Monroe Carell Jr. Children's Hospital in Vanderbilt	1017 hospitalized infants age <60 days who were treated with ≥1 dose of IV ACV for suspected or confirmed HSV disease from January 2011 through December 2015. Patient who did not have an SCr measurement both before ACV initiation and during or ≤48 hr after last dose of ACV, had AKI detected within 72 hr before initiation of ACV, received treatment for indication different from HSV, or had congenital kidney disease were excluded from the study. ACV was most often prescribed at a dosage of 60 mg/kg/day.	Primary outcome was detection of AKI per modified neonatal KDIGO criteria at any time after the first dose of ACV and through 48 hr after the last dose. The lowest SCr documented at any instance before ACV initiation was considered the baseline; severity of AKI was defined based on the maximum SCr obtained after the first dose and through the last dose. Only 31 of 1017 (3.0%) had confirmed HSV disease, including 15, 9, and 7 patients who had disseminated, CNS, and SEM disease, respectively. 5.6% (57 of 1017) of infants developed AKI during therapy or within 48 hr of ACV completion, with 28% (16 of 57) developing stage ≥2 disease. Seven infants (23%) with confirmed disease developed AKI during therapy. On Cox regression analysis, confirmed HSV disease, receipt of mechanical ventilation, admission to the pediatric or neonatal intensive care unit, and receipt of ≥2 concomitant nephrotoxic medications on the day preceding AKI diagnosis were all significantly associated with increased hazard of AKI.	Only a limited number of patients had proven HSV infection and received ACV ≥5 days. Data on fluid balance could not be captured adequately for all patients.

AKI, acute kidney injury; CNS, central nervous system; HD, high dosage; HSV, herpes simplex virus; ID, intermediate dosage; IV, intravenous; KDIGO, Kidney Diseases: Improving Global Outcomes; NICU, neonatal intensive care unit; RCT, randomized controlled trial; SCr, serum creatinine; SD, standard dosage; SEM; skin, eye, and/or mouth

*Only laboratory studies that evaluated ACV-associated nephrotoxicity are listed, although some studies also evaluated additional laboratory changes in patients receiving ACV.

Table 3. Summary of Studies on Intravenous Acyclovir (ACV)–Associated Nephrotoxicity in Children*

Author Study Type	Sample Size	Study Setting	Patient Population	Outcomes	Limitations
Brigden[5] Case series	354	Not specified	Patient population spanned from neonatal age group to age >65 yr and received variable individual dosing of ACV that ranged from 2.5 to 10 mg/kg q8 hr × 5 days. ACV dosing was initially administered as bolus injection to some of the patients, although was later administered as slow IV infusion during 1 hr. ACV dosing was reduced in patients with preexisting renal impairment. Study cohort included at least 1 neonate and 2 children ages 3 and 9 yr.	16.3% (58 of 354) of the overall study cohort had increase in plasma urea >75 mg/dL and/or SCr >1.5 mg/dL concentrations or significantly above already high concentrations. One neonate who died of HSV infection did not have elevated renal function test but was noted to have birefringent crystals in the renal tubules at postmortem examination. 79% (46 of 58) and 21% (12 of 58) of patients with elevated renal functions have received ACV by bolus IV injection and slow infusion, respectively. Surviving patients had gradual improvement in their renal function tests during or following completion of ACV therapy.	Case series. No breakdown of renal adverse effects by age group. Lack of detailed description of the characteristics of the study cohort.
Keeney[42] Placebo-controlled phase 2 studies	85	United Kingdom and United States	- 85 children (age <17 yr), enrolled in the "British" studies received "bolus" doses of ACV. 42 children (age <17 yr), including 17 neonates, enrolled in the "American" studies, received the same ACV dose as the "British" studies given as a 1-hr infusion.	Transient elevations in SCr and blood urea in 12% of children in the "British" studies. No reported renal adverse effects in patients in the "American" studies.	Absence of detailed description of patients' characteristics, dosing of ACV per weight or surface area, and degree of increase in SCr.
Sköldenberg[3] Open RCT	127	Six university hospitals in Sweden	127 patients, including 5 children who were age <3 yr (age, 4 wk to 76 yr) with suspected HSE were enrolled between March 1981 and December 1983. Among the 51 patients with confirmed HSV, 27 vs 24 patients received ACV at 10 mg/kg during 1 hr q8 hr vs vidarabine at 15 mg/kg/day during 12 hr for 10 days, respectively.	19% vs 50% (p = 0.04) of patients with confirmed HSE died by 7 mo following therapy in the ACV vs vidarabine groups, respectively. At 6 mo of follow-up, 56% (15 of 27) vs 13% (3 of 24) (p = 0.02) of patients in the ACV vs vidarabine groups had returned to normal neurologic function; at that time, the numbers who died or had severe sequelae were 9 (33%) vs 19 (76%) in the ACV vs vidarabine groups, respectively. Transient increase in SCr (with no further details) in 1 ACV vs 3 vidarabine recipients.	Follow-up limited to 6–7 mo. Limited inclusion of pediatric population. Lack of specificity in assessment of kidney function.

Table 3. Summary of Studies on Intravenous Acyclovir (ACV)–Associated Nephrotoxicity in Children* *(cont.)*

Author Study Type	Sample Size	Study Setting	Patient Population	Outcomes	Limitations
Whitley[43] Open RCT	208	26 US institutions	A total of 208 patients older than 6 mo (including 15 children) with suspected HSE were enrolled between September 1, 1981, and December 1984. Among the 69 patients with confirmed HSV, 32 vs 37 patients received ACV at 10 mg/kg q8 hr vs vidarabine at 15 mg/kg/day q8 hr for 10 days.	Death in 28% vs 54% (p = 0.008) of patients in the ACV vs vidarabine groups At 6 mo of follow-up, 38% vs 14% (p = 0.021) of patients with confirmed HSE who received ACV vs vidarabine, respectively, have returned to normal function. Less than 1% of study cohort had elevation in SCr >3 mg/dL (0 vs 2 patients in the vidarabine vs ACV groups).	Limited assessment of kidney function.
Potter[44] Case report	2	Children's Hospital Medical Center of Akron, OH	One of the 2 patients was a 12-yr-old girl with confirmed HSE who received ACV 500 mg/m^2 q8 hr during 1-hr infusion.	Crystalluria was observed with no change in renal function.	Case reports with only 2 patients included.
Bianchetti[45] Case series	19	University Children's Hospital, Inselspital, Switzerland	19 patients, including 12 immunocompromised children with HSV infections and 9 immunocompetent patients with HSE, received intravenous ACV as 1500 mg/m^2 per day given during 1 hr q8 hr for ≥8 days. Hydration was maintained at 1700 mL/m^2 and 1000 mL/m^2 in immunocompromised patients and children with suspected encephalitis, respectively.	Increase in SCr in 3 of 7 HSE patients with values peaking at 3.99 mg/dL and normalization of SCr levels with appropriate hydration and within 1 wk of stopping ACV.	Case series with only 19 patients.
Vachvanichsanong[46] Case report	1	Prince of Songkla University, Hat-Kai, Thailand	9-yr-old patient with presumed HSE received ceftriaxone and IV ACV at 10 mg/kg/dose IV during 1 hr q8 hr.	Increase in SCr with value peaking at 2.2 mg/dL that resolved with appropriate hydration and discontinuation of ACV.	Case report.
Vomiero[9] Case series	17	Children's Hospital of Eastern Ontario, Canada	17 children (age range, 1–14.9 yr) received IV ACV (mean dose, 1222 ± 304 mg/m^2/day) and ceftriaxone between October 2000 and March 2001, for presumed HSE. Patients received a median of 1.515 L/m^2 IV fluid during ACV administration.	After a median of 3 days of therapy, among 70% of patients (12 of 17), SCr increased to a median of 0.6 mg/dL (range, 0.3–4.5 mg/dL) with gradual return to baseline. Renal biopsy of 1 of the patients who developed ACV nephrotoxicity showed intratubular casts and a tubulointerstitial nephritis.	Case series with only 17 patients. Lack of specificity in the timing of the renal biopsy.

(Table cont. on page 498)

Table 3. Summary of Studies on Intravenous Acyclovir (ACV)–Associated Nephrotoxicity in Children* *(cont.)*

Scheiber[47] Retrospective chart review	126	Hospital for Sick Children and University of Toronto, Canada	Children were treated with IV ACV between July 2005 and January 2006. Study cohort included 14 neonates, 82 immunosuppressed patients, and 30 others. Patients were excluded if they were transferred from other hospitals and had received more than 2 doses of ACV, received <24 hr of ACV, received ACV for prophylaxis, or were age <7 days. eGFR on the first day of treatment was calculated and the peak SCr while on therapy was recorded. ACV dosing varied based on indication with a mean daily dosage of 33.6 ± 13.48 mg/kg and a mean duration of 9.7 days.	Significant increase in SCr (from 0.55 ± 0.53 to 0.63 ± 0.58 mg/dL) and decrease in eGFR levels (from 147.7 ± 45.2 to 127.1 ± 40.4 mL/min/1.73 m^2). The maximum change in SCr occurred during the first week of treatment. None of the patients had evidence of acute renal failure or needed interruption of ACV therapy because of nephrotoxicity. On multiple regression analysis, the use of nephrotoxic drug ($p = 0.02$) and impaired GFR ($p = 0.04$) at baseline were predictive for nephrotoxicity.	Limited SCr measurements in patients. Limited information regarding degree and timing of normalization in renal functions.
Kendrick[49] Retrospective chart review	61	British Columbia Children's Hospital, Canada	Patients ages 1 mo through 18 yr, receiving >1 dose of ACV between January 1, 2005, and April 30, 2009, for empiric treatment of HSE, were considered for inclusion. Patients were excluded if they had a presumed diagnosis of cancer, were immunocompromised and received ACV for HSV prophylaxis, received ACV for indications other than HSE, had low eGFR (<50 mL/min/1.73 m^2), or did not have reported SCr both prior to and during therapy. 32 vs 29 patients have received SD (30 mg/kg/day x 10 days) vs HD (60 mg/kg/day × 21 days) of ACV.	pRIFLE criteria was used to define renal injury and failure. If eGRF calculations were not available, doubling and tripling of SCr were used instead to determine renal injury and renal failure. No statistically significant difference in median change in SCr from baseline was detected between HD vs SD ACV groups. One child in the SD group and 3 children with one 12-yr-old in the HD group developed renal injury or failure that resolved after discontinuing or adjustment of ACV dosing.	Only 1 child in each group had confirmed HSE. Limited short median duration of ACV exposure of 3 days in both groups. Incomplete data availability precluding the calculation of eGFR or estimation or urine output. Possible lack of power in the study to determine risk factors for renal injury or failure.

Table 3. Summary of Studies on Intravenous Acyclovir (ACV)–Associated Nephrotoxicity in Children* *(cont.)*

Author Study Type	Sample Size	Study Setting	Patient Population	Outcomes	Limitations
Rao[50] Retrospective case-control study	371	Children's Hospital of Colorado	371 children (1 patient had 2 hospitalizations), ages from <1 wk to 19 yr old (including 148 with suspected or proven HSE) and who received ACV for various indications from October 2006 to January 2009, were included in the study. Hematology/oncology patients and those receiving oral ACV were excluded. For each case, all possible controls without renal dysfunction who had received at least the same number of ACV doses were identified.	- pRIFLE classification system was used to evaluate risk of AKI among study cohort. Renal risk, injury, and failure were detected among 81 (22%), 36 (9.7%), and 14 (3.8%) of 373 hospitalizations, respectively. On multivariable conditional logistic regression, ACV dosing >15 mg/kg; cumulative exposure > calculated cumulative exposure based on 500 mg/m^2/dose; and age >8 yr and concomitant use of ceftriaxone were significant predictors of renal risk, injury, and failure, respectively.	Study population was a subset of patients who had at least 1 SCr measurement after initiation of ACV. Concentration and infusion rate of ACV and volume of concomitant fluid administration were not evaluated.
Stefanski[51] Retrospective chart review	107	University of Rhode Island and UMass Memorial Children's Hospital Medical Center, MA	All patients age ≤21 yr with suspected HSV infection and who had received >1 dose of ACV during a 5-yr time line were enrolled in the study. Renal toxicity measured via bedside Schwartz calculation for eGFR and pediatric RIFLE criteria.	A total of 12 patients (11%) met pediatric RIFLE criteria, although they had reversible renal toxicity.	Study only published as an abstract with limited information on patients' characteristic or specific indication for HSV use.
Sandery[52] Retrospective chart review	150	Sydney Children's Hospital, Radwick and The Children's Hospital at Westmead, Sydney, Australia	150 patients, ages 2 days to 18.6 yr, including 43 patients who had presumed HSE and who received IV ACV from January 2015 through December 2015, were considered for inclusion. Patients who received oral ACV or did not have a baseline SCr or a level collected during ACV administration were excluded.	Primary outcome was degree of renal insufficiency as defined by the KDIGO criteria for AKI. Development of AKI was noted among 18% of overall study cohort. -Stages 1, 2, 3 AKI was noted in 8.7%, 6.7%, and 2.7% of study cohort. 29.3% of children receiving cancer treatment vs 10.9% of children with other diagnoses, developed AKI following IV ACV therapy (OR, 3.4; 95% CI, 1.5–8.2). On multivariable analysis, higher baseline eGFR was the only significant predictor of AKI.	Large proportion (58 of 150) of oncology patients.

(Table cont. on page 500)

Table 3. Summary of Studies on Intravenous Acyclovir (ACV)–Associated Nephrotoxicity in Children* *(cont.)*

Yalçinkaya[53] Retrospective chart review	472	Dr Sami Ulus Children's Health and Diseases Research Training Hospital, Ankara, Turkey	472 children (including 201 with presumed HSE), ages >1 to <18 yr who received at least 1 dose of IV ACV between January 2010 and December 2019 and had SCr at baseline and within 72 hr of the first ACV dose, were considered for inclusion. Patients were excluded if they had renal dysfunction or oncologic malignancies or received their treatment based on mg/kg dosing.	Using the KDIGO criteria, 6.8% (32 of 472) of patients developed AKI. AKI was diagnosed at a mean of 4.3 ± 2.5 days after ACV initiation, and SCr levels returned to normal at a mean of 7.3 ± 3.6 days. On multivariable analysis, being older than 100.5 mo, use of 1500 mg/m^2/day ACV, and use of concomitant nephrotoxic drugs were independently associated with the risk of nephrotoxicity	Exclusion of patients whose dosage was not based on surface area.

AKI, acute kidney injury; CNS, central nervous system; eGFR, estimated glomerular filtration rate; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; IV, intravenous; KDIGO, Kidney Diseases: Improving Global Outcomes; HD, high dose; pRIFLE, Pediatric Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; SCr, serum creatinine; SD, standard dose

*Some studies included adult, pediatric, and neonatal patients; only the data on the pediatric population (age <12 years) are reported in this table.

received a 1-hour infusion of ACV. In 1984, Sköldenberg et al[3] published the results of the first RCT that compared the efficacy of ACV vs vidarabine for the treatment of confirmed HSE among 53 patients, including 5 children ages <3 years. The authors reported significantly lower mortality and morbidity among ACV vs vidarabine recipients and described a transient increase in SCr in <1% of the study cohort. In a follow-up RCT in 1986, Whitley et al[43] compared the therapeutic use of ACV vs vidarabine among 208 patients (including 15 children) with suspected HSE. Consistent with previous findings, the authors reported lower mortality and morbidity among ACV vs vidarabine recipients. However, they described a higher risk of elevated SCr among ACV (6%) vs vidarabine (1%) groups. That same year, Potter and Krill[44] noted "massive crystalluria" with identification of needlelike crystals in the urine of 2 patients receiving ACV for HSV infection. They advocated for appropriate IV hydration and slow infusion of ACV to avoid the possibility of obstructive nephropathy. In 1991, Bianchetti et al[45] administered equal doses (per surface area) of ACV to 19 patients, including 12 and 7 immunocompromised and immunocompetent children with HSV infections and HSE, respectively. Hydration was restricted in patients with HSE as part of therapy for cerebral edema. Three children with presumed HSE developed an increase in SCr, whereas none of the immunocompromised children who received standard hydration showed renal laboratory disturbances. The authors observed that the renal disturbances resolved with appropriate hydration and were aggravated with the rapid infusion of the drug and the concomitant use of nephrotoxic drugs. A similar pattern of a reversible nonoliguric acute AKI was described in a 9-year-old who was fluid restricted and received IV ACV and ceftriaxone (another nephrotoxic drug) for presumed encephalitis.[46] The additive nephrotoxic effect of the concomitant use of ACV and ceftriaxone was highlighted in a case series of 17 children who received both medications for presumed HSE.[9] Twelve patients experienced a transient increase in SCr. One child even underwent renal biopsy with findings suggestive of tubulotoxic injury. In 2008, Schreiber et al[47] conducted a retrospective chart review of 126 children, including 14 neonates and 30 immunocompetent children, who received ACV for various indications, and they noted a significant overall increase in SCr and decrease in GFR within 1 week of therapy. On multivariable analysis, underlying renal dysfunction (impaired baseline eGFR) and concomitant use of nephrotoxic drug were the 2 main factors that predicted ACV nephrotoxicity and accounted for 11% of the change in eGFR.

In 2005, following the evaluation of pharmacokinetics of HD ACV among 16 pediatric patients, the FDA approved the use of HD ACV (20 mg/kg/dose or 500 mg/m^2/dose every 8 hours) for the treatment of HSE for children ages ≥3 months to 12 years.[47] The AAP Committee on Infectious Diseases endorsed these recommendations in 2006. However, in 2008, anecdotal reports of neurotoxicity and nephrotoxicity in older children receiving the HD ACV led the AAP to amend its recommendations on ACV dosing for HSE. Although the 2012 *Red Book* acknowledged that the FDA approved HD ACV for the treatment of HSE in children ages 3 months to 12 years, it recommended to use a dosage of 30 to 45 mg/kg/day in 3 divided doses.[48] In 2014, Kendrick et al[49] noted that the recommendation for HD ACV has not been consistently implemented at their institution secondary for concern for toxicity. Therefore, they designed a study to evaluate

the occurrence of renal toxicity in patients ages 1 month through 18 years who received SD vs HD regimen in their institution. Interestingly, only 1 child in each group had confirmed diagnosis of HSE. The authors used either the pediatric Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (pRIFLE)[30,31] criteria or doubling or tripling of SCr to define renal insufficiency (Table 1) but did not detect a significant difference in median change in SCr from baseline between HD and SD groups.

The concern about the use of HD ACV was reassessed in 2015 in a case control study by Rao and colleagues.[50] Their study cohort included 371 children ages <1 week to 19 years (including 148 with suspected or proven HSE) who received ACV for various indications. For each case, all possible controls without renal dysfunction who had received at least the same number of ACV doses were identified. The authors used the pRIFLE classification system to assess the degree of AKI. Renal risk, injury, and failure were detected among 22%, 9.7%, and 3.8% of 373 (1 patient had 2 hospitalizations) hospitalizations, respectively. Although SCr returned to the normal range following ACV dose reduction or completion, eGFR did not return to patient baseline in most of the study population. The authors advocated for IV ACV dosing at ≤15 mg/kg/dose or ≤500 mg/m^2/dose beyond the neonatal period to minimize the risk of nephrotoxicity and highlighted that beyond a weight of 20 kg, the ACV dose using 20 mg/kg/dose would exceed 500 mg/m^2/dose. A year later, Stefanski et al[51] described in a published abstract that 11% of all patients ages ≤21 years with suspected HSV infection who had received >1 dose of ACV in their institution, during a 5-year time line, met the pRIFLE criteria for AKI. However, their renal toxicity was transient. In 2020, Sandery et al[52] assessed ACV adverse effects among 150 children (including 58 with malignancies) who received ACV for various indications, including HSE and sepsis. The primary outcome was degree of renal insufficiency based on the KDIGO criteria (Table 1).[30] A total of 18% of children developed AKI, with 44% remaining in stage 1 on last measured SCr. The risk of AKI was significantly higher in oncology patients compared with the rest of the study group. Multivariate analysis showed that higher baseline eGFR was the only factor that significantly increased the risk of AKI. The authors speculated that elevated eGFR could be a manifestation of kidneys with little reserve or an indication of increased filtrate delivery hastening kidney injury. In 2021, Yalçinkaya et al[53] also evaluated the risk factors for ACV-associated AKI among 472 children (including 201 with presumed HSE) ages >1 to <18 years. The study cohort only included patients who did not have malignancies or baseline renal dysfunction and received ACV therapy at a calculated dosage of 1500 mg/m^2/day. Almost 7% of the study population developed AKI per the pediatric KDIGO criteria.[18] Multivariate analysis identified age >100.5 months, use of 1500 mg/m^2/day ACV, and use of concomitant nephrotoxic drugs as the variables that independently increased the risk of nephrotoxicity. The authors also highlighted that older children were typically receiving more ACV per surface area compared with the younger children and advocated for an investigation of the lowest possible therapeutic doses of ACV in this age group.

Conclusion

Multiple studies have shown an association between nephrotoxicity and IV ACV use for the treatment of HSV infections. Acyclovir-associated nephrotoxicity has been mostly attributed to the low urine solubility leading to its crystallization in the kidney tubules and secondary obstructive nephropathy. The risk of ACV-associated nephrotoxicity seems to be lower in the neonatal population compared with the pediatric population. This is likely due to diminished renal concentrating ability in neonates. Acyclovir-associated nephrotoxicity can be minimized in both populations by ensuring adequate hydration, maintaining a high urine flow, and administering ACV at a slow infusion rate rather than bolus injection. In addition, renal function should be closely monitored and ACV dosing should be adjusted in patients with underlying kidney disease.

Our review of ACV-associated nephrotoxicity in neonates showed that recent literature mostly evaluated risk among all infants exposed to ACV, including those who have received empiric therapy and limited doses of ACV therapy, rather than only patients with confirmed HSV disease who required a longer duration of treatment. Thus, these findings might not be generalizable to infants who received a longer duration of therapy for confirmed HSV infection. On the other hand, the risk of ACV-associated toxicity appeared higher in the pediatric population. Although the abandoned practice of fluid restriction for possible cerebral edema may have contributed to these findings in earlier studies, more recent reports showed that older age (>8 years), concomitant use of nephrotoxic drugs, and ACV dose >1500 mg/m^2 were associated with a higher risk of renal adverse effects in the pediatric population. However, these studies 1) included patients with a wide age range who had different thresholds of ACV-associated renal toxicity, 2) assessed different units of dosing (per weight or surface area) of ACV, 3) adapted a wide variety of AKI classifications, and 4) evaluated potential renal adverse effects among patients with limited ACV exposure in patients with suspected rather than proven ACV infections. Thus, the risk of ACV-associated nephrotoxicity in the pediatric population might be higher in children who received prolonged ACV therapy for confirmed HSE.

Through the years, the AAP recommendations for IV ACV dose have also changed to reflect evidence on its efficacy and effectiveness for treatment of neonatal HSV and potential drug toxicity in the pediatric patients. Although the efficacy and safety of SD vs ID and HD of IV ACV have been evaluated in a cohort of neonates

with confirmed HSV infections,[4,17] based on our review, no such study has been conducted for the management of HSE in the pediatric population.

During the last 3 decades, although the survival of neonates with disseminated HSV infections and the risk of long-term sequela of those with neonatal CNS disease have both improved,[4] 30% of patients with disseminated disease do not survive and 31% of patients with CNS disease have abnormal neurologic assessment at 12 months. In addition, the risk of long-term sequela of pediatric HSE remains substantial.[16] The goal is to identify the optimal ACV dose where efficacy is maximized and toxicities are minimized. Although the intent of using lower ACV doses is to minimize ACV toxicity, this practice may be associated with increased risks of adverse sequelae. Future studies on risk of ACV-associated nephrotoxicity should adopt the current standard definition of AKI in neonates and children and include a larger proportion of patients with confirmed rather than suspected HSV infections in order to evaluate the efficacy and toxicity of the current ACV dosing. Studies should also follow these patients for at least 1 year after therapy to better understand the long-term sequelae of ACV dosing.

Article Information

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