Clinical and Epidemiological Characteristics of Viral Associated Diarrhea (VAD) in Immunocompromised and Cancer Patients in MD Anderson Cancer Center (2005-2014)

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Introduction

- In the United States, Norovirus (NV), Rotavirus (RV) and Adenovirus (AV) are common causes of acute gastroenteritis in healthy individuals[1]. Infections are self limited and rarely require admission to the hospital.
- Virus associated diarrhea (VAD) due to NV, RV and AV contributes to mortality and morbidity in high risk populations such as immunocompromised and cancer patients[1].
- NV is a positive ssRNA virus and belongs to the Calciviridae family. Three known genotypes (I, II and II) affect humans.[2] Genotype II (GII) is the most common genotype identified worldwide[1].
- An earlier report suggested that around 18% of patients who underwent hematopoietic stem cell transplant (HSCT) contract NV within 1 year of HSCT[1], in some cases causing febrile viremia.
- RV is a dsRNA virus and belongs to Reoviridae family. It is the second most common cause of diarrhea in children[3]. Genogroups G1, G2, G3, G4P [8], P [4] are common worldwide[2].
- In HSCT patients, the incidence of RV has been reported to be as high as 10%[3].
- AV is a dsDNA virus and belongs to Adenoviridae family. It comprises of 51 different serotypes (AV-1 to -51) grouped into 6 species, A to F[2].
- Fifty percent of AV found in stool samples belong to type 40 and 41. Group F AV cause 1-20% of acute gastroenteritis cases[4].

Methods

- A retrospective chart review was conducted in cases in whom NV, RV and AV were identified by PCR or ELISA in stools submitted to the clinical microbiology laboratory from inpatient and outpatient clinics between 2005 and 2014.
- VAD cases occurring ≥ 72 hr. after admission were considered to be health care associated (HCA).
- Statistical analysis was performed by using STATA v13.0. P values <0.05 were considered significant.
- Comparison of categorical data were done by chi-square test and differences in continuous, non-parametric variables were compared by using the Kruskal Wallis test.
- Logistic regression analysis was performed to identify specific risk factor associations between NV VAD and VAD to RV and AV.

Results

- A total of 97 VAD cases were identified and included NV (n=49), RV (n=34) and AV (n=14).
- All infections were acquired within the USA.
- Most cases of NV (59%), RV (73%) and AV (78%) were identified in HSCT recipients. Patients with graft versus host disease (GVHD) were at the highest risk.
- Diarrhea of ≥ 2 weeks duration was more common in NV (p=0.000) and RV (p=0.001) than with AV, particularly in HSCT with viral shedding ranging from 46 to 270 days.
- Genotyping was performed in 9 NV cases. All were due to GII.
- Vomiting was absent in 39% of NV, 38% of RV and 86% of AV cases.
- Co-infections with other enteropathogens included *C. difficile* (7%), *E. coli* (4%) and *Salmonella* (2%).
- RV tended to cause VAD in younger patients. 20 patients with RV were >18 years of age.
- Patients with immunosuppression (OR 2.6 95% CI 1.15-5.99, P=0.02) and neutropenia (OR 4.8 95% CI 1.27-18.5, P=0.01) were identified as significant risk factors for NV diarrhea when compared to RV and AV associated diarrhea.
- 30% of the infections in adults were considered to be HCA.

Figure 1. Seasonality of Viral Diarrhea at a Large Cancer Center

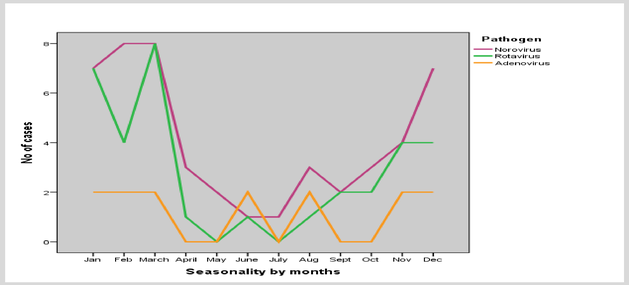

Figure 2.Duration of diarrhea after diagnosis of viral associated diarrhea due to NV, RV and AV.

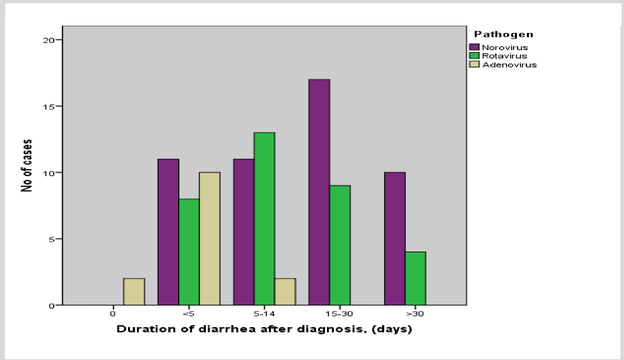

Table 1: Demographic characteristics of immunocompromised and cancer patients with viral associated diarrhea (N=97).

Characteristics	Norovirus (n=49) N (%)	Rotavirus (n=34) N (%)	Adenovirus (n=14) N (%)	P value
Age (years), mean (range)	51(5-81)	37(2-78)	36(5-69)	0.01
Gender				
Male	31(63)	18(53)	8(57)	0.66
Race				
White	30(61)	16(47)	7(50)	0.44
Black	3(6)	4(12)	4(28)	0.05
Hispanic	13(27)	13(38)	2(14)	0.23
Other	3(6)	1(3)	1(7)	0.69
Underlying Disease				
Leukemia	33(67)	17(50)	6(42)	0.13
Lymphoma	12(24)	5(14)	3(21)	0.57
Solid Tumor	2(4)	4(11)	1(7)	0.35
Myeloma	1(2)	5(14)	1(7)	0.06
Hematologic Dyscrasia	1(2)	2(6)	2(14)	0.17
Sickle Cell disease	0	1(3)	1(7)	0.12

Table 2: Clinical characteristics of immunocompromised and cancer patients with viral associated diarrhea (N=97).

Characteristics	Norovirus (n=49) N (%)	Rotavirus (n=34) N (%)	Adenovirus (n=14) N (%)	P value
HSCT				
Allogeneic	26(53)	18(53)	10(71)	0.50
Autologous	3(6)	7(21)	1(7)	0.13
Onset Post transplant (weeks)	30(1-421)	22(1-154)	12(2-35)	0.35
GVHD				
Skin	5(10)	6(17)	2(14)	0.55
Gastrointestinal	12(24)	10(29)	6(43)	0.41
ALC <1000	31(63)	20(58)	10(71)	0.71
ANC <500	12(25)	1(3)	2(14)	0.02
Diarrhea duration prior to VAD diagnosis, (days)	15(1-210)	7(1-90)	9(0-50)	0.03
Health Care Associated	9(18)	7(20)	2(14)	0.71
Symptoms at baseline				
Nausea	30(62)	19(55)	4(28)	0.09
Vomiting	30(61)	21(62)	2(14)	0.005
Loss of appetite	17(35)	17(50)	5(35)	0.36
Abdominal pain	21(52)	14(35)	5(35)	0.89
Weakness	5(10)	9(26)	2(14)	0.07
Fever	11(22)	9(26)	6(42)	0.31
Weight loss	15(30)	10(29)	5(35)	0.91
Amount of weight loss[mean,(range)]	1(0-8)	1(0-5)	1(0-9)	0.95
Rash and Altered mental status	4(8)	1(3)	1(7)	0.62
Bloody stools	0	3(8)	0	0.09
Immunosuppression	32(65)	13(38)	7(50)	0.005
Co-morbidities	25(51)	21(62)	4(28)	0.56
Outcome within 30 days				
Dead	5(10)	2(6)	3(21)	0.27
Alive	44(89)	32(94)	11(78)	0.27

Table 4: Association between possible risk factors and Norovirus diarrhea (N=97).

Risk Factors	n	OR	95% CI	P value
Transplant				
Yes	65	3.67	0.7-17.5	0.13
no	32	1.00		
Neutropenia				
Yes	15	4.86	1.27-18.5	0.01
No	82	1.00		
Immunosuppression				
Yes	52	2.63	1.15-5.99	0.02
No	45	1.00		
GVHD				
Yes	41	1.73	0.76-3.91	0.18
no	58	1.00		
Co-infections with other enteric pathogens				
Yes	9	1.53	0.4-5.8	0.5
No	86	1.00		
Duration of Diarrhea 15-30 days				
Yes	26	2.01	0.81-5.02	0.13
No	71	1.00		

Conclusions

- In immuocompromised and cancer patients, agents responsible for VAD occur year round but predominate in winter season; cause prolonged illness and frequently present without accompanying upper GI symptoms (nausea, vomiting).
- Prolonged NV infections were commonly observed and the majority belonged to GII .
- Rotavirus an agent of pediatric diarrhea, was identified in adults with VAD.
- VAD should be considered in differential diagnosis of GVHD. Early diagnosis of VAD might be helpful in such patients to decrease inappropriate empiric antibiotic therapy and in whom a decrease in immunosuppression can potentially be of benefit.
- Preventable NV and RV HCA infections were commonly seen. Infection control measures are essential to avoid HCA of NV.

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