Lower Urinary Tract Infections
Hemorrhagic cystitis

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Background

- Lower urinary tract symptoms include dysuria, frequency, hematuria, and hemorrhage.
- Hemorrhagic cystitis results from damage to the bladder's transitional epithelium and blood vessels; characterized by nonspecific findings of intense inflammatory infiltrates, chronic inflammation, and fibrosis
- Hemorrhagic cystitis has both infectious and noninfectious causes
- This condition most commonly develops as a complication of pelvic radiation or from toxicity related to the use of certain chemotherapeutic drugs (ex. cyclophosphamide, ifosfamide)

- Chemical hemorrhagic cystitis can develop when vaginal products are inadvertently placed in the urethra
- Causative infectious agents for hemorrhagic cystitis include the following:
  - *Escherichia coli*
  - Adenoviruses 7, 11, 21, and 35
  - Papovavirus: polyoma BK virus
  - Cytomegalovirus (CMV)

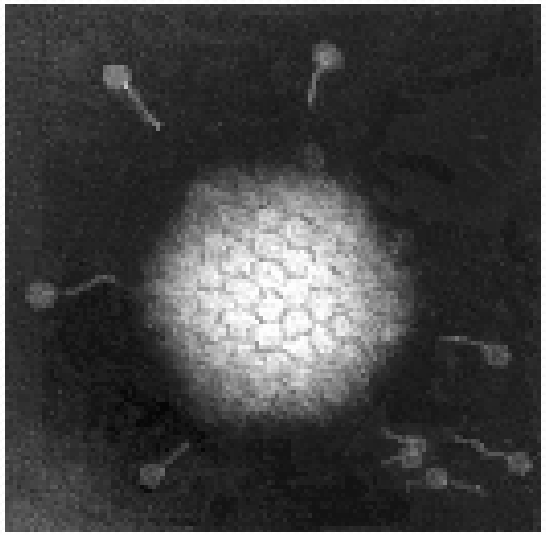
- Radiation-induced hemorrhagic cystitis
  - Nearly 25% of patients who undergo pelvic radiation develop bladder-related complications
  - The incidence in the pediatric population is less than that in adults
  - radiation therapy for cancer of the prostate, colon, cervix, or bladder
  - Urgency, frequency, dysuria, and stranguria may develop acutely during radiation or may begin months to years after completion of radiotherapy.

- Drug-induced hemorrhagic cystitis
  - The most common pharmacologic causes of hemorrhagic cystitis are the agents **cyclophosphamide** and **ifosfamide**
  - Cyclophosphamide can cause microscopic and gross hematuria that usually occurs within 48 hours of treatment
  - Cyclophosphamide itself is not toxic; the drug's toxicity is due to its hepatic conversion to the metabolite acrolein, which is excreted in the urine and causes bladder edema and bladder hemorrhage
  - Ifosfamide causes the release of tumor necrosis factor-alpha and interleukin-1 beta, mediating the release of nitric oxide and leading to hemorrhagic cystitis

Virus induced HC

- Patients undergoing therapy to suppress the immune system after solid organ, bone marrow, or cord blood transplantation—are at risk for hemorrhagic cystitis due to either the direct effects of chemotherapy or activation of dormant viruses in the kidney, ureter, or bladder
- The BK polyomavirus and adenovirus types 7, 11, 21 and 35 have been the most commonly described viruses in these cases. Cytomegalovirus, JC virus, and herpesviruses have also been identified as causative agents in these scenarios
- BK virus has also been suggested to be a causal transforming agent for bladder cancer

Adenovirus



- Virion:
  - Icosahedral, non-enveloped
  - Genome: Double-stranded DNA
  - Proteins: Important antigens (hexon, penton base, fiber) are associated with the major outer capsid proteins
  - Replication: Nucleus
  - Virus classification: Family: Adenoviridae; Genus: Mastadenovirus; Species: Human adenovirus (H Ad)
- At least 54 serotypes are known
- classified into 7 subgenera: A to G

Adenovirus

Outstanding characteristics

- virion has unique "spike" or fiber associated with each penton base of the capsid that aids in attachment to the host cell via the coxsackie-adenovirus receptor on the surface of the host cell; toxic to cells
- Adenovirus has tropism for cells of epithelial origin
- Replicative cycle is sharply divided into EARLY & LATE events
- Infect by oral route, droplet and fomites
- Epithelial cell replication, viremia, (kidney, bladder, liver, lymph nodes)
- May remain in lymphoid structures (tonsils and adenoids), reactivation and shedding asymptomatically for 6-18 months
- Integration of adenoviral DNA into host cell genome may occur and is associated with latency
- Produce smudgy intranuclear inclusion bodies

Clinical Syndromes

1. Pharyngitis 1, 2, 3, 5, 7
2. Pharyngoconjunctival fever 3, 7
3. Acute respiratory disease 4, 7, 14, 21
4. Pneumonia 1, 2, 3, 7
5. Follicular conjunctivitis 3, 4, 11
6. Acute haemorrhaghic cystitis 11, 21
    1. Acute hemorrhagic cystitis usually affects children aged 5-15 years but may also affect immunosuppressed adults (ex. from kidney or bone marrow transplantation, AIDS). Boys are affected more often than girls
    2. Dysuria, frequency, and grossly bloody urine are reported. Hematuria is self-limited to 3 days, and other symptoms resolve later. Symptoms may be more prolonged in hematopoietic stem cell recipients where nephritis may occur as well, manifested by fever, hematuria, and flank pain
7. Acute infantile gastroenteritis 40, 41

Laboratory Diagnosis

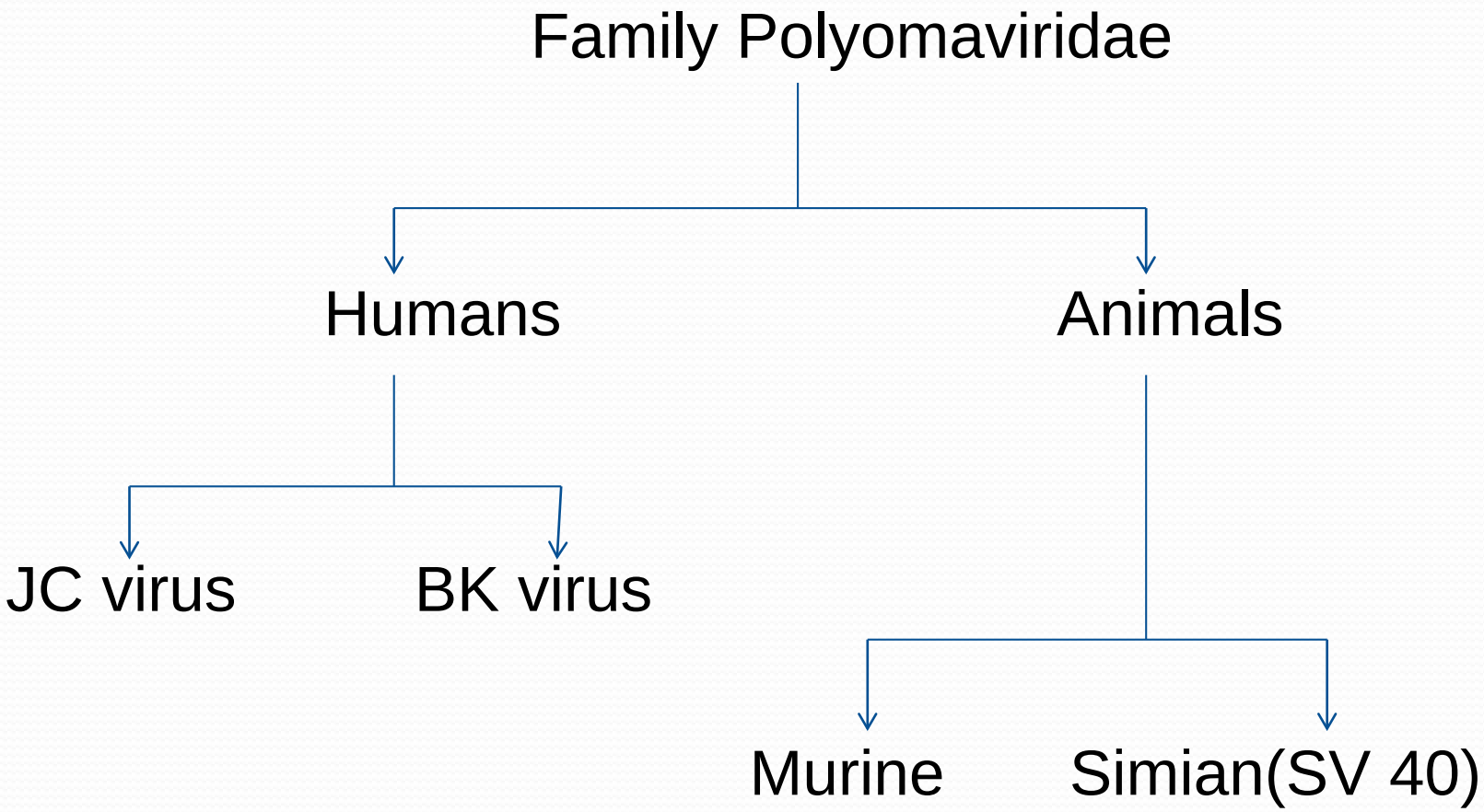
- In addition to a complete medical history and physical examination, diagnostic tests for adenoviruses may include:
  - Blood tests
  - Urinalysis
- Virus isolation: Primary human embryonic kidney cells, expensive.
- PCR: highly specific on urine samples
- Antigen detection: Indirect immunofluorescence assays may be used for direct examination of tissue specimens
- Serology: Not useful in the acute clinical setting. By age 4 years, approximately half of all children have positive adenovirus titers.
- Urine cytology should be considered to exclude other causes if hemorrhagic cystitis does not resolve within 5 days.
- Adenovirus typing is usually accomplished by hemagglutination-inhibition and/or neutralization with type-specific antisera. Since adenovirus can be excreted for prolonged periods, the presence of virus does not necessarily mean it is associated with disease.

Management & Prevention

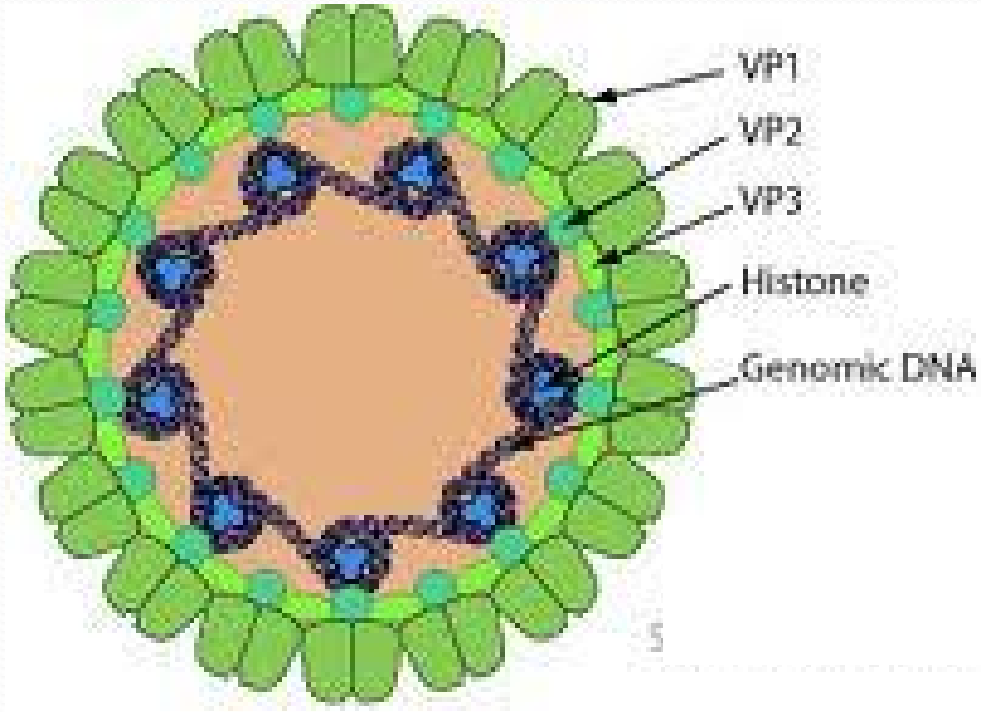
- Treatment with continuous bladder irrigation and clot evacuation is implemented as in other cases of hematuria
- Viral hemorrhagic cystitis in children generally spontaneously resolves within a few days
- There is no specific antiviral therapy, though patients might benefit from cidofovir treatment
- There are currently no vaccines available to protect against the adenovirus.
- A vaccine is available against Adult Respiratory Distress Syndrome only. It consists of live adenovirus 4, 7, and 21 in enterically coated capsules. It is given to new recruits into various arm forces around the world.

- **Continuous bladder irrigation** in combination with **mesna** - 2-mercaptoethane sulfonate Na - (which neutralizes the toxicity of the cyclophosphamide-metabolite acrolein), hydration, and urinary alkalization during bone marrow transplantation may prevent hemorrhagic cystitis.
- Good hygiene in the form of hand washing is still the best way to avoid picking up the adenovirus from an infected person.

Virology


Family Polyomaviridae
Humans
Animals
JC virus
BK virus
Murine
Simian(SV 40)

Virology



Icosahedral,40-44 nm diameter

- Double stranded circular DNA
- Naked
- Encode early and late genes
- Early: small, middle and large T antigens involved in mRNA transcription, DNA replication, cell growth and transformation.
- Late: capsid proteins VP1, VP2 and VP3.
- 4 major sero/genotypes: group I, II, III and IV
- Associated with latency
- Route of transmission not clear (respiratory or oral; contaminated food or water)
- Do not cause malignancies in their natural host

History of BKVN (BK virus nephropathy) – BKVAN (BK Virus-Associated Nephropathy)

- The term “BK” originated from a renal transplant patient's initials, in whom it was first detected in 1971.
- No reported cases of this disease for the next 24 years, until Purighalla and co-workers observed their first case in early 1995.
- Subsequently there has been a surge in reported cases worldwide.

Epidemiology of BKV infection

- Approx. 80% of the general population has a detectable antibody to BKV, which appears early in life and remains elevated throughout life.

- The prevalence of this virus in the ESRD population, kidney donors, and transplant recipients has not been well defined.

- The prevalence of BK viruria, viremia, and nephritis after renal Tx has been estimated at 30, 13, and 8%, respectively.

Epidemiology of BKV infection

- BKVN is also seen in other Solid Organ Transplants but at a much lower rate. It also has been observed in patients with HIV infection, other immunodeficiency states and rarely also in SLE.

- Primary Infection occurs in early life when it is either asymptomatic or with mild URTI. Thereafter BKV largely persists in the kidneys and urinary tract in a latent form.

- The principal routes of transmission are fecal-oral, respiratory, transplacental, or from donor tissue.

Source of infection

Two proposed hypotheses:

1. Transmission occurs through the donor kidney.
2. Reactivation in the recipient renal epithelium after transplantation.

Humoral immunity

- BKV-specific antibodies provide *incomplete protection* against BKVAN for patients after kidney transplantation.
- However, they *may attenuate the severity* of BKV infection and its clinical manifestations.
- In addition, evaluation of BKV-specific antibody titers can provide information on the *severity* of past or current BKV infections and on *prognosis.*

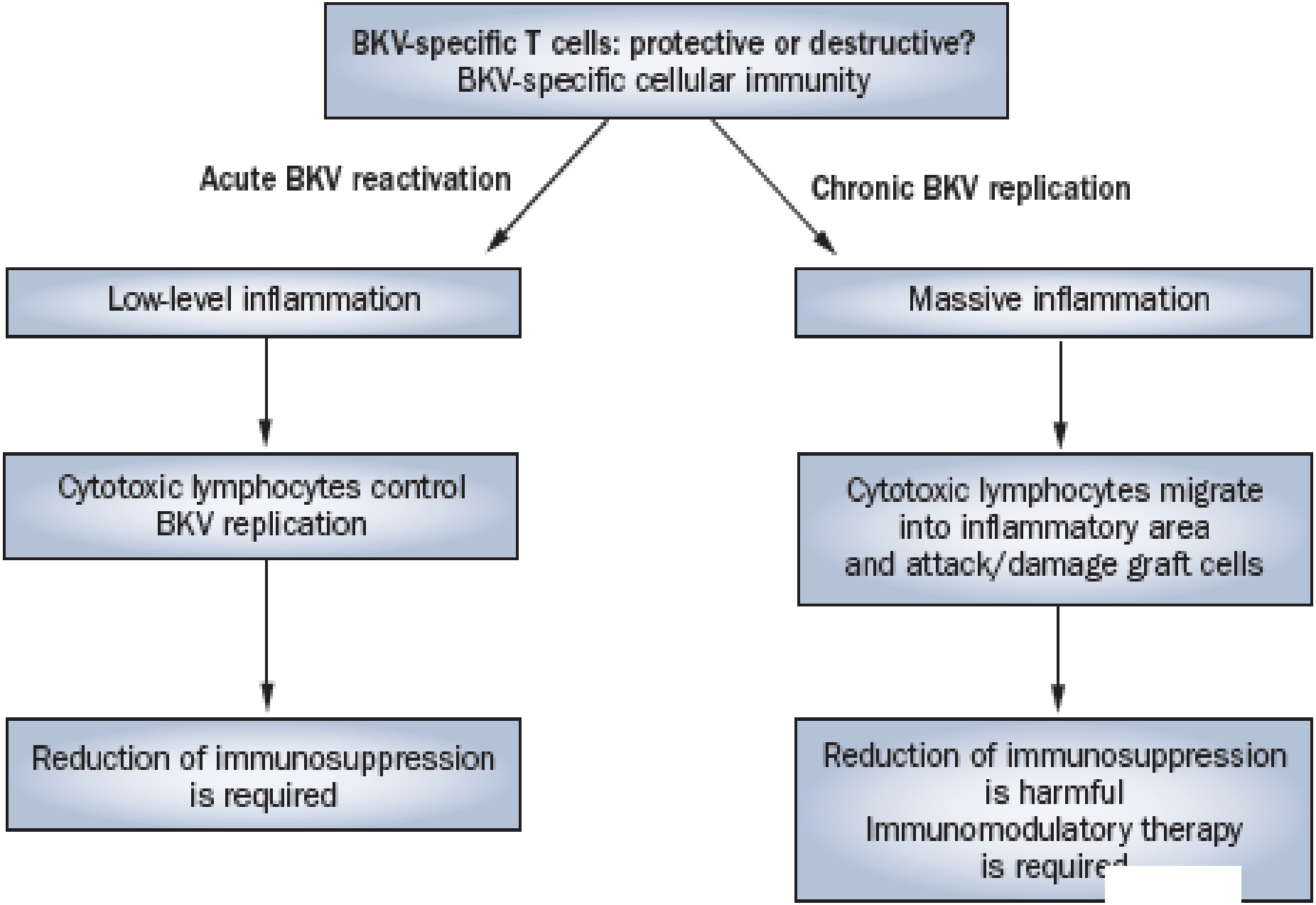
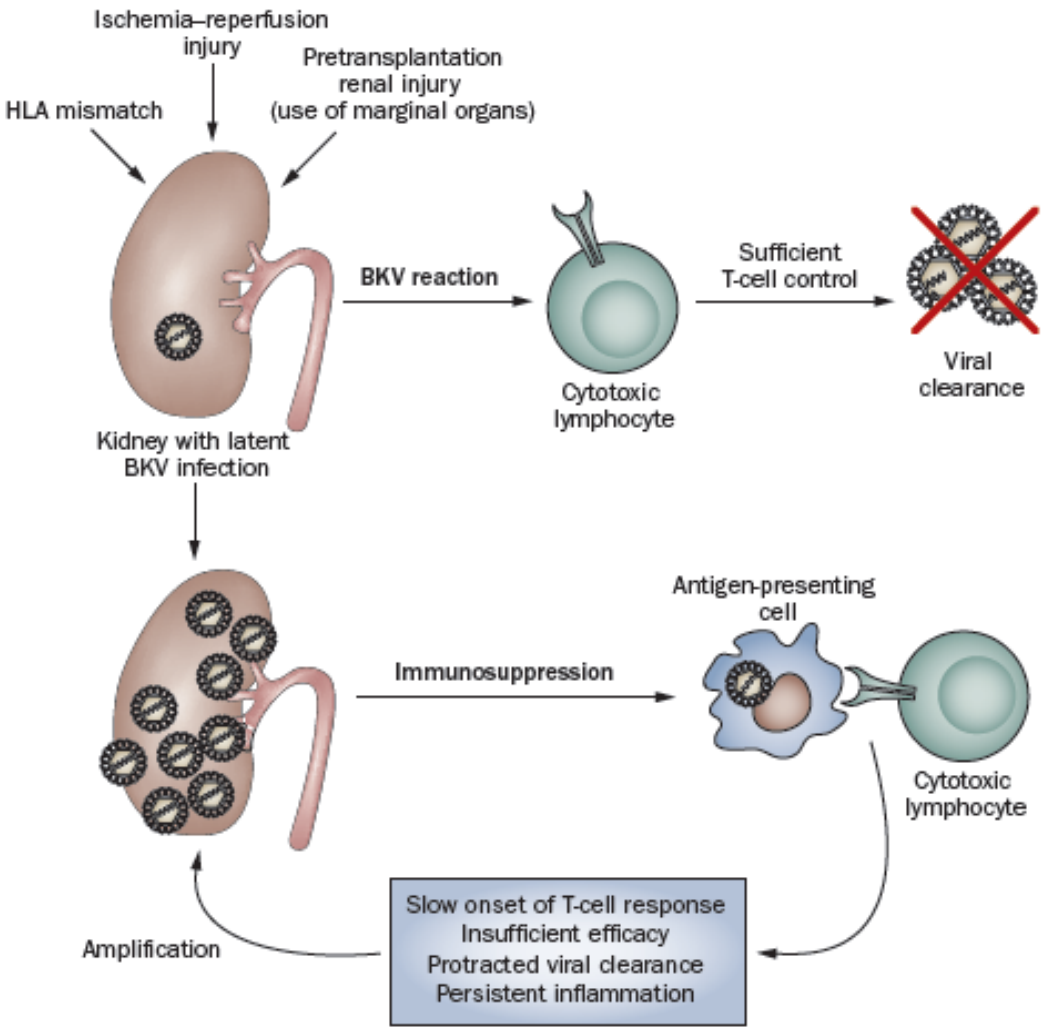


Figure 2 | The dual role of BKV-specific cytotoxic T cells in BKV infection. If cellular

Immunology of BKVN: Cellular immunity



Role of Immunosuppressive medications

- Prior to 1995; when tacrolimus and 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 may be related to the overall degree of immunosuppression.

Other factors in pathogenesis

- *Tropism* of the virus for renal tubular cells and their replication in these cells.
- *Higher virulence* acquired by BKV can contribute.
- *HLA mismatch* between the donor and recipient.
- Age >50yrs, male gender and diabetes have also been found to have increased risk.

Clinical Features of BKV infection

- Fifty percent of patients who develop BK viremia do so by 3 months after kidney transplantation.

- Ninety-five percent of BKV nephropathy occurs in the first 2 years after kidney transplantation.

Clinical Features of BKV infection

- 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 also present with *ureteric obstruction* and *hydronephrosis*. Cases of cystitis have been reported.

- Routine post-transplant protocol biopsy has also detected BKVN in the absence of serum creatinine elevation.

Diagnosis of BKVAN

Diagnosis of BKV infection

Documentation of viral cytopathic effects

Demonstration of the virus itself

Demonstration of immunity to virus

Histologic findings

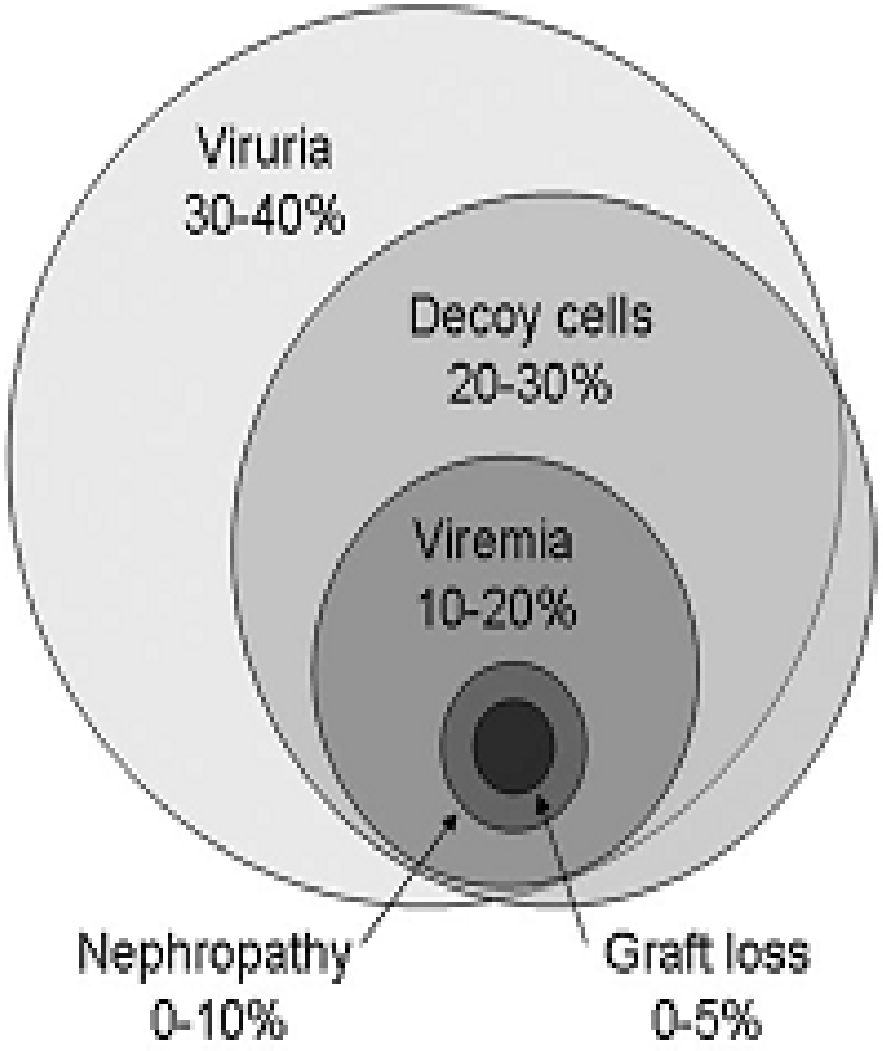


Figure 1. Type and prevalence of BK virus (BKV) infections in kidney transplant recipients.

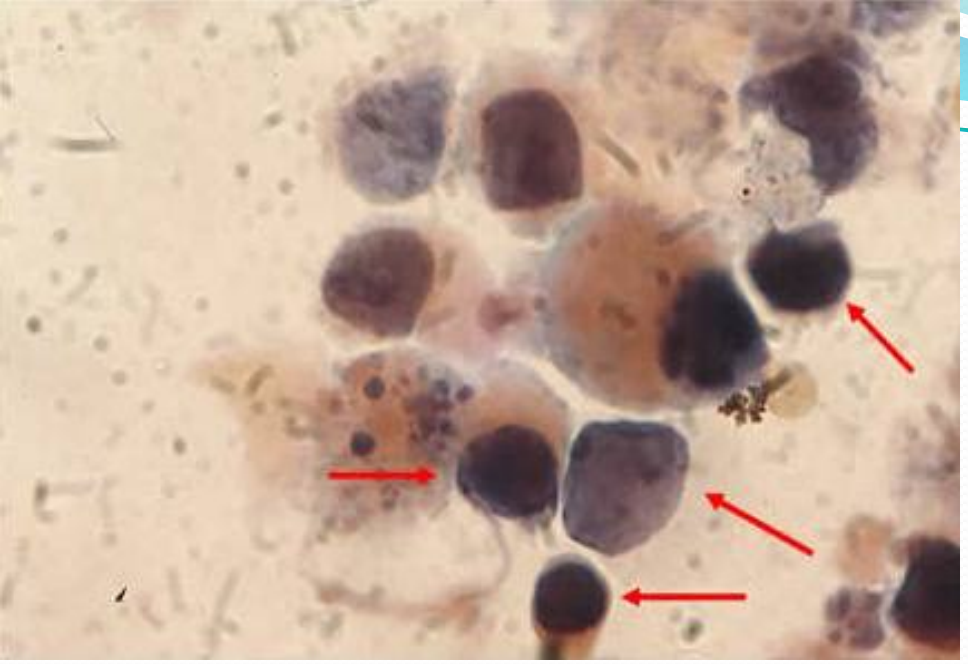
Cellular changes due to BKV

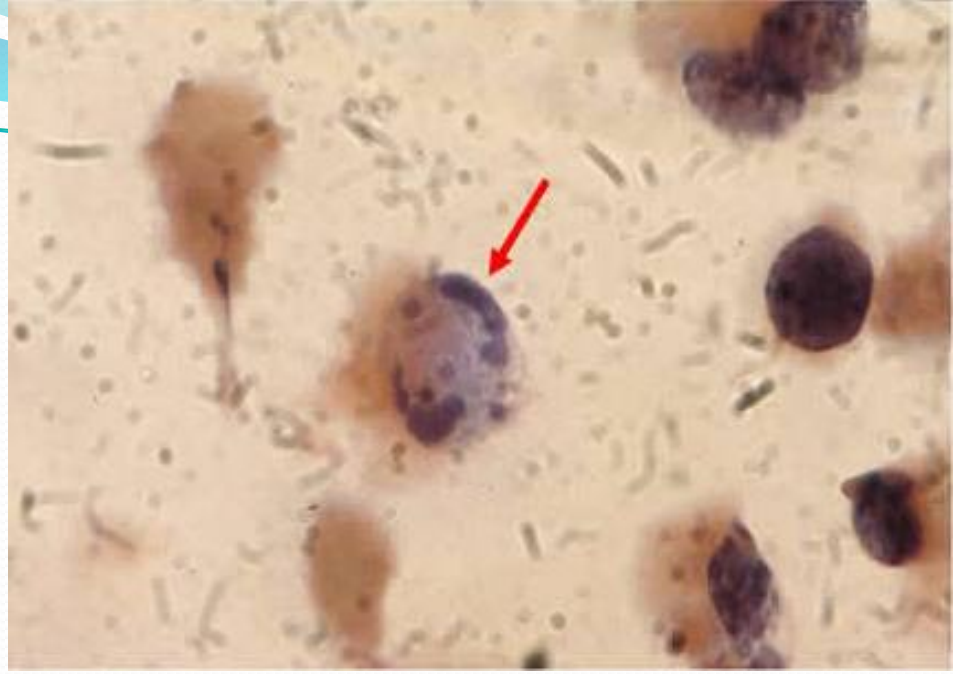
- Enlarged nucleus (“Ground-glass” appearance).
- Chromatin margination.
- Irregular chromatin pattern.
- Multiple nuclear inclusion bodies of various shapes and sizes.
- Single nuclear inclusion body with a **“bird-eye”** appearance.
- Intracytoplasmic vacuoles and vacuolated cytoplasm(rare)
- **Decoy cells** are renal tubular or urothelial cells with intranuclear BKV-bearing inclusion bodies.

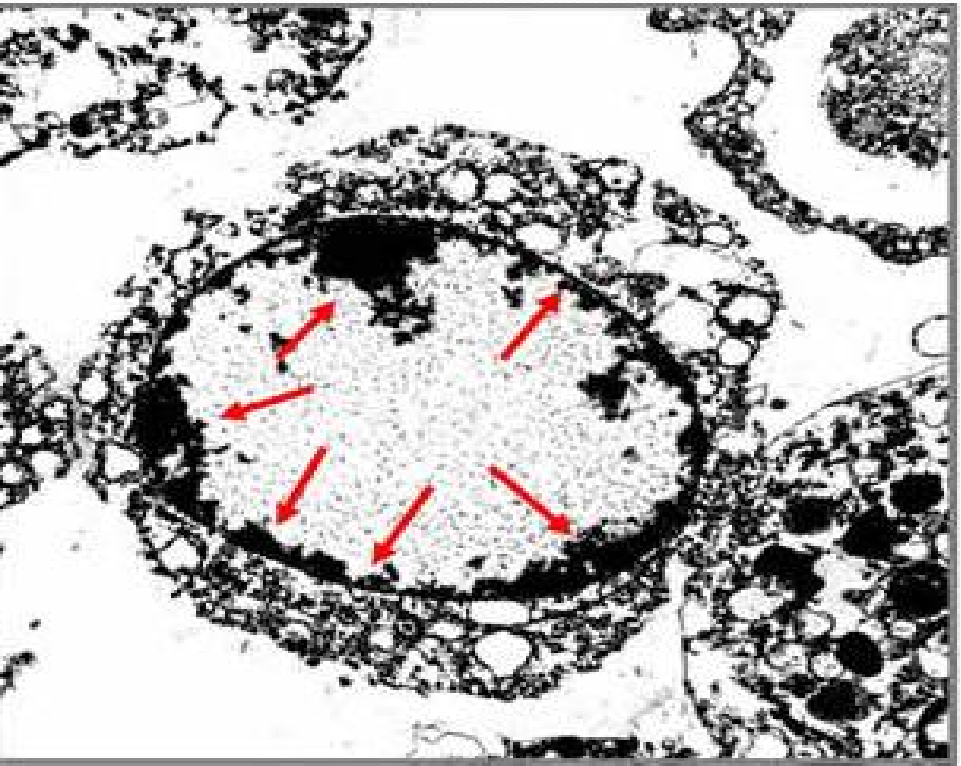
Urine cytology in BKV infection

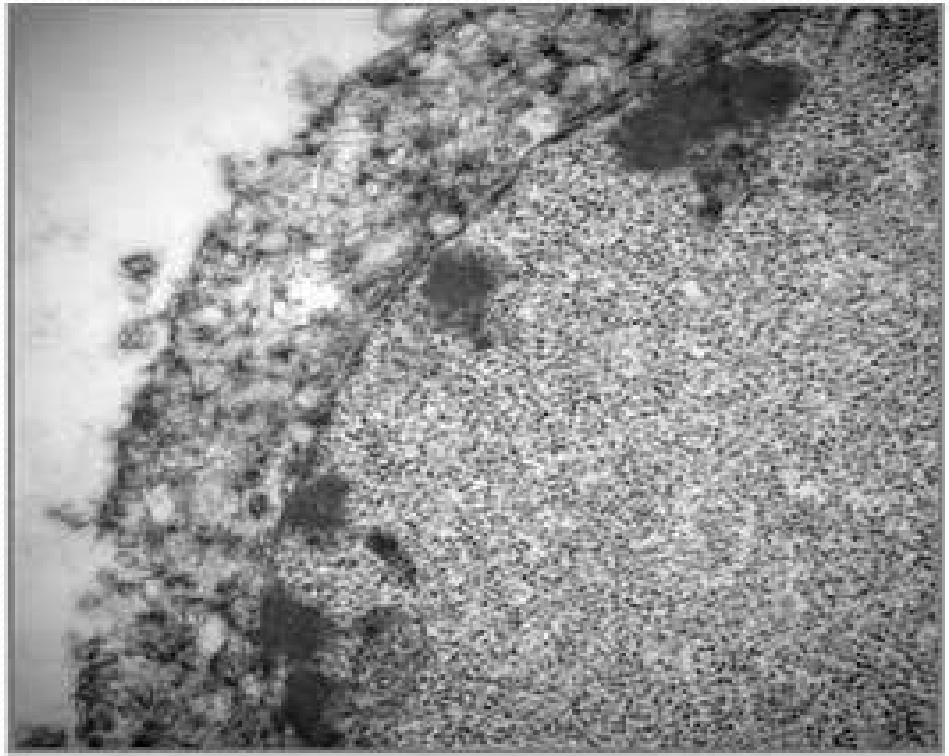
Decoy cells are seen with three methods:

- Papanicolaou stains
- Electron microscopy
- Phase contrast microscopy









Current screening guidelines (KDIGO)

- Screen all kidney transplant patients for BKV using quantitative PCR of serum or plasma samples at the following time points:
  - Monthly for the first 3–6 months after transplantation, then every 3 months until the end of the first post-transplantation year.

- In addition, patients should undergo PCR-based screening for BKV every time an unexplained rise in serum creatinine occurs, and after treatment for acute rejection.

- ***Screening test:*** Decoy cells in urine, Urine DNA-PCR for BKV, EM for BKV in urine.

Histology of BKVAN

- Renal biopsy is the gold standard in the diagnosis of BKVAN.
- “Skip lesions” can cause false negative results (up to 36.5%) and therefore two cores containing medullary tissue should be examined.

Table 2. Histologic patterns of BKV nephropathy

Histologic Pattern	Biopsy Findings	Outcome (ESRD)[a]	Differential
A	Intranuclear viral inclusions Minimal inflammation tubular cell necrosis fibrosis	13%	Normal Coexisting diagnosis
B	Intranuclear viral inclusions Moderate to severe interstitial inflammation Tubular cell necrosis Minimal tubular atrophy and fibrosis	55%	Interstitial nephritis Acute tubular necrosis Acute rejection
C	Intranuclear viral inclusions Moderate to severe tubular atrophy and fibrosis	100%	Chronic allograft nephropathy

Outcome of BKVAN

- Approximately 40–60% of renal grafts with BKVN develop progressive graft loss.

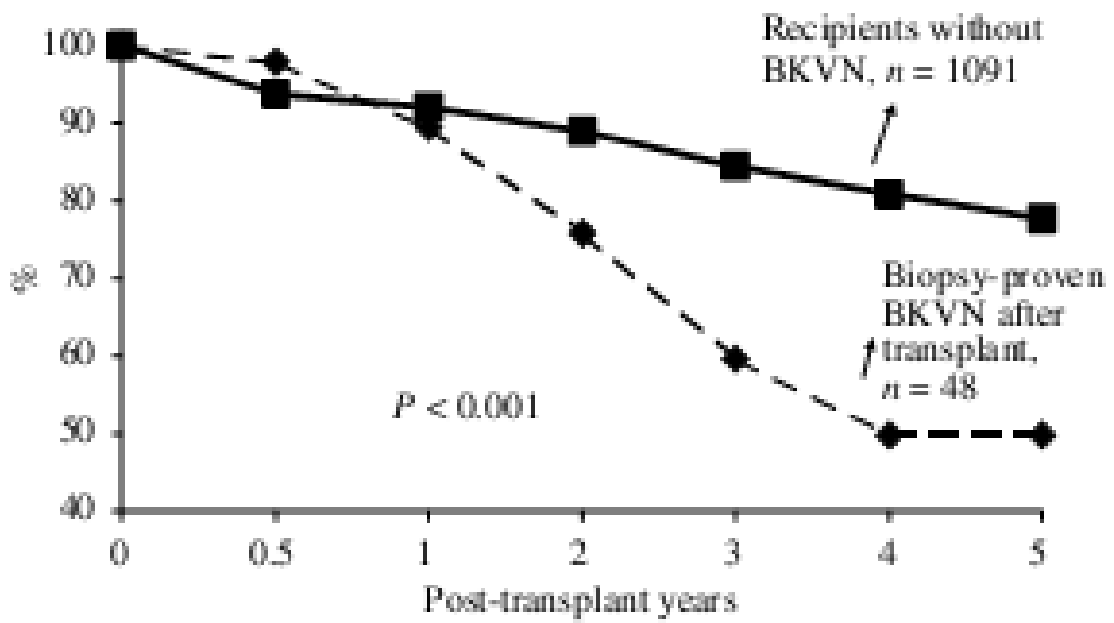
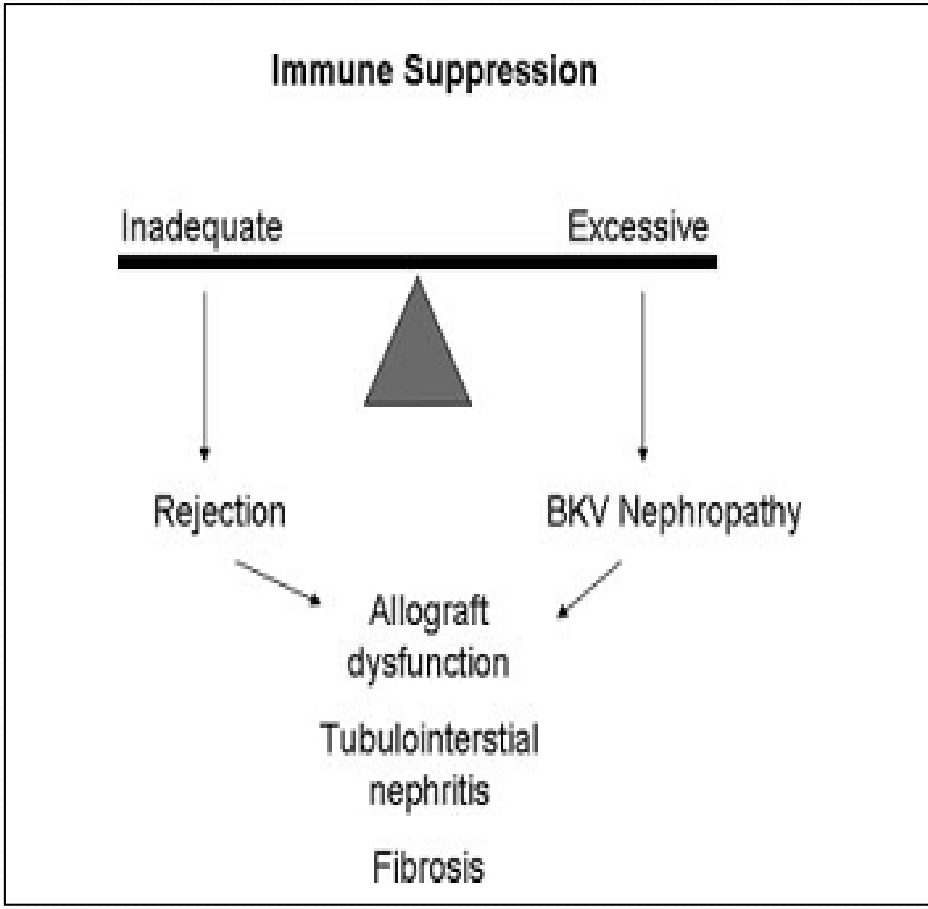


Figure 3 | Lower actuarial graft survival rates in patients with BKVN – results from the Medical College of Wisconsin 1996–2004.

Treatment of BKVAN

Reduction of immunosuppression

- The most important component of management of BKVAN is a decrease in immunosuppression.
- Most centers withdraw the anti-metabolite and decrease Calcineurin inhibitors to the lowest possible dose.



Adjunctive therapies

- ***Quinolone antibiotics***: may have anti-BK virus properties by inhibiting DNA topoisomerase activity and SV40 large T antigen helicase.

- ***IVIG:*** in doses of 500mg/kg have been used. The additional advantage of IVIG is that it is also used for Rx of rejection.

Adjunctive therapies

- ***Leflunomide:*** is a prodrug whose anti-metabolite, A77 1726, has both immunosuppressive and anti-viral activity.
  - Dosage: 100mg/d X 5 days followed by 20–60 mg daily, with a target trough blood level of 50–100 mg/ml

- ***Cidofovir:*** a nucleotide analogue of cytosine that is active against various DNA viruses.
  - Dosage: 0.25-0.33mg/kg/dose X 1-3 doses every 2-3 weeks
  - Problem with cidofovir is that it is nephrotoxic.

Retransplantation after BKVAN

- Retransplantation remains a viable option for patients developing graft loss after BKVAN.
- In a review in 2005, BKVAN recurred in 15% of retransplantations compared with 5% of primary transplantations
- Dharnidharka et al. showed that the outcome in 126 re-Txs was almost similar to controls without BKVAN with respect to outcomes as well as immunosuppression.

Take home message

- BKV infection is very common and this limits the improvement in transplantation outcomes.
- Screening and early detection of infection is necessary to initiate pre-emptive measures.
- Reduction of immunosuppression remains the only validated measures for treatment.
- This approach is tricky due to the risk of rejection.

CMV

- Belong to the betaherpesvirus subfamily of herpesviruses
- double stranded DNA enveloped virus
- Nucleocapsid 105nm in diameter, 162 capsomers

- 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 Manifestations

- 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

HIV

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