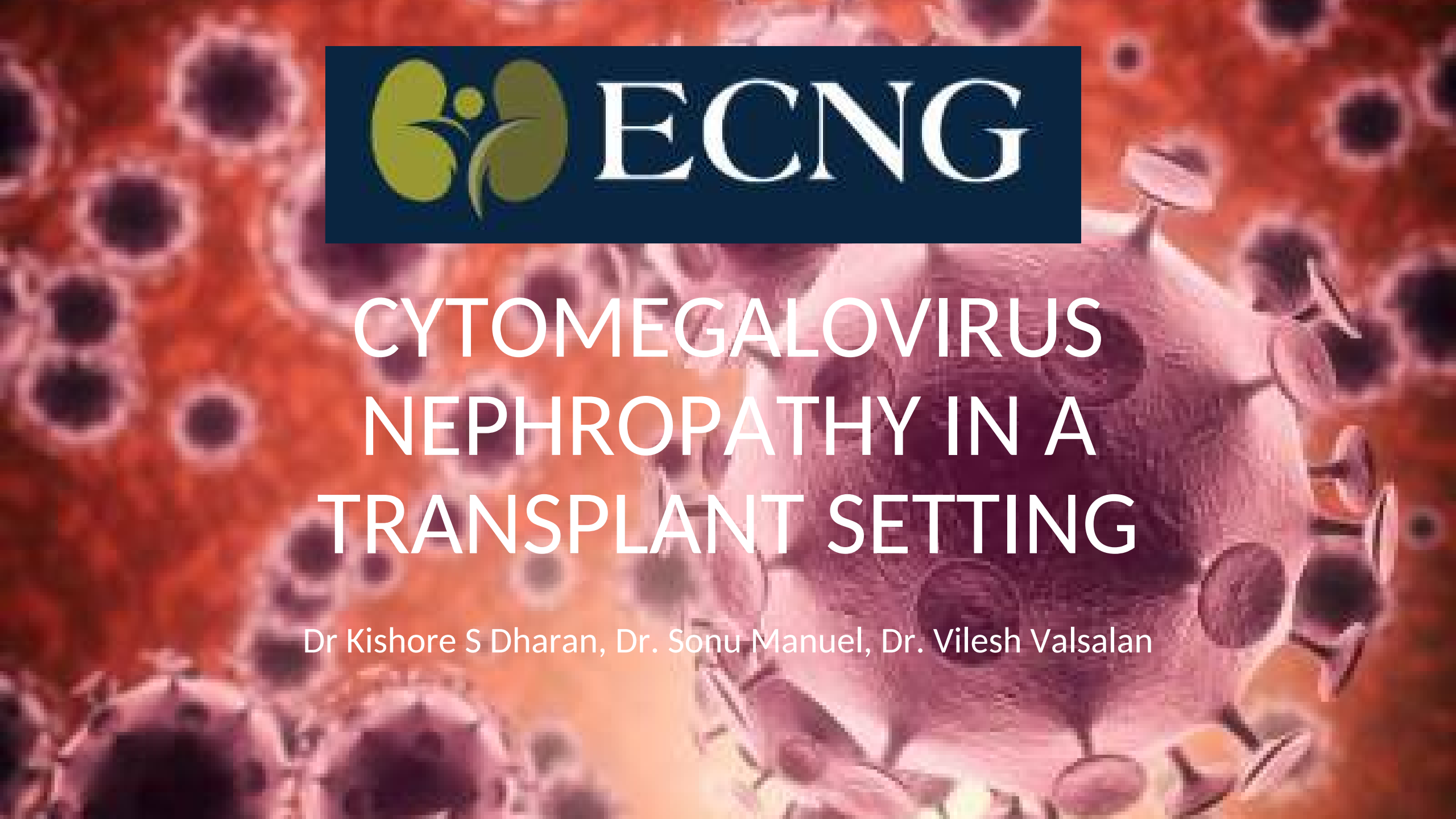

CYTOMEGALOVIRUS NEPHROPATHY IN A TRANSPLANT SETTING

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Overview of Cytomegalovirus (CMV) in Transplantation

- **The Pathogen**
  - β-Herpes virus with the largest genome in the herpes family[1111].
  - Double-stranded linear DNA virus that replicates only in human cells[2].
- **Clinical Spectrum**
  - **CMV Syndrome:** Viral replication + constitutional symptoms (fever, malaise, leukopenia) without tissue invasion [3].
  - **Tissue-Invasive Disease:** Evidence of end-organ damage (e.g., Nephritis, Colitis, Pneumonitis, Retinitis) [4].
- **Indirect Effects**
  - Increased risk of bacterial/fungal infections and Post-Transplant Lymphoproliferative Disorder (PTLD) [5].
  - Associated with cardiovascular events and new-onset diabetes [6].

Epidemiology & Risk Stratification for CMV Nephritis

- **Prevalence**
  - Rare complication: Identified in ~0.2% of kidney transplant biopsies.
  - Typical Onset: 1–7 months post-transplant.
- **High-Risk Factors**
  - **Serology:** Donor Positive / Recipient Negative (D+/R-) is the highest risk group.
  - **Immunosuppression:**
    - Induction with Antithymocyte Globulin (ATG).
    - Maintenance with Mycophenolate Mofetil (MMF).
  - **Clinical History:** Sepsis, neutropenia, and previous acute rejection episodes.

Diagnosis: The Gold Standard

- **Laboratory Testing**
  - **PCR (Quantitative NAT):** First-line systemic test. High viral load supports diagnosis but is *not* confirmatory for nephritis .
- **Renal Biopsy (Gold Standard)**
  - **Pathognomonic Feature:** "Owl’s eye" intranuclear and intracytoplasmic viral inclusion bodies.
  - **Location:** Primarily tubular epithelial cells; occasionally endothelial cells or podocytes.
  - **Histological Pattern:**
    - Patchy lymphoplasmacytic infiltrate with tubulitis.
    - Cytopathic changes: Enlarged tubular epithelial cells with enlarged nuclei.
    - Most common lesion: Tubulointerstitial nephritis

Differential Diagnosis: CMV vs. Acute Rejection

- **The Diagnostic Challenge**
  - CMV triggers acute cellular rejection (ACR) via HLA upregulation and innate immune activation .
  - Differentiation is critical as treatments are opposing (reducing IS for CMV vs. increasing IS for Rejection).
- **Histological Clues**
  - **Favoring CMV Nephritis:** Viral inclusions, plasma cell-rich infiltrate, focal necrosis, patchy inflammation .
  - **Favoring Acute Cellular Rejection:** Moderate to severe tubulitis (without inclusions), Endothelitis, Arteritis (Banff v-lesions) .
- **Co-Infection:**
  - Polyomavirus (BK Virus) can coexist and may induce CMV gene expression .

Antiviral Management Strategies

- **First-Line Therapy**
  - **IV Ganciclovir:** 5 mg/kg every 12 hours. Preferred for severe illness or high viral loads.
  - **Oral Valganciclovir:** Equally effective as IV ganciclovir for solid organ transplants; well-tolerated .
- **Second-Line / Alternative Agents**
  - **Foscarnet:** For resistant strains; highly nephrotoxic (requires hydration).
  - **Maribavir:** Oral agent inhibiting UL97; no kidney toxicity .
  - **Cidofovir:** Nephrotoxic; usually last-line.
- **Duration of Therapy**
  - Treat until symptoms resolve AND two consecutive PCRs (1 week apart) are undetectable .
  - Typical minimum duration: 21 days

Immunosuppression & Drug Resistance

- **Modifying Immunosuppression**
  - **Strategy:** Stop or reduce antimetabolites (Mycophenolate) depending on severity/drug levels [31].
  - **mTOR Inhibitors:** Switching to mTORs (e.g., everolimus) reduces CMV incidence due to improved T-cell functionality [32].
- **Genotypic Resistance Testing**
  - **Indications:** Persistent viremia $\ge$ 2 weeks despite therapy, rising viral load, or breakthrough disease on prophylaxis [33].
  - **Resistance Profiles:**
    - **UL97 Mutation:** Ganciclovir resistance $\rightarrow$ Switch to Foscarnet or Maribavir [34].
    - **UL54 Mutation:** DNA Polymerase mutation; may confer multi-drug resistance $\rightarrow$ Foscarnet or combination therapy [35].

Summarising..

- CMV nephritis is a rare but significant complication, with profound implications on allograft function and outcomes
- CMV nephritis can coexist with rejection/ other viral infections and can be a diagnostic dilemma
- Early identification and treatment is imperative in ensuring graft survival

Thank You