
# MICROBIOLOGY

☑ Sheet ○ Slide ○ Handout

Number

1

Subject

Viral Lower UTIs

Done By

Omar Mahafza

Corrected by

---

Doctor

Ashraf Khasawneh

Date: **00/00/2016**

Price:

بسم الله الرحمن الرحيم

# Viral Lower Urinary Tract Infections

This lecture was written according to the recording of section 3, topics of this sheet are a little bit different from that in the recording.

❖ Viruses that cause UTIs (Urinary Tract Infections):-

- Polioma BK virus (It was called Papovavirus in the past)
- Cytomegalovirus (CMV)
- Adenovirus (7, 11, 21, 35)

*Ps.) The most common cause of lower UTI is bacterial, specifically* ***E.coli****.*

➔ What is common between these viruses?

1) They are all **DNA** viruses.
2) They are all characterized by **latency**.
   (The best examples for latent viruses are Herpesviridae, including CMV)
3) They are all **carcinogenic in VITRO** (capable of transforming normal cells into cancerous cells in the lab, but NOT in their natural host).
4) They can infect children or adults, but the infection passes unnoticed **(asymptomatic)** in most of the times.

➢ These viruses can hide anywhere in the urinary tract (e.g. Kidney, ureter, bladder), thus taking cyclophosphamide will trigger their reactivation and causing disease.

The seven families of DNA viruses are: (2H, 4P, 1A)

**H**erpesviridae / **H**epadnaviridae (Hepatitis B)
**P**apillomaviridae / **P**oliomaviridae / **P**oxviridae / **P**arvoviridae
**A**denoviridae

➢ Urinary Tract Infections could be either: **Hemorrhagic cystitis** or **Nephritis**.

☸ **A Typical Scenario:** A 14 year old male has underwent a renal transplantation and he is on Cyclophosphamide. He presented to the ER (Emergency Room) with a reddish discoloration of the urine, and upon Kidney-function tests there were increased levels of Creatinine, and urine analysis has revealed the presence of RBCs & epithelial cells (Cast cells) ➔ *What is the differential diagnosis?* (What should you think of?)

Ps.) *Cyclophosphamide*: An I*mmunosuppressant to prevent graft rejection.*

The diiferential diagnosis should be:-

1) **Either:** Immunorejection
2) **Or:** Viral infectious disease (reactivation) due to immunosuppression;
   - ⇨ The source of the virus could be either from the ***donor*** or the ***recipient***.

---

## ☙ Hemorrhagic cystitis

- Inflammation of the bladder's epithelium and blood vessels.
- Symptoms:
  - Θ **Urgency** – The very urgent need to urinate.
  - Θ **Frequency** – Excessive urination, reaching 10-15 times per day instead of 3-4.
  - Θ **Dysuria** – Burning sensation during urination.
  - Θ **Stranguria** – The need to urinate but inability to excrete it.
- Non-specific findings: Inflammatory infiltrates, chronic inflammation and fibrosis.
- Acute hemorrhagic cystitis usually affects children aged 5-15 years, but may also affect immunosuppressed adults.
- Boys are affected more often than girls
- Hematuria is self-limited to 3 days, and other symptoms resolve later. (The disease is self-limiting)
- Hemorrhagic cystitis could be either:-
  - **Infectious:** viral or bacterial.
  - **Non-infectious:**
    - Radiation-induced; (e.g. Pelvic radiation)
    - Drug-induced; by chemotherapy.
    - When vaginal products are inadvertently placed in the urethra.

---

## ➔ Radiation-induced hemorrhagic cystitis

- The incidence in the pediatric population is less than that in adults
- Radiation therapy for pelvis (25%) & cancers of prostate, colon, cervix or bladder.
- Symptoms are the same ones mentioned above.

## ➔ Drug-induced hemorrhagic cystitis

- Most common with Cyclophosphamide, Ifosfamide.
- Cyclophosphamide can cause microscopic and gross hematuria that usually occurs within 48 hours of treatment.
- Cyclophosphamide itself is not toxic; the toxicity is due to its hepatic conversion, forming the toxic metabolite **acrolein**; which is excreted in the urine, causing bladder edema & hemorrhage.
  - ⇨ Ps.) A drug that is used to reverse the effects of acrolein is called **Mesna**.
- Ifosfamide causes the release of TNF-α and interleukin-1 β, thus mediating the release of nitric oxide (NO), eventually leading to hemorrhagic cystitis.

---

## ➔ Viral-induced hemorrhagic cystitis

### ❖ Adenoviruses

- ds-DNA virus, Non-enveloped (naked virus)
- Icosahedral capsid
- It replicates inside the nucleus.
- Infect by oral route, droplet & fomites.
- There are more than 100 serotypes, 50 of which can cause infections.
- They have projections on their surface called "pentons" and each of these have a spherical head called "penton base"; these facilitate the **attachment** to cells, and at the same time they are **toxic** to target cells.
- They have a tropism for infecting **epithelial cells**, thus they can infect the Meninges, Respiratory, GI and Urinary tracts.
- May remain in lymphoid structures (Tonsils & Adenoids)
- The name is derived from Adenoids (An oropharyngeal/retronasal structure); When a child undergoes a tonsillectomy, the virus might hide in the adenoids and might remain for 6-18 months without showing any symptoms (due to latency).
- Produce intranuclear inclusion bodies.
- Integration of the virus can occur.

> ***General rule:*** When viruses are found integrated, (especially with latent viruses) then they currently are NOT during latency.

- How do adenoviruses evade immunity? There are 3 mechanisms;

1) **The E1B gene ➔** Inhibits apoptosis of the cell, therefore eventhough the cell is diseased, this gene will inhibit its programmed-cell death, therefore allowing the virus to replicate more inside cells.
2) **The E3 gene ➔** It will trap the keep the major histocompatibility complex (MHC) trapped inside the endoplasmic reticulum, so viral antigens will NOT be presented by MHC on cell surfaces, thus immune cells of the body would not detect the presence of the virus.
3) **Late proteins of the adenovirus ➔** These are capable of lysing the cell, resulting in the release of progeny viruses and spreading the infection.

- Diseases caused by Adenoviruses include:

**Pharyngitis – Pharyngoconjunctival fever – Respiratory disease – Pneumonia – Follicular conjunctivitis – Acute hemorrhagic cystitis (11, 21) – Gastroenteritis**

- Diagnosis

- Clinical picture / History / Physical examination
- Urine & Blood tests
- PCR is highly specific in urine samples
- Viral isolation is expensive and not widely done
- Serology is **NOT** useful; because it's an acute infection and by the time the antibodies have become detectable the symptoms might've already been resolved.
- Antigen detection & Urine cytology can be help in the diagnosis.

- Prevention & Treatment

- ✓ There is no specific antiviral drug or vaccine.
- ✓ Few cases can benefit from taking the antiviral drug Cidofovir.
- ✓ Early military recruits (المنضمين للجيش) take a live-attenuated vaccine for some viral strains that can cause upper respiratory infections.
- ✓ Continuous bladder irrigation (غسل المثانة) in combination with Mesna, hydration, and urinary alkalization during bone marrow transplantation may prevent hemorrhagic cystitis.

***Bladder irrigation*** *is done by inserting a Foley catheter in the urethra going to the bladder, then inject IV fluids (e.g. Normal Saline) to break any clots that can cause obstruction and help in the replication of the virus and then aspirate its contents.*

## ❖ Poliomavirus

- Circular ds-DNA virus
- Non-enveloped (naked virus)
- Encode early and late
- Capsid proteins VP1, VP2 and VP3
- This family has 2 viruses that can infect humans, which are:
  - Polioma JC virus: causes encephalitis.
  - Polioma BK virus: causes urinary tract infection.
- Route of transmission is not clear yet (respiratory, transplacental, or fecal-oral).
- Polioma BK virus has been suggested to be a transforming agent and therefore can contribute in causing bladder cancer.
- The first reported case of BK infectious disease was in the year 1971, then there were no other reported cases for 20-25 years after that.

➔ Now with increased use of immunosuppressive therapy and translplantation surgeries the incidence of diseases caused by the reactivation of BK virus has increased drastically.

➢ About 80% of the general population has a detectable antibody to BK virus, **but** the virus in most of these is latent, causing no symptoms, so whenever the immunity of a person drops, there'll be a high chance for reactivation and disease

➢ After renal transplantation, the prevalence of:

Θ BK-induced Viruria – 30%

Θ BK-induced Viremia – 13%

Θ BK-induced Nephritis – 8%

➢ The prevalence of BK in End-Stage Renal Disease population, Kidney donors & Transplant recipients has not been well defined.

*Some terminology:*

- **BKVN** – BK virus nephritis.
- **BKVAN** – BK virus associated nephritis.

**They both have the same meaning.**

➢ BKVN is also seen in **other** Solid Organ Transplants but at a much lower rate.

## ➢ What's the role of immunity in BKVN/BKVAN?

⇨ BKV-specific antibodies provide **incomplete** protection against BKVAN;

⇨ This means that even if the BKV-oinfected person has developed seroconversion (developed antibodies against BK virus) and undergone organ transplantation, there's still a chance he might develop BKVAN.

➔ However, they may attenuate the severity of BKV infection and the clinical manifestations.

➔ In addition, evaluation of BKV-specific antibody titers provide information on the severity of past or current infections and on prognosis.

*Remember:*

- **IgM** – Recent infection.
- **IgG** – Past infection.

## What's the role of the BKV specific T-cells?

It could be either protective **or** destructive.

→ We have two scenarios here:

1) **Acute BKV reactivation**: Here we have **little inflammation**, the cytotoxic T-cells control the replication of the virus. → So any increase in the number of T-cells is going to "contain" the virus infection and prevent increase in the virus number.

   Here, cytotoxic T-cells are protective, so you must *reduce immunosuppression* in order to let these cells do their job.

2) **Chronic BKV reactivation**: Here we have **massive inflammation**, cytotoxic T-cells are going to attack & damage graft cells, so you must *increase immunosuppression*.

In graft transplant, you may have immune-rejection or infection as said earlier;

The decision you should take as a physician in this case is either:

→ Lower the immunosuppression dose, withdraw it completely, or keep it the same.

Some physicians might not investigate the graft and mislead the condition as rejection instead of infection, so they increase the dose of immunosuppressive drug, ending up in increasing the infection → you will lose the graft.

⇨ From every 12 cases of which the physicians mislead the case as graft rejection instead of infection, 8 of them lost the graft.
(They patients more immunosuppression instead of decreasing it).

## ➢ Role of Immunosuppressive medications

- ✓ Prior to 1995 (Before tacrolimus & mycophenolate mofetil (MMF) were introduced), BKVAN was a rare entity.
- ✓ Reduction or pre-emptive withdrawal of immunosuppressive medication was associated with BKV clearance.
- ✓ The occurrence of BKVN is not due to specific immunosuppressive agents, but it is related generally to the overall degree of immunosuppression.

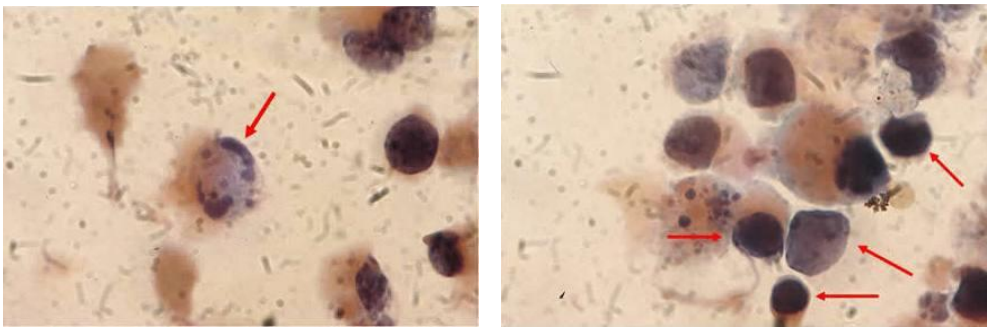
## ➢ Other factors in pathogenesis:

➔ ***Tropism*** of the virus for **renal tubular cells** and their replication in these cells.

So, when doing urine analysis, renal tubular cells are going to be found in the sample

→ Under the microscope, you'll notice two things:-

1) Chromatin margination (found on the edges of the cell).
2) **Decoy cells**: These are renal tubular cells (found in the center of the cell) and they have a ground-glass appearance of inclusion bodies. (Figure)



Ps.) Decoy cells are diagnostic & indicative of BKV (mostly) or CMV infection.

Patients who do kidney transplant and get infected with BKV are only 15%, and among these:-

- 50% develop BK viremia 3 months after kidney transplantation.
- 95% occurs in the first 2 years after kidney transplantation.

To prevent the infection you should:-

☞ Do screening every month for the first 3 months after the kidney transplant by **PCR**,
☞ Then screen for the virus every 3 months until 1 year has passed since the transplant.

(Most probably if the virus didn't show up until the first year, it won't show up at all)

## ➢ Clinical Manifestations of BKV

- Most renal transplant recipients with BKVN manifest with ***renal dysfunction***.

  ➔ Progressive renal failure has been reported in approximately 30–60% of cases.

- Occasionally, subjects can present with *ureteric obstruction* & *hydronephrosis*.
- As said earlier, we should always measure the creatinine level, its elevation indicates rejection/infection, **BUT** some routine post-transplant biopsies reveal BKVN in the absence of serum creatinine elevation!

## ➢ Treatment

Lowering the dose of immunosuppressive therapy, or even withdraw it completely (some studies say that lowering/withdrawing the therapy has the same effect).

You can also use the help of:-

1- ***Quenolone*** antibiotics can be given, they prevent the viral replication by inhibiting DNA topoisomerase.

2- ***IVIG*** (IV immunoglobulins) against BKV.

*3-* ***Leflunomide***: is a prodrug which acts as an anti-metabolite.

*4-* ***Cidofovir***

⇨ If the patient graft has been rejected after being infected (BKVAN), he can once again try re-transplantation.

⇨ In a review in 2005, BKVAN recurred in 15% of re-transplantations, compared with 5% of primary transplantations but still there's a chance of 85% that he'll accept the graft

** **The doctor stopped here and asked us to self-study the rest of the slides** **

---

**CMV (كملو السلايدات لحالكو)**

Belong to the betaherpesvirus subfamily of herpesviruses.

• Transmission may occur in utero, perinatally or postnatally. Once infected, the person carries the virus for life which may be activated from time to time, during which infectious virions appear in the urine and the saliva.

• Reactivation can also lead to vertical transmission. It is also possible for people who have experienced primary infection to be reinfected with another or the same strain of CMV, this reinfection does not differ clinically from reactivation.

**clinical manifistations:**

• Immunocompromised patients such as transplant recipients and AIDS patients are prone to severe CMV disease such as pneumonitis, retinitis, colitis, and encephalopathy.

• Reactivation or reinfection with CMV is usually asymptomatic except in immunocompromised patients.

**Treatment:**

Immunocompromised patients - it is necessary to make a diagnosis of CMV infection early and give prompt antiviral therapy. Anti-CMV agents in current use are ganciclovir, forscarnet, and cidofovir.

**Other viral causes**

1- HIV

2- INFLUENZA A

• Cystitis last 2-5 days

• Manifestations: dysuria, frequency and hematuria

• Influenza A virus can be rarely recovered from urine

• Increased titre from day 1 to 6-8 weeks

---

**The sheet is over, Goodluck everyone ♥**

**Huge thanks to Hassan Saadi**