ENDOTHELIAL INJURY AND OUTCOMES IN SIROLIMUS-BASED GVHD PROPHYLAXIS: A SYSTEMATIC REVIEW

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Introduction

- Sirolimus widely used for **GVHD prophylaxis** in allo-HSCT due to immunosuppressive and antiproliferative effects.
- Concern for **endothelial injury**: thrombotic microangiopathy (TMA), sinusoidal obstruction syndrome (SOS).
- Incidence and impact on **outcomes, GVHD, and survival** remain unclear

Aim

To systematically evaluate the **incidence of endothelial injury** and **transplant outcomes** in patients receiving sirolimus-based GVHD prophylaxis.

Objectives

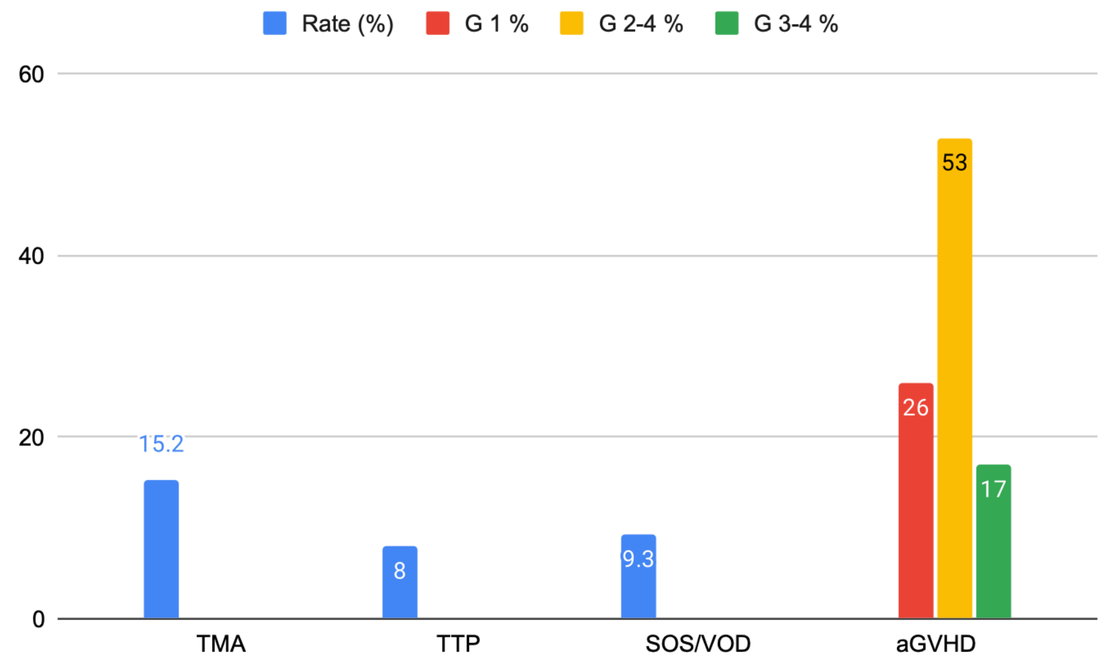
- Assess rates of **TMA, SOS/VOD, TTP** in sirolimus-based regimens.
- Evaluate **GVHD grade distribution** and **infection rates**.
- Review **non-relapse mortality (NRM)** and **disease-free survival (DFS)** in this setting.

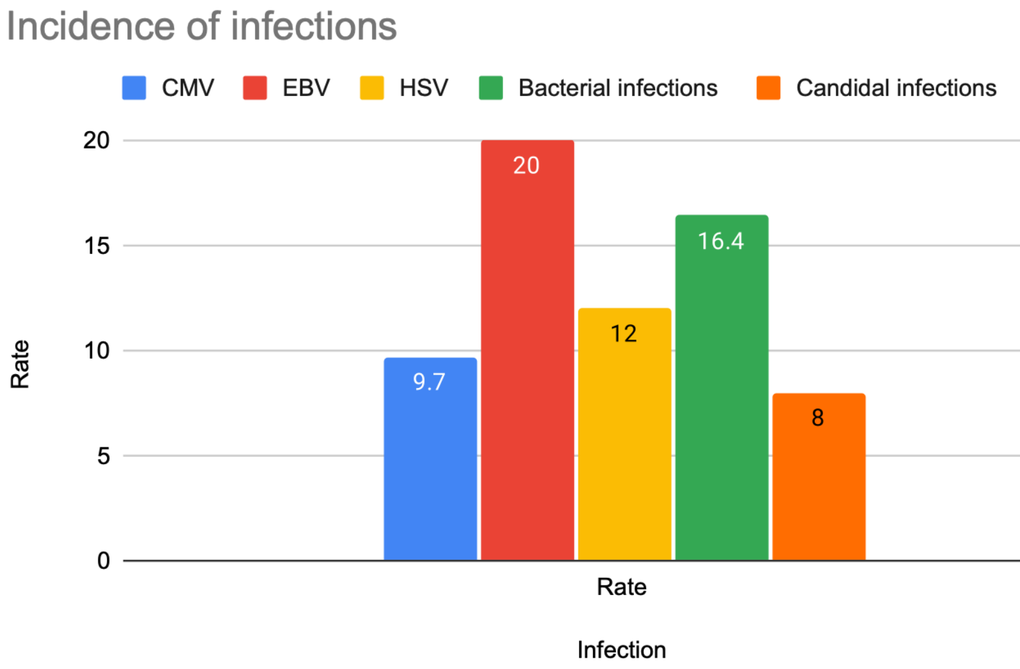
Methods

- Systematic review following **PRISMA guidelines**.
- Databases: **PubMed, Embase, Cochrane** up to March 2025.
- Total screened: 3,991 → **7 studies** (2 RCTs, 5 observational) → **641 patients**.
- Data extracted: demographics, endothelial complications, GVHD grades, sirolimus levels, survival, infections, conditioning, prophylaxis regimen.

Results

- **Patients:** 641; median age 43 (18–72); 57.6% male.
- **Endothelial injury:**
  - TMA: 49/322 (15.2%), median onset day 40.
  - TTP: 2/25 (8%).
  - SOS/VOD: 47/505 (9.3%).
- **Sirolimus levels** (n=111): median 6.1 ng/mL (target 3–12).
- **GVHD (n=334):**
  - Grade 1: 26%
  - Grades 2–4: 53%
  - Grades 3–4: 17%
- **NRM:**
  - 100 days: 3.9%
  - 1 year: 19.6%
  - 2 years: 68.6%
  - 4 years: 27.4%*
- **DFS:** 88% at 2 years; 11% at 4 years (n=125).
- **Infections:** CMV 9.7%, EBV 20%, HSV 12%, bacterial 16.4%, Candida 8%.
- **Most common diagnoses:** AML (137), AML/MDS (85), MDS (47), NHL (48), ALL (36).
- **Conditioning regimens:** Cy/TBI (272), Bu/Flu (103), Flu/Mel (85), Flu-Bu-TT (50).
- **GVHD prophylaxis combos:** Tac + Siro (322), Tac + Siro + MTX (247), Tac + Siro + ATG (25), others (47).





Summary

- Sirolimus-based prophylaxis associated with **notable endothelial injury (≈15% TMA; 9% SOS)**.
- Early outcomes favorable, but **late NRM and infections increase**.
- **High DFS early**, but sharp decline at 4 years.
- Close monitoring of **sirolimus levels** and **patient selection** critical.

Discussion

- Sirolimus improves GVHD control but may contribute to **microvascular toxicity**.
- Need for **risk stratification tools** to identify high-risk patients.
- Potential benefit in **early survival** but offset by long-term complications.
- Supports integration of **therapeutic drug monitoring and endothelial biomarkers** in allo-HSCT.

References

1. https://doi.org/10.1016/j.jtct.2023.11.010 (https://www.sciencedirect.com/science/article/pii/S2666636723016779)

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