Cidofovir Prescribing Patterns and Outcomes in Hospitalized Adults and Children

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Introduction

- Cidofovir (CDV) is an antiviral agent used for the treatment of infections caused by DNA viruses commonly seen in immunocompromised patients[1]
- Recommended dosing regimens used in practice are off-label, based on limited clinical evidence, and vary by indication with 5 mg/kg every 1-2 weeks and 1 mg/kg 3 times weekly being the most commonly cited regimens[1-5]
- Cidofovir-induced nephrotoxicity is a significant concern
  - Routine lab monitoring, renal dose adjustments, and co-administration with intravenous (IV) fluids and probenecid are recommended to limit CDV-induced nephrotoxicity but lack a standard approach[1]

Objectives

- **Primary**: Describe CDV prescribing patterns in adult and pediatric patients
- **Secondary**: Evaluate rates of nephrotoxicity, virologic response, and IV fluid and probenecid use

Methods

Study Design

- Retrospective, multicenter medication use evaluation

Inclusion Criteria

- Admission to Atrium Health's Carolinas Medical Center or Levine Children's Hospital in Charlotte, NC
- Receipt of at least one dose of IV CDV during an admission from August 2014 through June 2021

Clinical Outcome Analysis

- **Exclusion**: prior CDV use or receipt of non-IV CDV during same admission
- **Nephrotoxicity**: acute kidney injury (AKI) defined by an increase in serum creatinine to 150% baseline or an increase of 0.3 mg/dL in 48 hours
- **Full virologic response**: minimum of 1 log reduction in associated viral load within 2 weeks of treatment initiation
- **Partial virologic response**: decrease in viral load < 1 log reduction within 2 weeks of treatment initiation

Results

- A total of 38 adult patients and 26 pediatric patients received 44 and 60 CDV doses, respectively

Abbreviations

AKI	Acute kidney injury	**CDV**	Cidofovir	**IBW**	Ideal body weight
AdjBW	Adjusted body weight	**CMV**	Cytomegalovirus	**JC virus**	John Cunningham virus
ADV	Adenovirus	**GU**	Genitourinary	**SOT**	Solid organ transplant
BKV-AN	BK virus-associated nephropathy	**HHV-6**	Human herpesvirus 6	**TBW**	Total body weight
BKV-HC	BK virus hemorrhagic cystitis	**HSCT**	Haemopoietic stem cell transplant		

Results

Table 1. Baseline Characteristics

Baseline Characteristic	Adults (n = 38)	Pediatrics (n = 26)
Female sex, n (%)	6 (15.8)	9 (34.6)
Age in years, median (range)	49 (21-76)	7 (0-27)
BMI in kg/m², median (range)	27.8 (17.9-42.2)	17.8 (9.8-26.9)
Serum creatinine in mg/dL, median (range)	1.5 (0.7-8.7)	0.33 (0.1-2.08)
Creatinine clearance in mL/min, median (range) [a]	58.5 (9-143)	128.5 (42-199)
Estimated GFR in mL/min/1.73m², median (range) [b]	-	158.5 (45-256)
New start cidofovir, n (%)	26 (68.4)	21 (80.8)
Serum creatinine > 1.5 mg/dL, n (%)	12 (46.1)	2 (9.5)
Creatinine clearance ≤ 55 mL/min, n (%)	10 (38.5)	1 (4.8)
Renal replacement therapy, n (%)	3 (11.5)	1 (4.8)
ANC in cells/mm³, median (range)	3875 (0-26660)	1375 (0-10200)
Immunosuppression, n (%)		
Solid organ transplant recipient	22 (57.9)	2 (7.7)
Stem cell transplant recipient	14 (36.8)	21 (80.8)
Other	2 (5.3)	3 (11.5)
Primary treatment indication, n (%)		
BK virus	29 (76.3)	11 (42.3)
Adenovirus	6 (15.8)	11 (42.3)
Cytomegalovirus	1 (2.6)	2 (7.7)
Other DNA virus	2 (5.3)	2 (7.7)
Additional indication for CDV, n (%)	6 (15.8)	10 (38.5)
More than one admission with cidofovir, n (%)	5 (13.2)	15 (57.7)

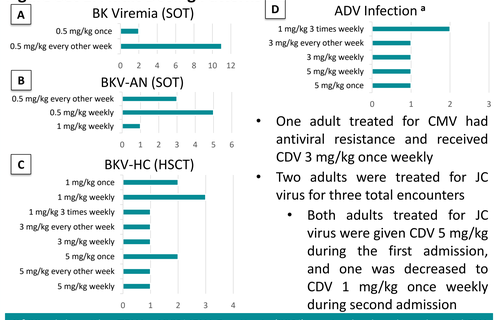
BMI = body mass index; GFR = glomerular filtration rate; ANC = absolute neutrophil count; DNA = deoxyribonucleotide acid
[a] CrCl was calculated using the Cockcroft-Gault equation; 6 patients in the pediatric group used this calculation due to age > 18 yr
[b] Calculated using the Schwartz equation; 20 patients in the pediatric group used this calculation

Table 2. Supportive Care

Characteristic, n (%)	Adults (n = 44)	Pediatrics (n = 60)
Order set used	13 (32.5)	37 (61.7)
IV fluid bolus given in 2 hours prior to dose	20 (45.5)	49 (81.7)
Normal saline	13 (65.0)	49 (100)
IV fluid bolus given in 2 hours after dose	13 (29.5)	42 (70.0)
Normal saline	8 (61.5)	42 (100)
Three doses of probenecid doses administered	14 (31.8)	16 (26.7)
Dose > 1 mg/kg without probenecid given [a]	5 (16.7)	0 (0)

[a]Sample without probenecid n = 30 for adults and n = 44 for pediatrics

Figure Set 1. Adult Dosing Patterns

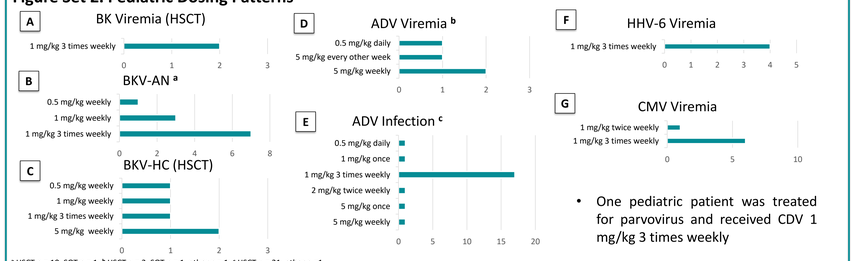


- One adult treated for CMV had antiviral resistance and received CDV 3 mg/kg once weekly
- Two adults were treated for JC virus for three total encounters
  - Both adults treated for JC virus were given CDV 5 mg/kg during the first admission, and one was decreased to CDV 1 mg/kg once weekly during second admission

Of 23 adults with a TBW > 120% IBW, 5 patients (22%) received a dose based on AdjBW

[a] SOT n = 4, HSCT n = 1, other n = 1

Figure Set 2. Pediatric Dosing Patterns



- One pediatric patient was treated for parvovirus and received CDV 1 mg/kg 3 times weekly

[a] HSCT n = 10, SOT n = 1; [b] HSCT n = 2, SOT n = 1, other n = 1; [c] HSCT n = 21, other n =1

Nephrotoxicity

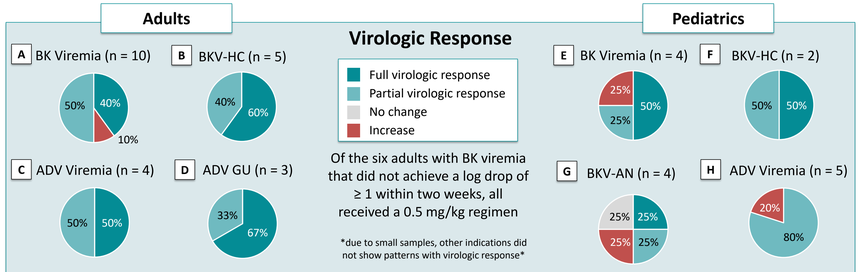
29% (6/21) of adults developed AKI

- Five of the six patients received 3 mg/kg or more during the first week when AKI occurred
- Preventative measures
  - Fluid boluses were given to 3 of the 6 patients before and after cidofovir administration
  - Probenecid was given to 2 of the 6 patients
- All received nephrotoxins within 7 days of cidofovir
  - Five received multiple nephrotoxic agents
  - 93% of all first doses were given within 7 days of another nephrotoxin
- Median AKI onset was 1.8 days (range 0.3-6.9 days)
- Response: one discontinuation

14% (3/21) of pediatrics developed AKI

- Two patients received 1 mg/kg three times weekly, and one received 1 mg/kg weekly
- Preventative measures
  - Fluid boluses were given to all patients before and 2 patients after cidofovir administration
  - Probenecid was given to 1 of the 3 patients
- All received multiple nephrotoxic agents within 7 days of cidofovir
  - 85% of all first doses were given within 7 days of another nephrotoxin
- Median AKI onset was 3.6 days (range 3.1-5.5 days)
- Response: one discontinuation, one dose decrease

Virologic Response



Of the six adults with BK viremia that did not achieve a log drop of ≥ 1 within two weeks, all received a 0.5 mg/kg regimen

due to small samples, other indications did not show patterns with virologic response

Discussion

Adults

- Dosing in adults was highly variable, but the most common regimens included:
  - 0.5 mg/kg weekly for BKV-AN
  - 0.5 mg/kg every other week for BK viremia
  - 1 mg/kg weekly for BKV-HC
  - 1 mg/kg three times weekly for ADV infection
- About one fifth of obese patients received cidofovir dosed by adjusted body weight
- Less than half of all adults received fluid boluses with cidofovir and about 65% of the boluses were normal saline
- Probenecid use was inconsistent and 17% of the patients that did not receive probenecid received a CDV dose greater than 1 mg/kg
- The rate of nephrotoxicity was 29% and was more common with higher doses
- All but one patient evaluated had a decrease in viral load during the first two weeks

Pediatrics

- The most common dose used for pediatric patients was 1 mg/kg three times weekly, used in 67% of patients across all indications
- Over 75% received fluid boluses with CDV and all were normal saline
- All patients with a CDV dose greater than 1 mg/kg received probenecid
- The rate of nephrotoxicity was 14% and all received multiple additional nephrotoxins
- Three evaluated patients had an increase in viral load but no similarities in dosing or indication were noted

Limitations

- Retrospective design
- Limited to inpatient use
- 7-year evaluation period
- Small sample size and groups

Conclusions

- High variability in CDV prescribing patterns highlights the need for standardized, indication-specific dosing
- Standardization of IV fluid and probenecid use along with guidance on cidofovir dose adjustments may help decrease the risk of CDV-associated nephrotoxicity
- Evaluation of virologic response was limited by small sample size and further assessment is needed

References

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Disclosures

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation.

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