City Wide

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ID fellow, 1st Year

Drexel

Case presentation

- 28 yo male presented with nonproductive cough and chest pain for several days, now with fevers and feeling short of breath for the past day so came to the ED.
- Recently incarcerated, released 2 weeks PTA. Currently homeless.
- Reported an assaulted and hit with wooden stick on face, back, stomach and legs.

PMHx: untreated HCV, testicular CA (2008, recurrence 2013) s/p bilateral orchiectomy and chemotherapy (2013), schizophrenia, vitiligo

PSHx: remote hx of hernia surgery, bowel perforation repaired by laparoscopic surgery

SHx: homeless, IVDU (heroin/fentanyl/K2), recent incarceration. Denied tobacco & marijuana. Sexually active MSW.

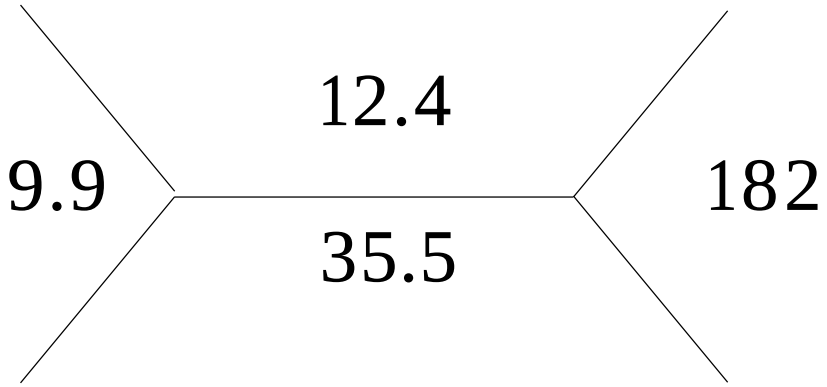
FHx: NC

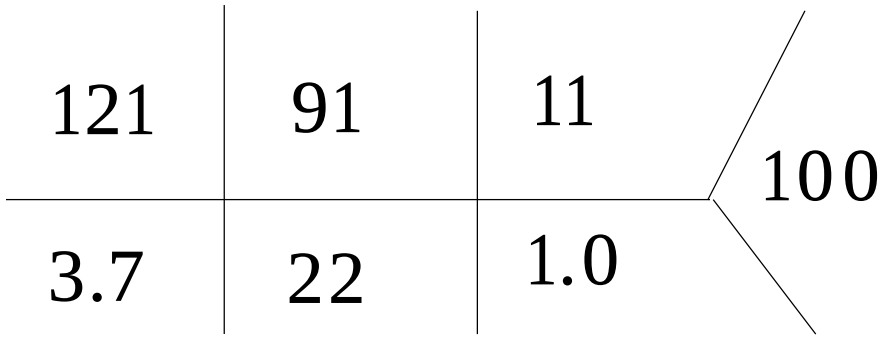
ROS: no chest pain, syncope, HA/vision changes, focal weakness, GI/GU sx, rash, edema, bleeding, joint pain or inflammation, weight changes.

Physical exam

- Vitals: T103, HR 113, RR 20, BP 129/66, 95% O2 Sat on room air
- Gen: thin Caucasian male, WD, WN, NAD, A&Ox3
- HEENT: PERRLA, EOMI, no scleral icterus or pallor, oropharynx clear, no cervical LAD, bilateral periorbital ecchymosis
- Lungs: no respiratory distress; no use of accessory muscles, diffuse wheezing, crackles RLL/LLL
- CV: RRR, normal S1/S2, no m/r/g
- Abd: soft, NT, ND, BS+
- Ext: No LE edema, DP/PT palpable b/l
- Neuro: strength 5/5 UE and LE, sensation symmetric, CNs grossly intact
- Skin: scattered ecchymoses and abrasions. No diffuse rash. Scattered areas of vitiligo.

Admission labs



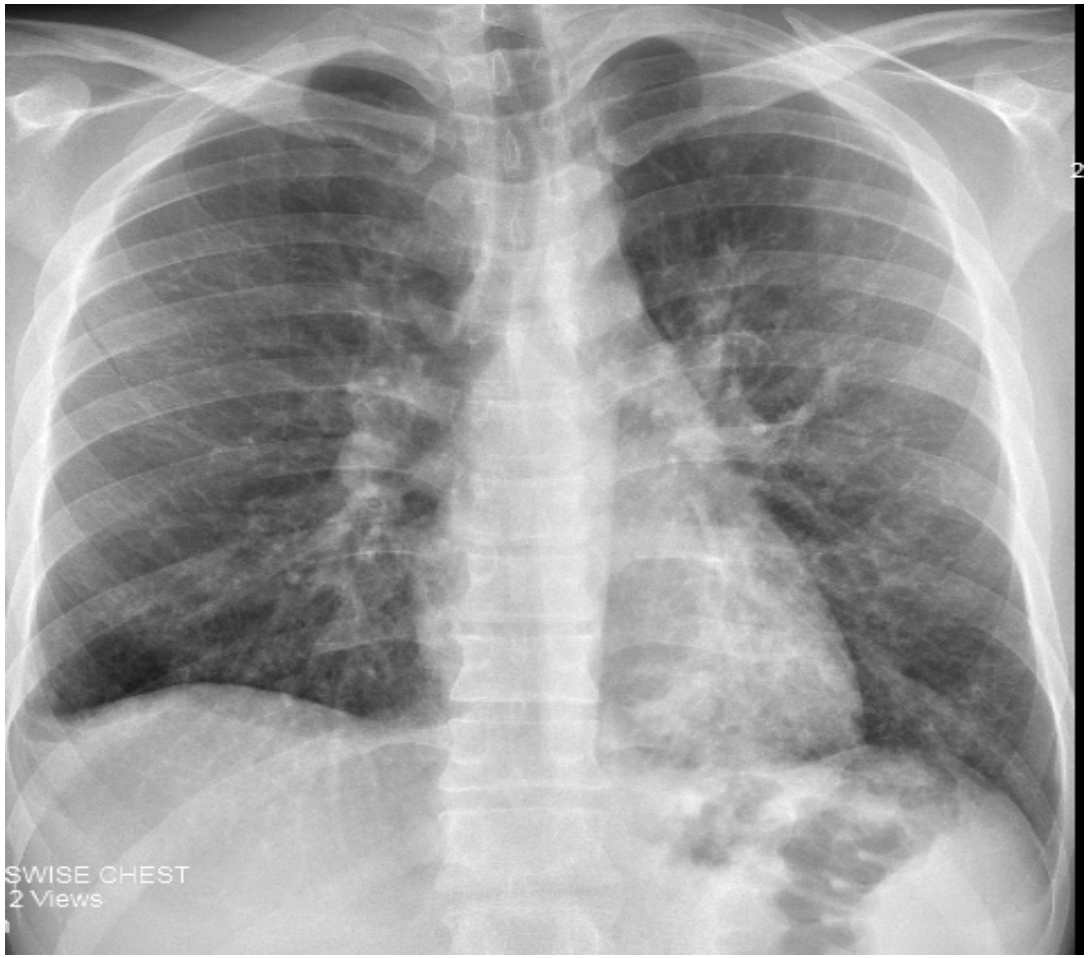


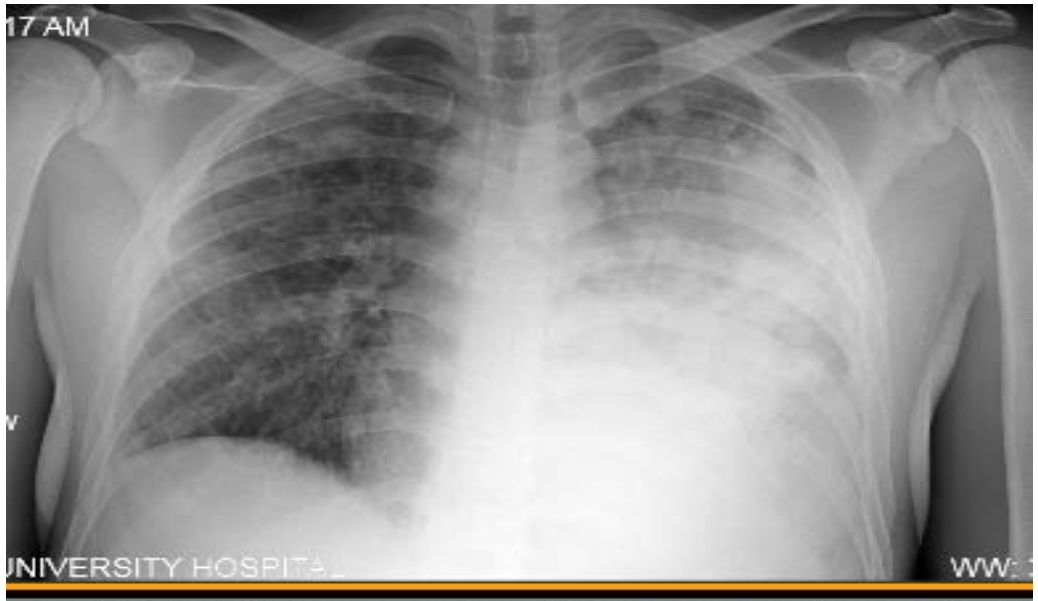
- Lactic acid 1.1
- LFTs normal
- Rapid Influenza A/B & RSV negative
- Rapid HIV screen negative

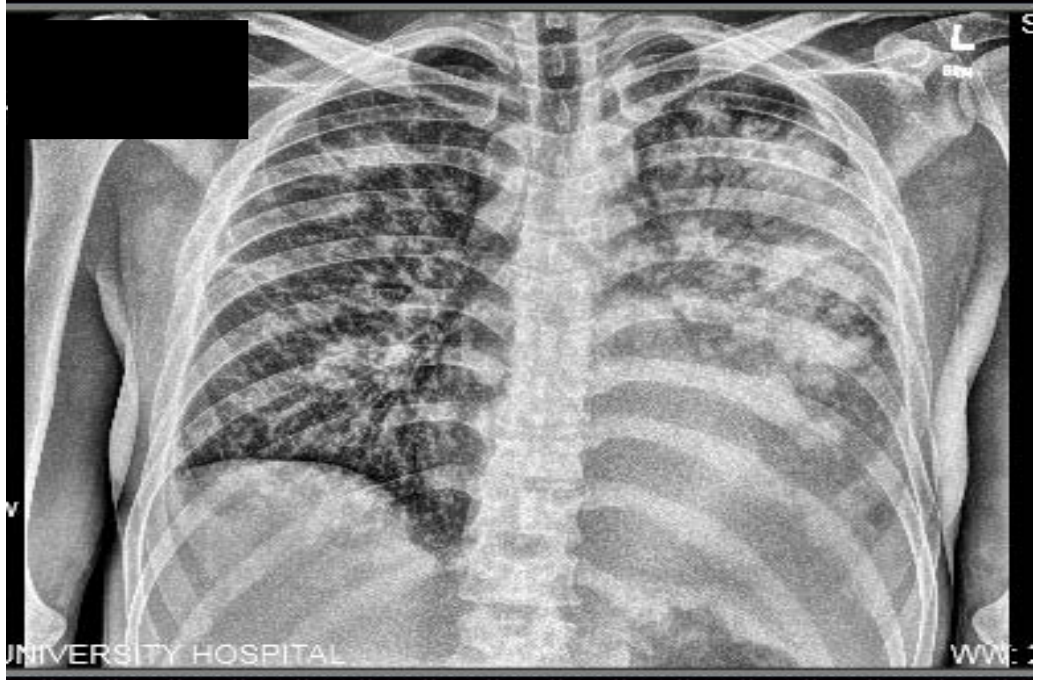
Hospital course

- Started on antibiotics for CAP with ceftriaxone and azithromycin.
- Continued to have fever, so regimen was broadened to vancomycin, cefepime, metronidazole.
- Patient requested tx for withdrawal, urine drug screen was equivocal, patient seen by psychiatry and suboxone not recommended.
- Because of this, he refused doses of antibiotics intermittently.
- ID was consulted HD#3.

Initially on room air, by HD#8 developed AMS and hypoxic respiratory failure.







Differential diagnosis

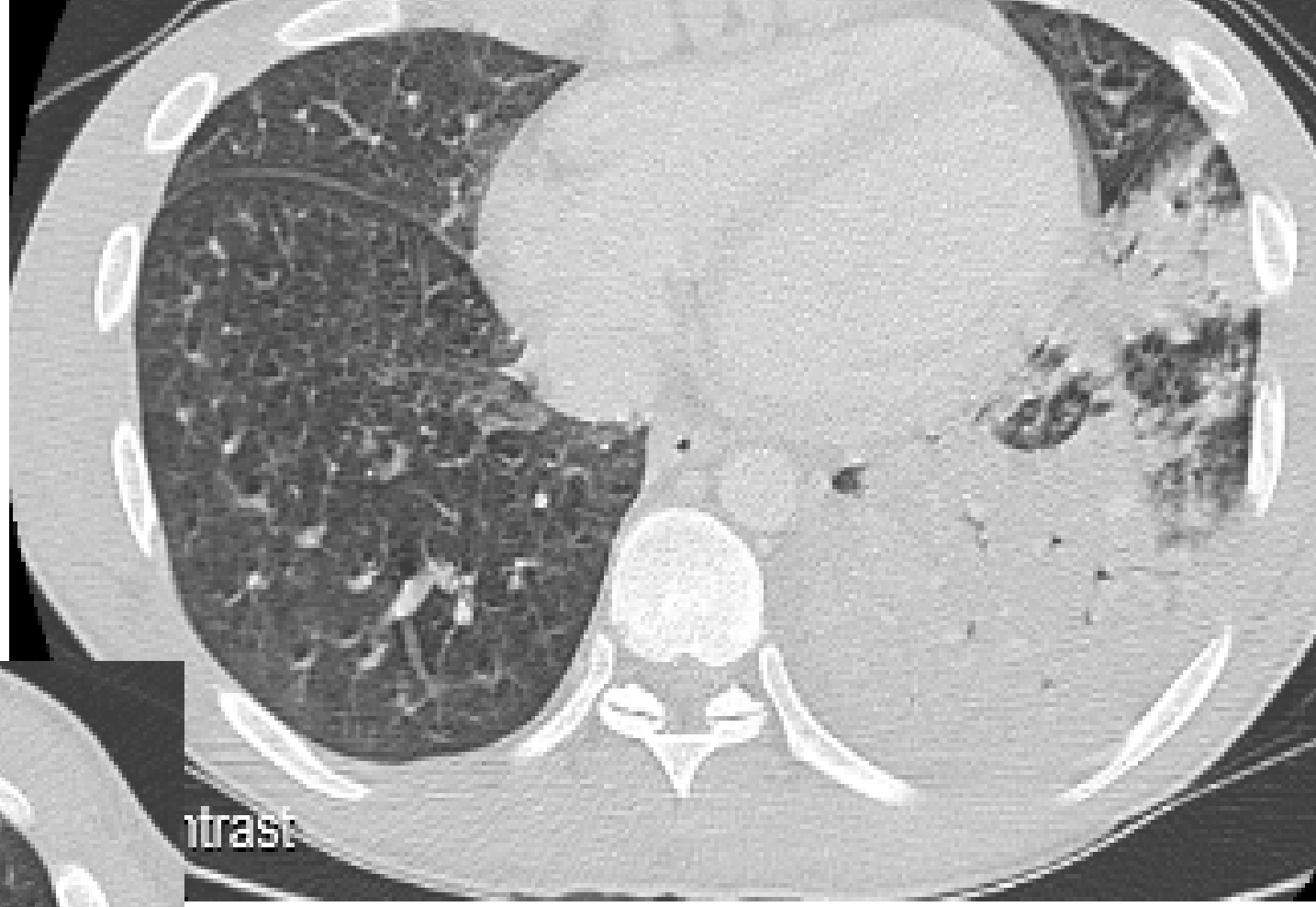
- Acute HIV
- Mononucleosis (EBV/CMV)
- Viral hepatitis
- Respiratory viral illness
- Pulmonary TB vs non-TB mycobacterium
- Disseminated Histoplasmosis
- Autoimmune disorder/vasculitis/Immunodeficiency

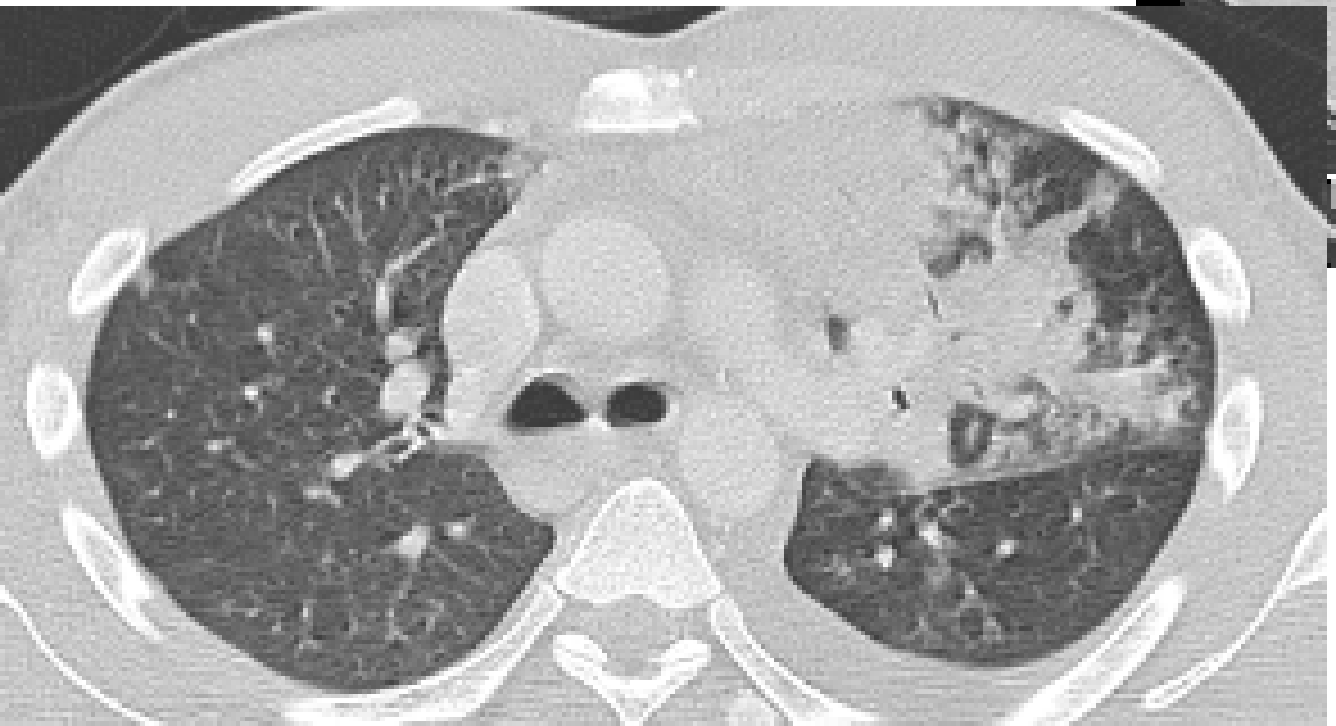
Hospital course

- HD#8, MICU consult called for tachycardia, hypoxic respiratory failure, patient requiring non-rebreather.
- Cultures negative (blood, sputum)
- Labs: progressive leukopenia, anemia, thrombocytopenia.
- Wbc 1.6k, hgb 11.6, Hct 35.3, Plts 66
- Peripheral smear with few shistocytes

- ABG shows pH 7.462/CO2 29/pO2 56.4
- Now with septic shock on pressors, intubated
- CT chest done to rule out PE shows worsening multifocal PNA
- Bronchoscopy– unrevealing. no significant secretions, obstructive lesions or abnormal mucosal changes.
- LFTs with steady increase (AST/ALT/ Alk phos peaking at 264/267/1667, nml Tbili and low normal albumin)
- Oliguric renal failure, requiring CVVH

HD #12





Summary

28 yo male initially admitted with CAP, with progressively worsening hypoxic respiratory failure, no clinical improvement on broad spectrum antibiotics, negative infectious workup to date, unrevealing findings on bronchoscopy. CT with worsening MF PNA and ARDS. Labs notable for pancytopenia, transaminitis, and acute renal failure. multi-organ failure, ventilator and RRT dependent.

Additional studies

- Multiple blood cultures neg. resp cultures negative.
- AFB smear/Cx neg from bronch, MTB PCR not detected
- Ur histo AG, not detected
- EBV serology unrevealing for acute infection
- CMV IgM, elevated, neg PCR
- Abd US showed thickening of central intrahepatic biliary ductal walls, nml extrahepatic duct. Neg AMA, ASMA, MCRP unremarkable
- ANA & ANCAs neg
- Immunodeficiency workup: HIV RNA PCR not detected; IgG levels, subclasses nml, no e/o chronic granulomatous disease
- HSV 1/2 IgG

Hospital course

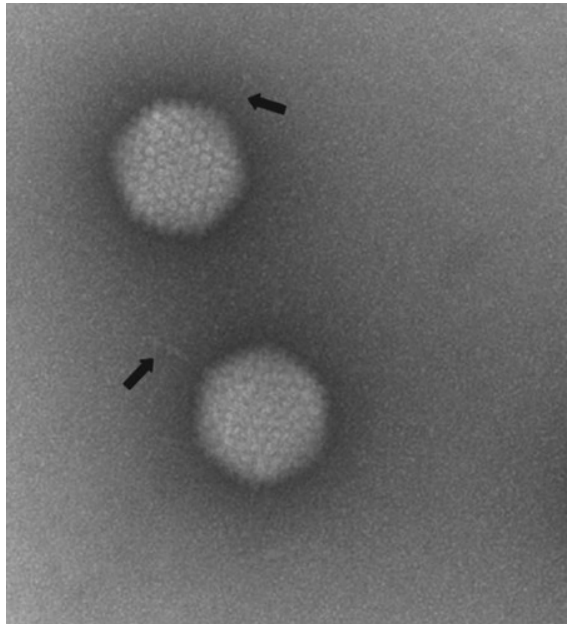
- By HD#14, he was given 14 days of broad spectrum antibiotics (vancomycin, meropenem, levofloxacin, and empiric doxycycline) without improvement. All antibiotics are discontinued.
- Now, there is concern for HLH trigged by infection...?
- Ferritin 9400, TGs 748, pancytopenia, abnormal LFTs of unclear etiology, INR 1.3, PRES
- By HD#14, a pending test result returns...

Diagnosis

- Respiratory viral panel PCR (BioFire) positive for Adenovirus (no serotype available).
- Given multi-organ failure, decision made by MICU to treat with cidofovir. Single dose given.
- Adenovirus blood PCR was > 2 million
- Diagnosed with disseminated adenovirus
- On repeat, PCR was 392,000 three days later
- Bronchoscopy repeated HD#17. No mucus plugging or purulence in airways. Edematous mucosa. Pulmonary edema. CT with continued MF PNA with no improvement, ARDS.

Human adenovirus

- non-enveloped, lytic DNA viruses
- HAdVs are classified into 7 groups (A to G); 72 types isolated from clinical specimens so far.



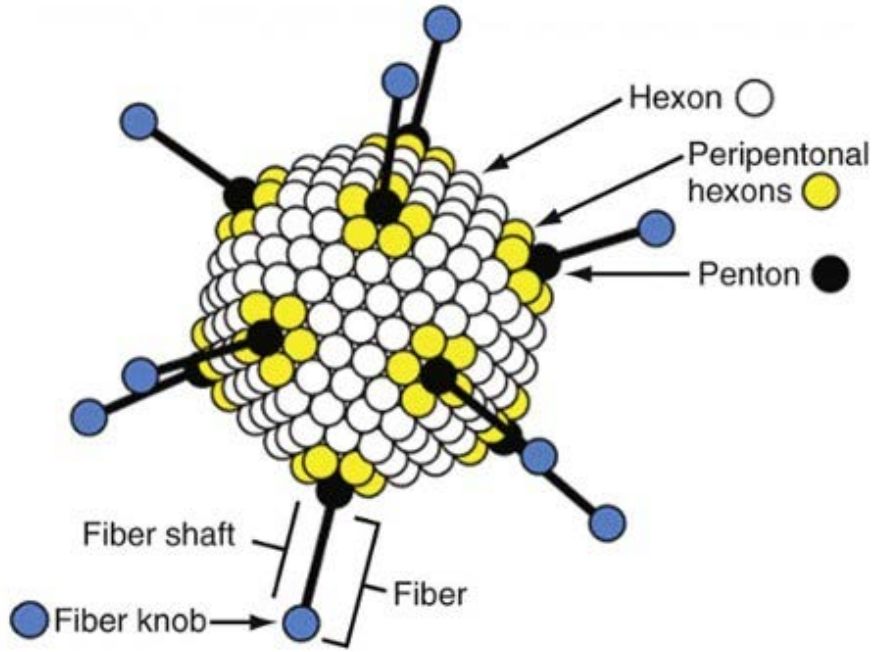


TABLE 145-1 Classification of Adenoviruses

GROUP	HEMAGGLUTINATION GROUPS	TYPES	COMMON SITES OF INFECTION
A	IV (little or no agglutination)	12, 18, 31	GI tract, respiratory tract
B	I (complete agglutination of monkey erythrocytes)	3, 7, 11, 14, 16, 21, 34, 35, 50, 55	Respiratory tract, genitourinary tract
C	III (partial agglutination of rat erythrocytes)	1, 2, 5, 6, 57	Respiratory tract, liver
D	II (complete agglutination of rat erythrocytes)	8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54, 56, 58-60	Eye, GI tract
E	III	4	Respiratory tract
F	III	40, 41	GI tract
G	III	52	GI tract

GI, gastrointestinal.

Clinical Syndromes

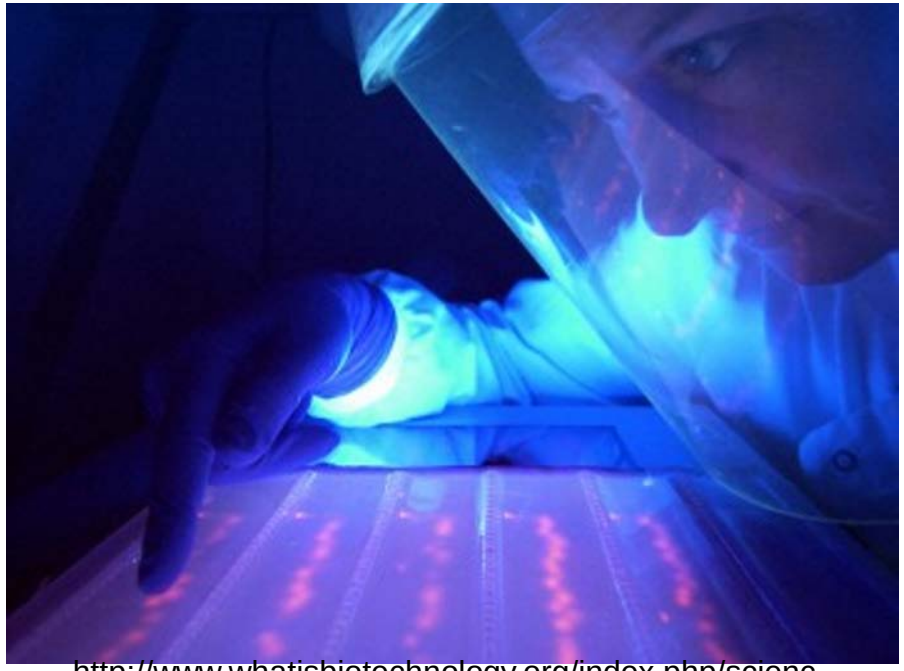
TABLE 145-2 Clinical Diseases Caused by Adenovirus Infection

CLINICAL DISEASE	POPULATIONS AT RISK	CAUSAL ADENOVIRUS TYPES
Pharyngitis	Infants, children	1-7
Pharyngoconjunctival fever	Children	3, 7
Pertussis-like syndrome	Children	5
Pneumonia	Infants, children	1-3, 21, 56
	Military recruits	4, 7, 14
Acute respiratory disease	Military recruits	3, 4, 7, 14, 21, 55
Conjunctivitis	Children	1-4, 7
Epidemic keratoconjunctivitis	Adults, children	8, 11, 19, 37, 53, 54
Gastroenteritis	Infants	31, 40, 41
	Children	2, 3, 5
Intussusception	Children	1, 2, 4, 5
Hemorrhagic cystitis	Children	7, 11, 21
	HSCT recipients, renal transplant recipients	34, 35
Meningoencephalitis	Children, immunocompromised hosts	2, 6, 7, 12, 32
Hepatitis	Pediatric liver transplant recipients	1-3, 5, 7
Nephritis	Renal transplant recipients	11, 34, 35
Myocarditis	Children	7, 21
Urethritis	Adults	2, 19, 37
Disseminated disease	Neonates, immunocompromised hosts	1, 2, 5, 11, 31, 34, 35, 40

HSCT, hematopoietic stem cell transplant.

Diagnosis

- Diagnosis is not routinely pursued because most infections are mild and self-limited.
- HAdVs are detected by routine viral tissue culture (except types 40 and 41) and can be recovered from swabs, samples, and tissues; immunofluorescence assay, enzyme-linked immunosorbent assay, acute/convalescent serum titers can establish diagnosis.
- PCR is highly sensitive and specific (96% to 100%) in immunocompetent adults.



http://www.whatisbiotechnology.org/index.php/science/summary/pcr

Emergent severe acute respiratory distress syndrome caused by adenovirus type 55 in immunocompetent adults in 2013: a prospective observational study (Sun et al)

Crit Care. 2014 Aug 12;18(4):456. doi: 10.1186/s13054-014-0456-6.

- prospective, Chinese, single-center observational study of PNA with ARDS in immunocompetent adults admitted to ICU (2011)
- n= 5 pts with severe ARDS & confirmed HAdV-55 infection: young men, median age 32 yrs;
- ABG with profound hypoxia (avg paO2 58);
- Mean duration from 1st first positive CXR to b/l multilobar infiltrates 4.8 days
- VL > 10k→ 100 Mil; 1 pt with neg VL who was the only patient to survive
- Mean time to NPPV failure and IMV failure were 30.8 hours and 6.2 days, respectively. 4 pts received V-V ECM. 4 of 5 pts died despite appropriate respiratory support

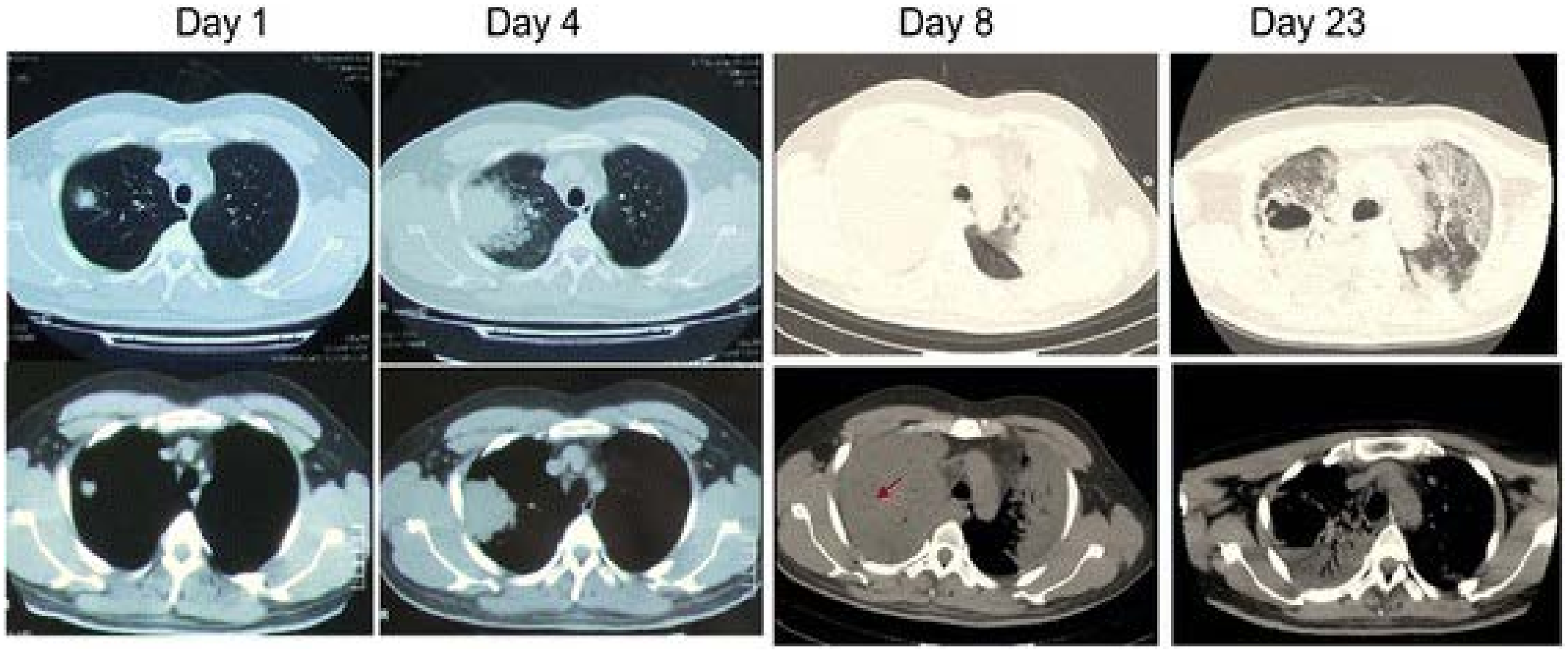
- Persistent high fever, dyspnea and rapid progression to respiratory failure within 2 weeks, together with b/l consolidations, are the most frequent clinical manifestations of HAdV-55-induced severe ARDS.

- Labs: WBC low or normal; elevated AST, LDH

- Viral load monitoring may help predict disease severity & outcome.

- NPPV & IMV failure rates very high, but ECMO may still be an option

- most frequently dominant CT pattern was consolidation +/- surrounding GGO (subpleural and peri-bronchovascular distributions). Acta Radiol. 2017 Aug;58(8):937-943. doi: 10.1177/0284185116681039. Epub 2016 Jan 1.



Crit Care. 2014; 18(4): 456.

Dynamic changes on chest CT scans for human adenovirus type 55 pneumonia in patient 3. Chest CT taken on D1 show a nodular shadow in the RUL. The nodular shadow expanded dramatically within 3 days and was surrounded by GGO on D4.
The lesion was diffuse in both lung fields on D8. A cavity was observed on D23 and the mediastinum window shows the formation of pulmonary abscess in the RUL (red arrow). The lung abscess tested negative for *Legionella*, *Staphylococcus* and tuberculosis.

Infections in Immunocompromised Patients

- ADV - opportunistic pathogen in hematopoietic stem cell transplant and solid-organ transplant pts.

- Blood PCR levels, degree of immunosuppression, lymphopenia, rising viral load increase risk for serious clinical disease.

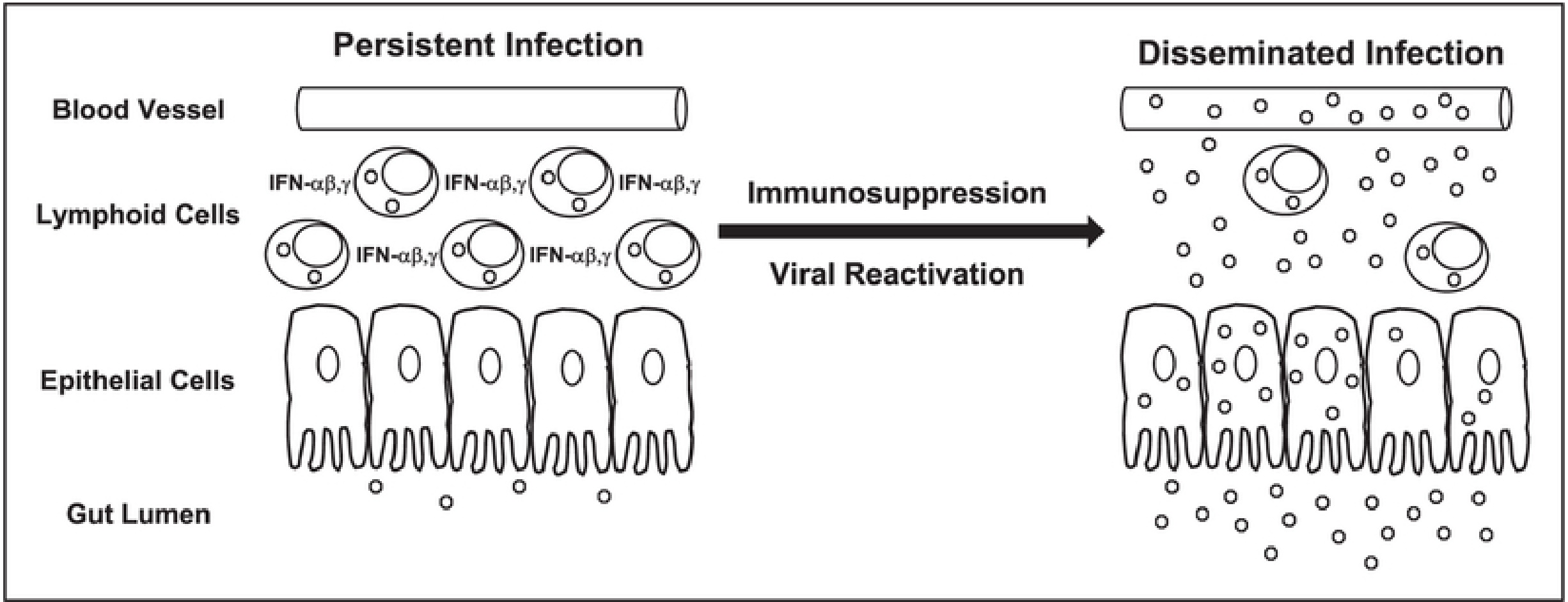
- pneumonia, hemorrhagic cystitis, pneumonitis, tubulointerstitial nephritis,, cholangio/hepatitis, encephalitis, and disseminated disease have been reported
- transplanted organ typically primary site of disease in SOT pts.

- Severe disease with dissemination more common in the pediatric liver and lung recipients

https://academy.esicm.org/enrol/index.php?id=188

Human adenovirus infections: update and consideration of mechanisms of viral persistence. (Radke et al)

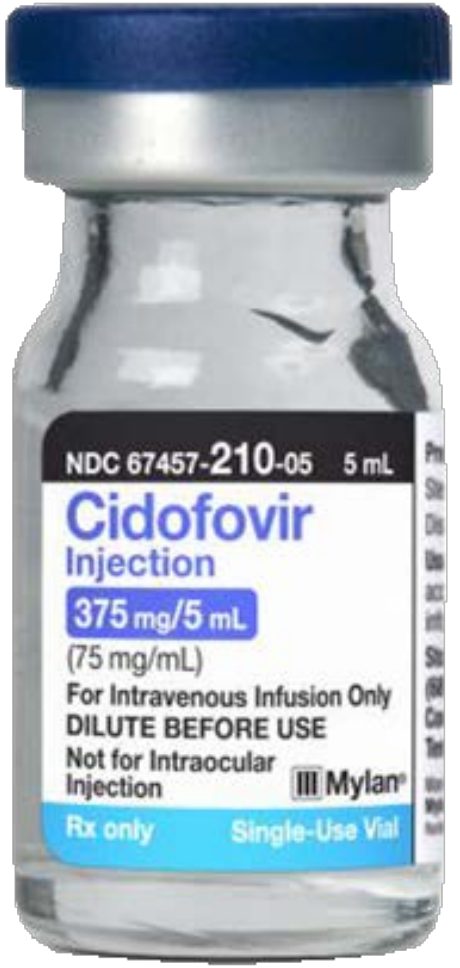
Curr Opin Infect Dis. 2018 Jun; 31(3): 251–256.



Treatment

- cidofovir, brincidofovir, ribavirin, and ganciclovir demonstrate in vitro activity against the virus
- Ppx not recommended
- no vaccine available for prevention
- Cohorting, contact and droplet precautions for the duration of an infected pt's hospital stay is recommended

- Cidofovir: Case series report good in vitro activity to AV, partial clinical response, but substantial nephrotoxicity in HSCT/SOT.



http://www.mylan.com/en/products/product-catalog/product-profile-page?id=eb83bb19-1500-44c7-99a2-3b35ed3195ca

Treatment

- IV cidofovir is favored by most studies because it retains activity against all ADV serotypes (Ganapathi et al., 2016)
- While support for the use of antiviral agents is based largely on case reports and series, most transplant centers favor the use of IV cidofovir only for the treatment of severe, progressive, and disseminated disease.
- Brincidofovir better tolerated, less nephrotoxic
- Ribavirin in HSCT recipients –mixed results.
- Vidarabine and ganciclovir - in vitro, scant clinical data

https://www.nydailynews.com/life-style/health/new-drug-brincidofovir-treating-ebola-expert-article-1.1986681

Hospital course

- The patient was already requiring RRT and had significant pancytopenia, therefore due to risk of nephrotoxicity and further myelosuppression, ID did not recommend further cidofovir. Blood PCR levels declined without additional doses.

- Course c/b ventilator-dependent resp failure requiring tracheostomy and PEG feeding tube, PRES, MRSA VA-PNA, line-related fungemia (with negative TEE), depression, continued elevation of AST/ALT/AP without clear etiology and negative workup, liver biopsy deferred. Pt was eventually discharged to LTAC with hepatology follow up.