MESENCHYMAL CELL THERAPY (MSC) IN REFRACTORY GI- GVHD IN PEDITRIC HSCT .

CASE PRESENTATION

Bibi Shahin Shamsian. MD

HSCT, ALLO HSCT

- Allogeneic hematopoietic stem cell transplantation (HSCT) ; a potential cure for various diseases, including hematological and non-hematological diseases.
- Despite significant **advances** in transplantation technologies, **including high-resolution HLA typing and the advancement of immunosuppressive medications, supportive care**

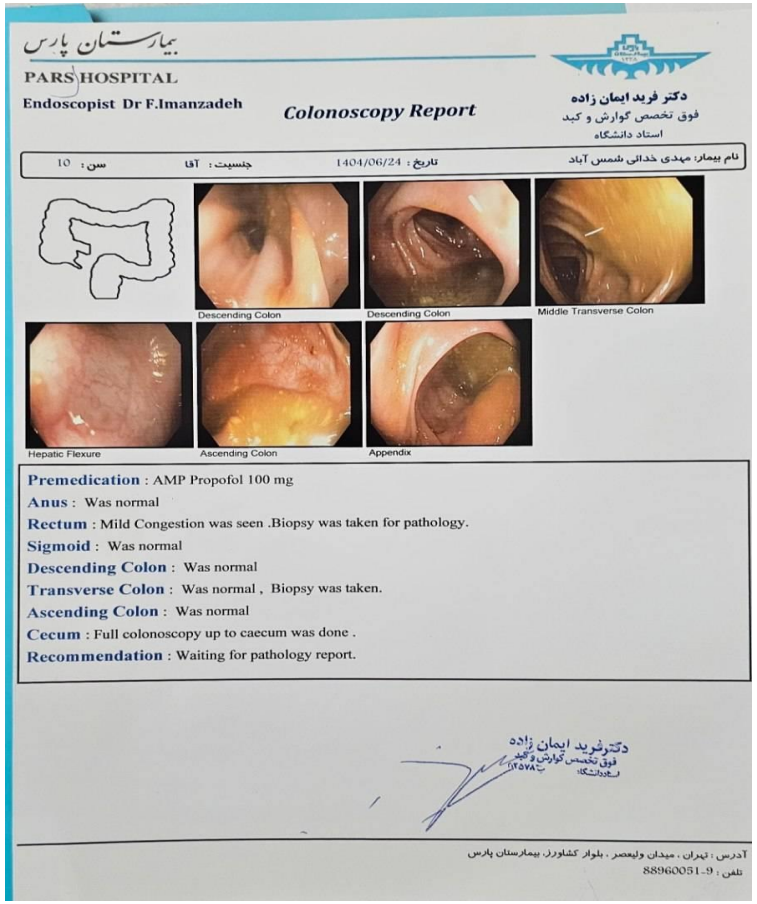
Complications in HSCT : Morbidity and mortality

- **Infections**
- **Disease relapse**
- **Graft rejection**
- **Acute or chronic graft-versus-host disease (GvHD)**

Case presentation

- A 9 y old male , 20 kg , 4th children, sibling healthy , first causin parents
- CC: Neutropenia, Anemia , Mild IBD , Nl report of endoscopy , Vitiligo, also vitiligo in grand father , (IVIg & CS , No response to GCSF)
- NGS : kabuki syndrome, PID
- 11/ 1404 ALLO HSCT : Grand Father , PB , MRD, Full match 10/10
- CR - RIC : Flu , Mel ,R- ATG GVHD:Cyclsopurine + MMF
- Engraf day + 15 Chime; full donor x 3 times 100%
- Day + 20- 25 : GVHD skin stage 2-3 and, GI GVHD stage IV(abdo pain- bloody diarrhea ,massive gI bleeding several times .
- Treat : supportive care , CS -methyl 2mg / kg/ day , methyl pulse , Cyclospurine , Ruxolitinb , IVIG , Infliximab x 3….. , MSCx 4
- CMV pos :F oscarnet and gancyclovirr
- Still h is on IS therapy ,now day + > 100 post HSCT , CMV neg

Endoscopy report 1 PRE HSCT



بیمارستان پارس

PARS HOSPITAL

Endoscopist Dr F.Imanzadeh

Colonoscopy Report

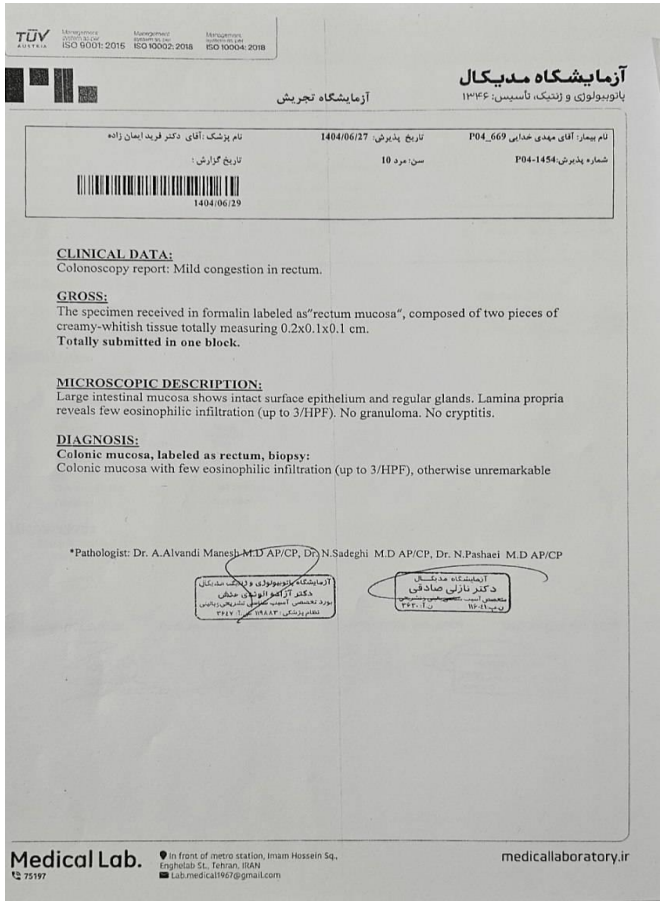
دکتر فرید ایمان زاده
فوق تخصص گوارش و کبد
استاد دانشگاه

نام بیمار: مهدی خدائی شمس آباد | تاریخ: 1404/06/24 | جنسیت: آقا | سن: 10

Premedication : AMP Propofol 100 mg
Anus : Was normal
Rectum : Mild Congestion was seen .Biopsy was taken for pathology.
Sigmoid : Was normal
Descending Colon : Was normal
Transverse Colon : Was normal , Biopsy was taken.
Ascending Colon : Was normal
Cecum : Full colonoscopy up to caecum was done .
Recommendation : Waiting for pathology report.

دکترفرید ایمان زاده
فوق تخصص گوارش و کبد
۱۲۵۷۸

آدرس : تهران ، میدان ولیعصر ، بلوار کشاورز، بیمارستان پارس
تلفن : 88960051-9



TÜV AUSTRIA ISO 9001:2015 ISO 10002:2018 ISO 10004:2018

آزمایشگاه پاتوبیولوژی و ژنتیک، تاسیس: ۱۳۹۴

آزمایشگاه مدیکال

آزمایشگاه تجزیه

نام بیمار: آقای مهدی خدایی P04_669 | تاریخ پذیرش: 1404/06/27 | نام پزشک: آقای دکتر فرید ایمان زاده
شماره پذیرش: P04-1454 | سن/مرد 10 | تاریخ گزارش:
1404/06/29

CLINICAL DATA:
Colonoscopy report: Mild congestion in rectum.

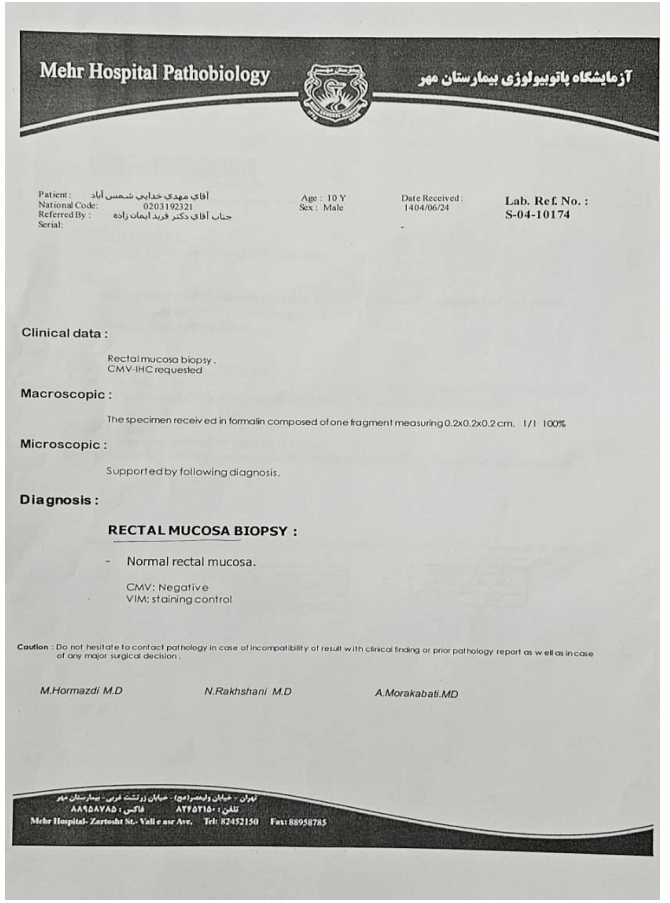
GROSS:
The specimen received in formalin labeled as"rectum mucosa", composed of two pieces of creamy-whitish tissue totally measuring 0.2x0.1x0.1 cm.
Totally submitted in one block.

MICROSCOPIC DESCRIPTION:
Large intestinal mucosa shows intact surface epithelium and regular glands. Lamina propria reveals few eosinophilic infiltration (up to 3/HPF). No granuloma. No cryptitis.

DIAGNOSIS:
Colonic mucosa, labeled as rectum, biopsy:
Colonic mucosa with few eosinophilic infiltration (up to 3/HPF), otherwise unremarkable

*Pathologist: Dr. A.Alvandi Manesh M.D AP/CP, Dr. N.Sadeghi M.D AP/CP, Dr. N.Pashaei M.D AP/CP

Medical Lab. 75197 | In front of metro station, Imam Hossein Sq., Enghelab St., Tehran, IRAN | Lab.medical1967@gmail.com | medicallaboratory.ir



Mehr Hospital Pathobiology

آزمایشگاه پاتوبیولوژی بیمارستان مهر

Patient : آقای مهدی خدایی شمس آباد | Age : 10 Y | Date Received : 1404/06/24 | Lab. Ref. No. : S-04-10174
National Code: 0203192321 | Sex : Male
Referred By : جناب آقای دکتر فرید ایمان زاده
Serial:

Clinical data :
Rectal mucosa biopsy .
CMV-IHC requested

Macroscopic :
The specimen received in formalin composed of one fragment measuring 0.2x0.2x0.2 cm. 1/1 100%

Microscopic :
Supported by following diagnosis.

Diagnosis :

RECTAL MUCOSA BIOPSY :

- Normal rectal mucosa.

CMV: Negative
VIM: staining control

Caution : Do not hesitate to contact pathology in case of incompatibility of result with clinical finding or prior pathology report as well as in case of any major surgical decision .

M.Hormazdi M.D *N.Rakhshani M.D* *A.Morakabati.MD*

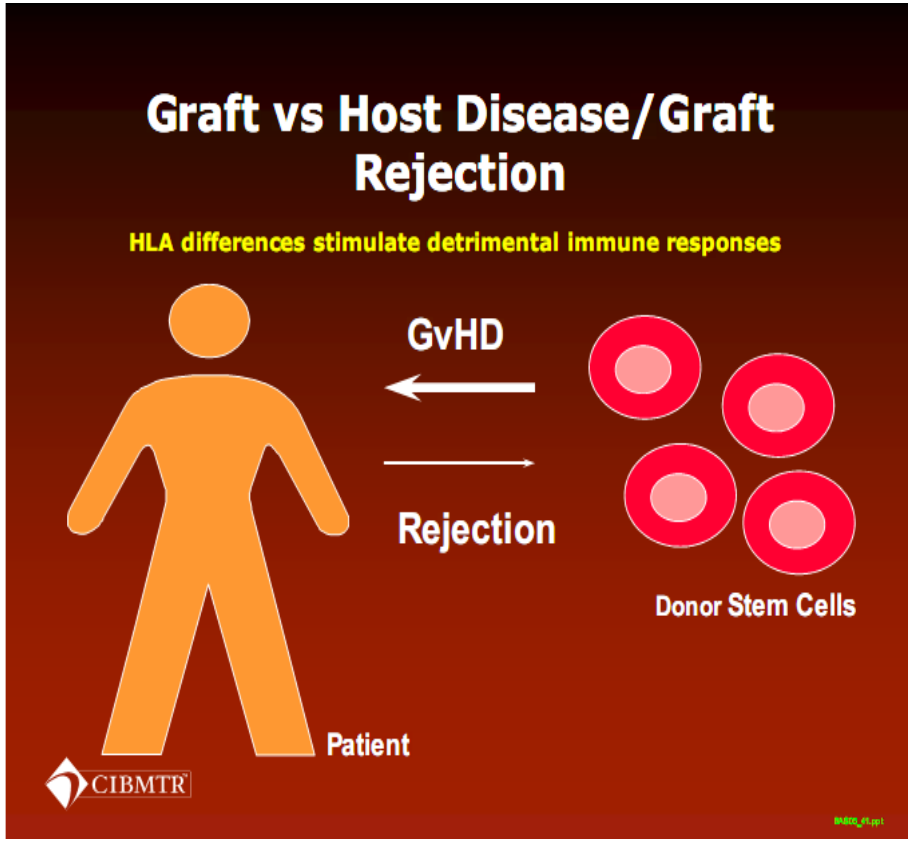
تهران - خیابان ولیعصر(عج) - خیابان زرتشت غربی - بیمارستان مهر
تلفن : ۸۲۴۵۲۱۵۰ فاکس : ۸۸۹۵۸۷۸۵
Mehr Hospital- Zartosht St.- Vali e asr Ave. Tel: 82452150 Fax: 88958785

GVHD & Allo HSCT

- **GVHD :** Systemic inflammation arises from donor lymphocytes within the transplanted tissue recognizing the recipient as foreign.

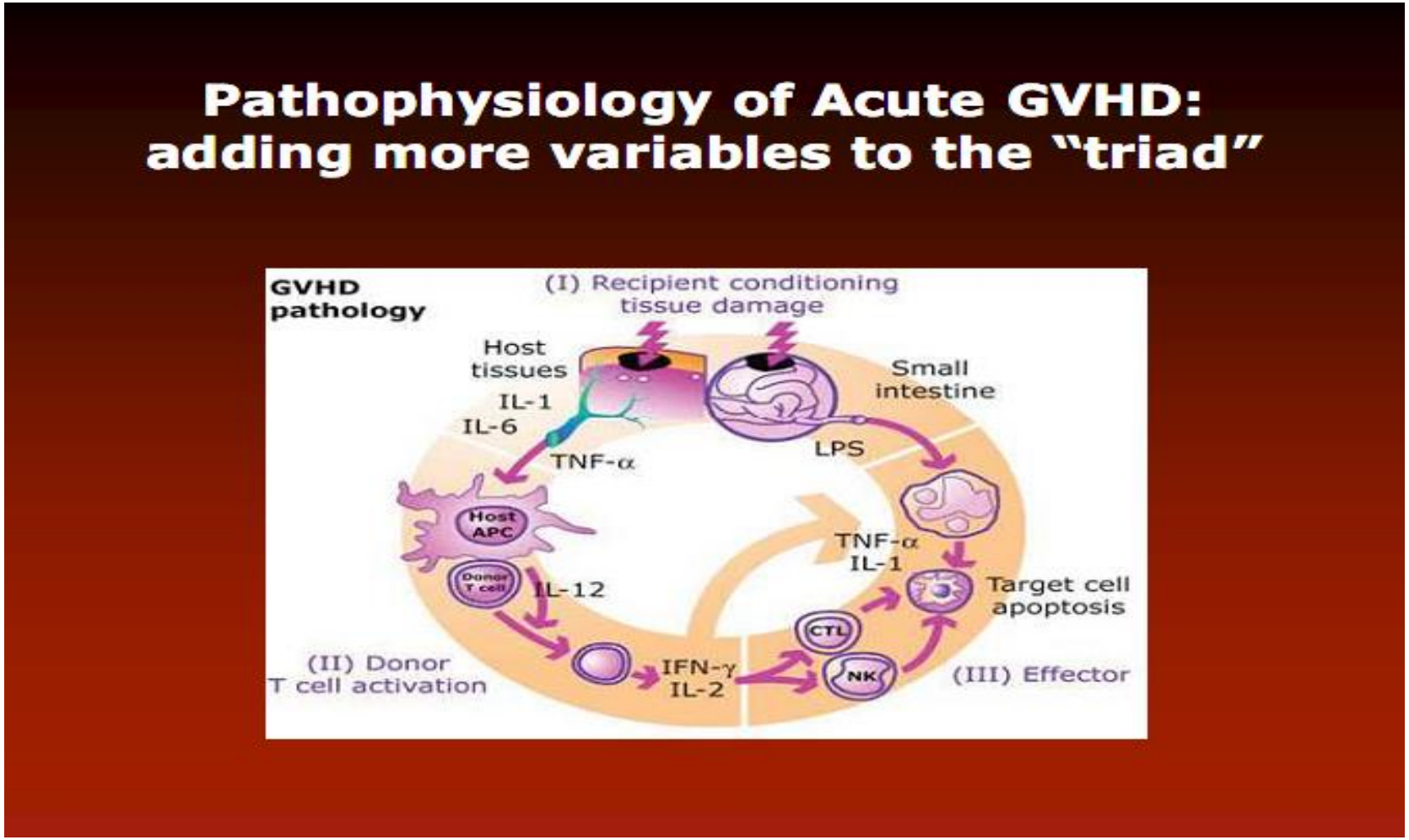
- **GVHD:** Triggers an immune response where activated T cells strive to eliminate antigen-carrying cells in the host, leading to severe organ damage.

GVHD: Graft Versus Host Disease



- Damaged host tissue→ cytokines (TNFα, IL1)→ stimulate APCs→ recognition of host Ag by donor T cell
- Donor T cell activated→ cytokines (IFNγ, IL2)→ induce CTL, NKC, phagocytes
- Phagocytes release more cytokines→ cell lysis/apoptosis→ tissue destruction

Pathophysiology Of GVHD

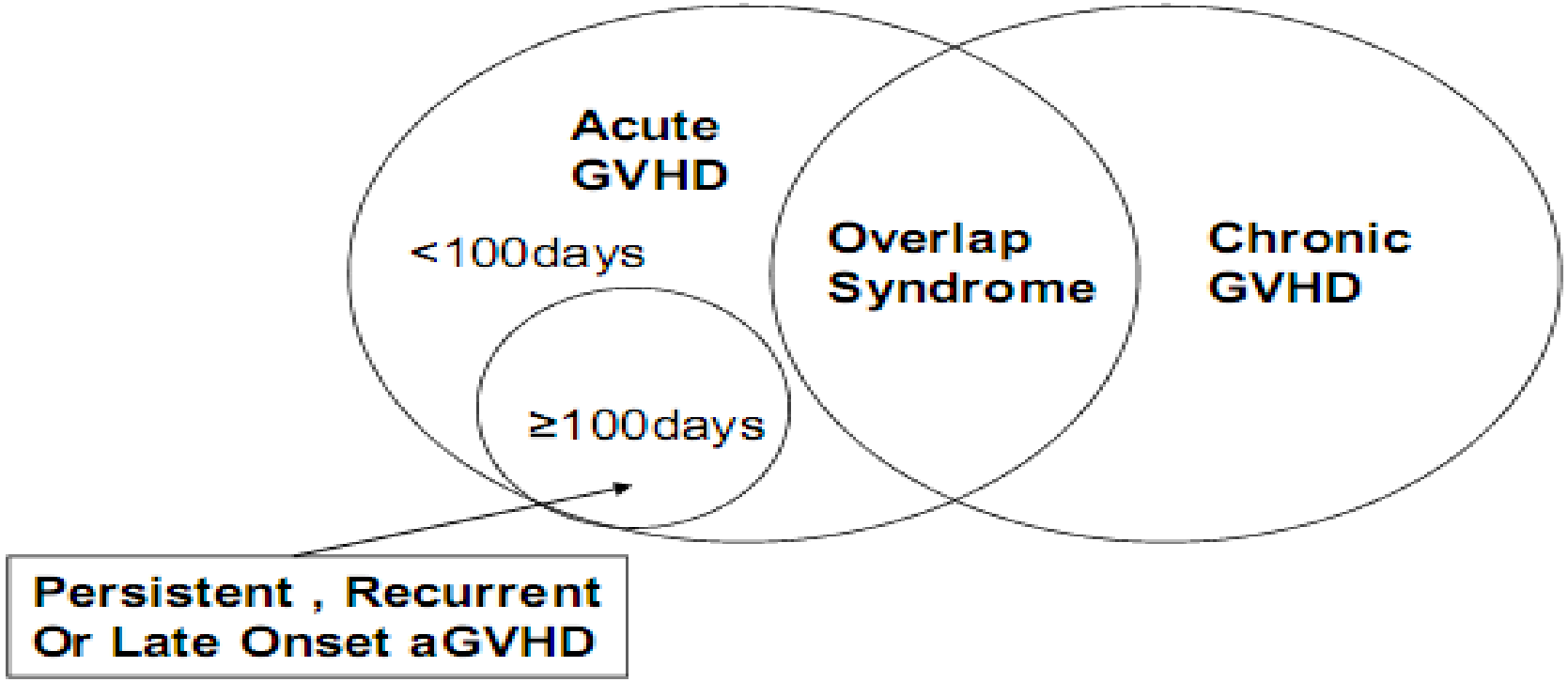


GVHD & Allo HSCT

- GVHD : classified into acute or chronic forms
- Taditionally distinguished by the onset time; if it occurs within the first 100 days, acute GvHD
- Nevertheless, acute GvHD can extend beyond the first 100 days, leading to an overlap between the **acute and chronic syndromes**
- **Graft-versus-host disease (GVHD)** is a multisystemic, inflammatory and/or fibrotic disease significantly contributing to **morbidity and non-relapse mortality**

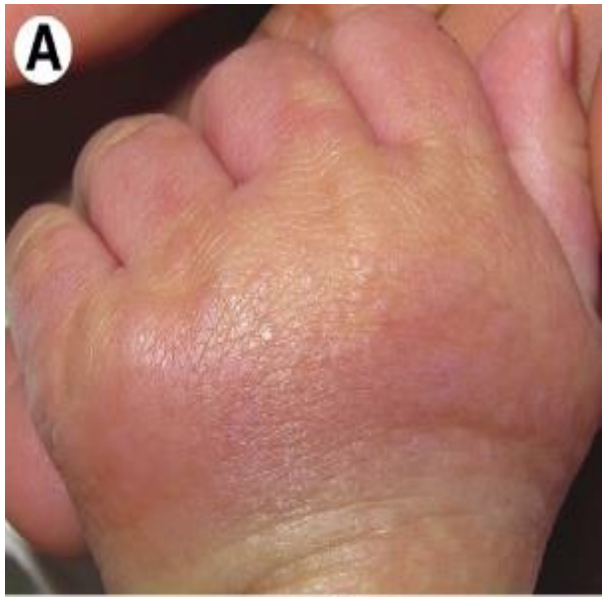
Classification: NIH Consensus

(DR Alexandara Fillipovich)

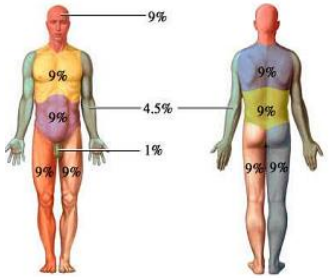


ACUTE GVHD

- **Classic acute GVHD (aGVHD)** is a reaction of transplanted donor immune effector cells against epithelial structures of the host
- Targeted organs ; **skin**, the **lower and upper gastrointestinal tract** and **the liver,**
- **S**igns and symptoms such as erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic liver disease
- **Acute GVHD is one of the most frequent complications of allo-HSCT and is associated with delayed recovery and complicated post-transplant courses, particularly in patients who do not respond to first-line treatment with steroids**

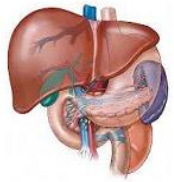


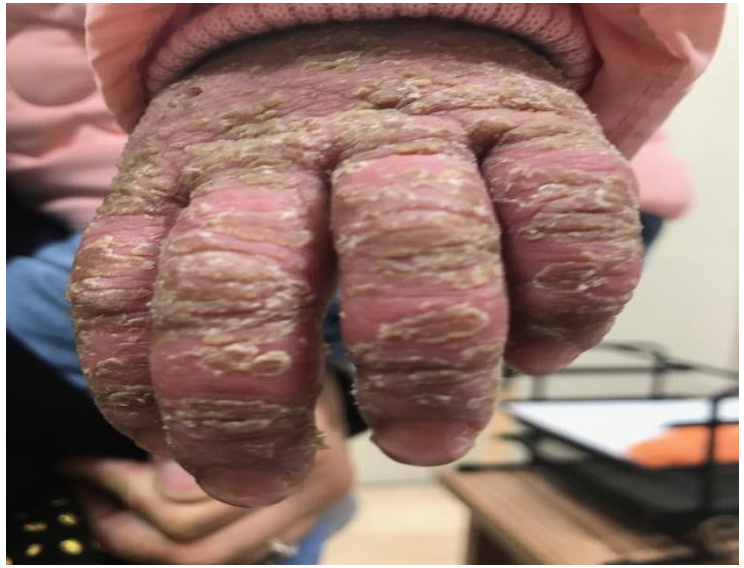
Skin: Rule of 9's

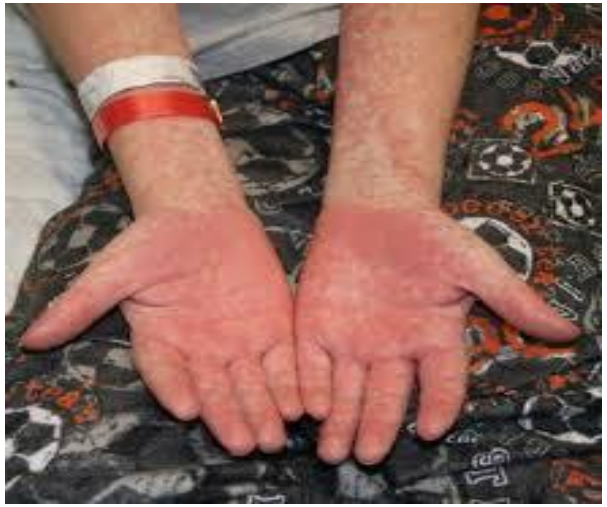


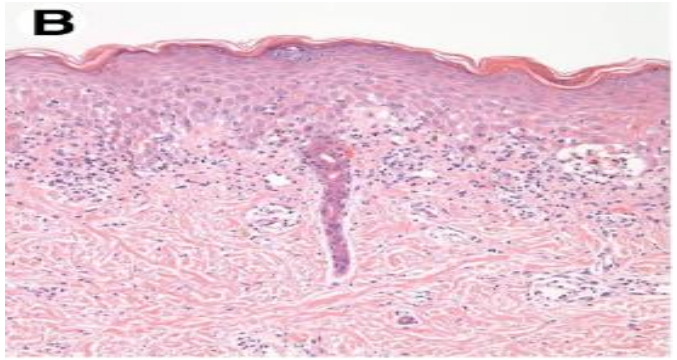
GI: stool volume/24hrs

Liver: Bilirubin









Improving- Skin GVHD after Treatment

Pathogenesis - Chronic GVHD:
3 Main Mechanisms /cGVHD

Inflamation , Immune dysregulation & Fibrosis

- T-cell allo-reactivity directed against recipient antigens.
- T-cell auto-reactivity & B-cell dys regulation.
- Skin, Ocular , Gastrointestinal, Hepatic , Lung
- **Most : Skin , Eye , Oral**

Report Of GI - GVHD

- Acute GVHD can involve the skin, the liver, and the upper and lower intestinal trac
- **Chronic GVHd : every organ especially : Skin , eye , oral ….**
- Risk factors of cGVHD **: Grades II–IV aGVHD, PB grafts ,R age ≥12 y.**
- **cGVHD children, (GIT) ;39%, skin ;62%, liver in 27%**
- study / 173 cGVHD children ; 28% liver , **24% GI involvement**
- **GI involvement in GVHD ; Optimal diagnostic approach, in particular, the place of endoscopy to improve the diagnostic yield.GI symptoms DD ,Operative risks, such as duodenal Hematoma, high anaesthetic risks, thus, endoscopy indication should be carefully assessed.**

Acute- GVHD Staging

Stage	Skin	Liver	Upper GIT	Lower GIT
0	No active rash	Total bilirubin <34 µmol/L	No/intermittent nausea, vomiting or anorexia	Stool volume <10 mL/kg/day or <4 episodes/day of diarrhoea
1	Maculopapular rash <25% BSA	Total bilirubin 35–51 µmol/L	Persistent nausea, vomiting or anorexia	Stool volume <20 mL/kg/day or <6 episodes/day of diarrhoea
2	Maculopapular rash 25%–50% BSA	Total bilirubin 52–102 µmol/L		Stool volume <30 mL/kg/day or <10 episodes/day of diarrhoea
3	Maculopapular rash >50% BSA	Total bilirubin 103-255 µmol/l		Stool volume >30 mL/kg/day or >10 episodes/day of diarrhoea
4	Generalized erythroderma + bullous formation and desquamation >5% BSA	Total bilirubin >255 µmol/L		Severe abdominal pain with or without ileus or grossly bloody stool

Abbreviations: BSA, body surface area; GIT, gastrointestinal tract; GVHD, graft versus host disease.

Symptoms Acute & Chronic GVHD

TABLE 1 Symptoms of acute and chronic GVHD.

Acute GVHD		Chronic GVHD	
Skin	Maculopapular rash	Skin	Lichen planus or skin manifestations of scleroderma
Upper GIT tract	Persistent nausea and/or vomiting	GIT tract	Dryness of the oral mucosa
Lower GIT tract	Abdominal pain		Weight loss
	Watery diarrhoea		Ulcerations/fibrosis of the GIT
	Bloody diarrhoea		
	Ileus		
Liver	Elevated bilirubin	Liver	Elevated bilirubin

Abbreviations: GIT, gastrointestinal tract; GVHD, graft versus host disease.

GVHD & Allo HSCT

- Currently Despite the prophylactic use of calcineurin inhibitors & Methotrexate,
- 30–50% of patients undergoing allogeneic HSCT develop acute GvHD
- 30–70% develop chronic GvHD

Risk of GVHD in HSCT

- **Various factors, mainly on the degree of match between donor and recipient, graft type, T cell depletion/ repletion, conditioning regimen, GVHD prophylaxis, & age of the patient/donor**

- Incidence and mortality of aGVHD have decreased during recent years, **aGVHD as a post-transplant complication still occurs in up to 70% of allo-HSCT patients**

First-line treatment in aGVHD

- The starting dose of methylprednisolone is 2 mg/kg/d, or 2-2.5 mg/kg/d prednisone.
- Nonabsorbable oral steroids, like budesonide (9 mg/day) or oral beclomethasone .3–2.0 mg, four times daily) .
- **Around one third 1/3 of paediatric patients require a second-line IS treatment.**
- The addition of immunosuppressants (mycophenolate mofetil, anti-T-cell globulin, infliximab or anti-IL2 antibody) besides steroids

Risk of GVHD in HSCT

- 50% of aGVHD- p; responding to high-dose corticosteroids.
- Response rate in patients with grade IV disease does not exceed 30%
- The outcome for patients who do not respond to corticosteroids (steroid-resistant aGVHD [SRaGVHD]) is poor,Long-term survival ranging ; 5 - 30%

c GVHD Treatment

First-line treatment in cGVHD

According to NIH criteria, decision to start treatment is based on symptom type and severity.

First-line treatment is steroids (1 mg/kg/day orally

Corticosteroid-refractory aGVHD

- Disease progression after 3 days of treatment with methylprednisolone 2 mg/kg per day equivalent,
- Lack of improvement after 7 d of treatment with methylprednisolone 2 mg/kg per day equivalent,
- Progression to a new organ after treatment with methylprednisolone 1 mg/kg per day equivalent for skin and upper gastrointestinal GVHD
- Recurrence during or after a corticosteroid taper

Refractory GVHD treatment

Acute GVHD remains a major challenge in the management of allo-HSCT, particularly for patients with severe SR-aGVHD

No approved therapeutic options :

Therefore RR-aGVHD continues to pose a high unmet medical need

Successful treatment with mesenchymal stromal cells-Frankfurt am Main in a pediatric patient with steroid-refractory and ruxolitinibrefractory acute gastrointestinal graft-versus-host disease Jana Ernst. Annals of Hematology .(2025) 104:4237–4243

- **Second-line treatment for A gvhd**

- **CS**
- **Ruxolitinib ,in 2022, ruxolitinib (JAKAVI®) was approved for the treatment of patients aged 12 years and older with acute or chronic GVHD**

Data about other novel agents used in the pediatric population of aGvHD patients is scarce:

- **Teduglutide, a human recombinant GLP-2 analog,** beneficial as an adjunctive and non-immune suppressive agent for managing GI-aGVHD, due to its tissue protective and regenerative properties
- **Vedolizumab, a novel antiα4β7 integrin monoclonal antibody,** treatment of lower GI aGVHD, but caution for concurrent infections is warranted

Second-line treatment in acute- GI -GVHD

- **There is no consensus on second-line treatment for GI- GVHD.**
- According to the recommendations of the European Society for Blood and Marrow Transplantation:**Second-line treatments include(IS drugs)**
  - Mycophenolate mofetil, Methotrexate and sirolimus
  - Biologics (alemtuzumab, basiliximab, daclizumab,vedolizumab, Janus kinase [JAK] inhibitors) , Infliximab
  - Cell therapy including mesenchymal stromal cells (MSCs)
  - Extracorporeal photopheresis
  - Faecal microbiota transplantation
  - Pentostatin & Anti-thymocyte serum.

Mesenchymal stem cells in GVHD.MSCs" are spindle-shaped, express the cluster of differentiation (CD) markers CD73, CD90, and CD105, lack expression of hematopoietic stem cell markers, and can differentiate into chondroblasts, osteoblasts, and adipocytes under appropriate culture conditions

What are MSCs and their abilities?

- Mesenchymal stem cells, alternatively known as multipotent stromal cells or mesenchymal stromal cells (MSCs)
- postnatal stem cells that can **self-renew and maintain a versatile capacity to differentiate into multiple lineages**, such as osteoblasts, adipocytes, and chondroblasts
- Mesenchymal stem cells typically display **low immunogenicity.**
- They exhibit only moderate levels of major histocompatibility complex I **(MHC) expression and show little to no expression of MHC II antigens and co-stimulatory molecules**

دستروسل- سلول مزانشیمال

- نخستین محصول سلولی آلوژنیک ساخت ایران، با پشتوانه متخصصان شرکت دانش‌بنیان «زیست‌بازساختی تسکین»
- دارو برای بیماران مبتلا به بیماری پیوند علیه میزبان (GVHD) طراحی شده است؛ عارضه‌ای شدید که پس از پیوند مغز استخوان بروز می‌کند.
- منشا : **سلوبها استرومال مشتق از جفت و پرده های جنینی**
- سلول‌های به‌کاررفته در این فرآورده با **کاهش التهاب و تنظیم عملکرد سیستم ایمنی، نقش درمانی** مؤثری ایفا می‌کنند.
- رحالی‌که داروی آمریکایی هر دوز آن حدود 194 هزار دلار قیمت دارد، نسخه تولید داخل تنها با نزدیک به پنج‌هزار دلار عرضه می‌شود.

Mesenchymal stem cells (MSCs)

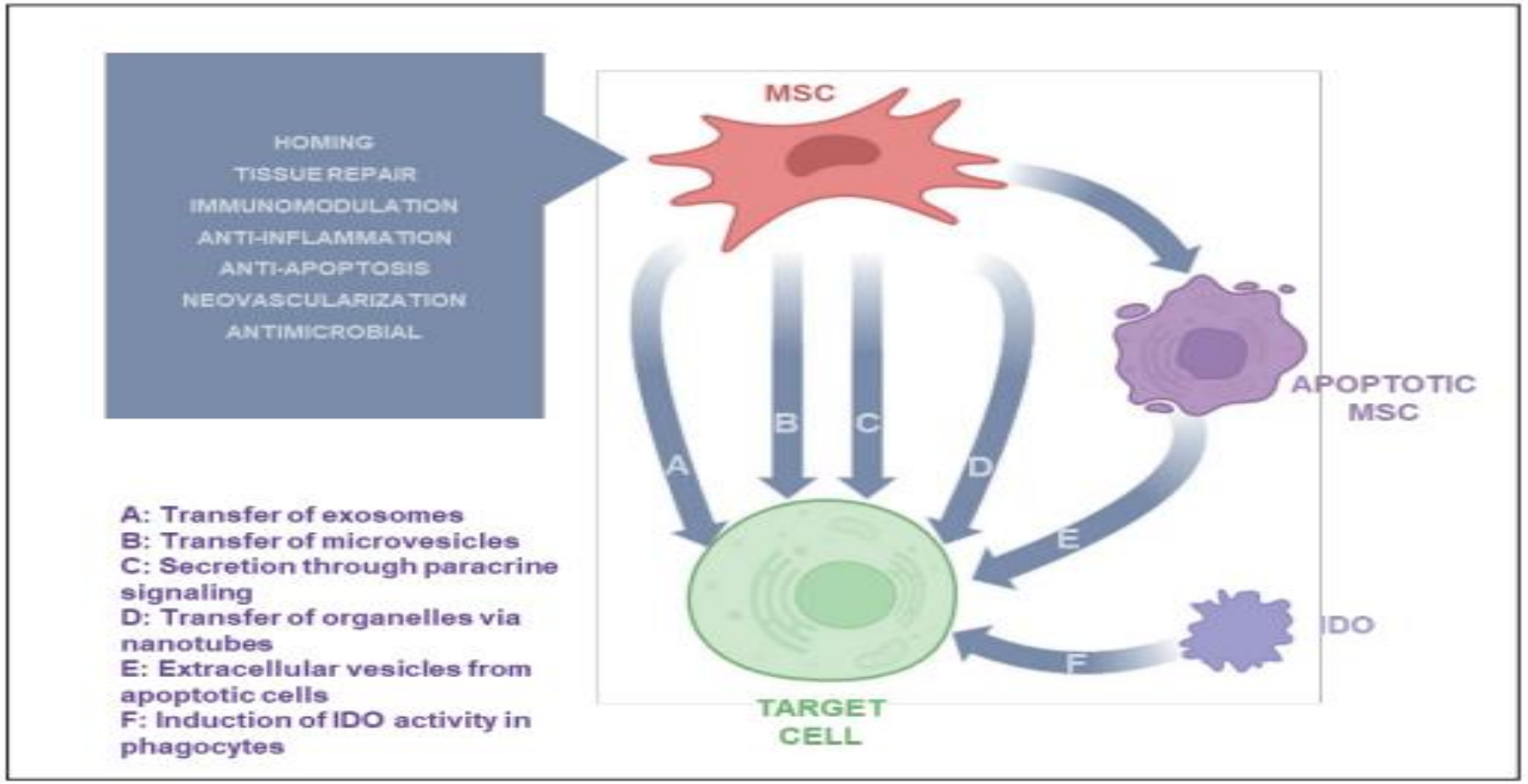
Turkish J Pediatr Dis/Türkiye Çocuk Hast Derg / 2024; 18: 203-210

- (MSCs) are pluripotent stem cells ;derived from various sources like **bone marrow, adipose or placental tissue**
- MSC : immunosuppressive effect on GvHD by inhibiting T cell and natural killer cell proliferation, inhibiting Th17 and B cell differentiation, increasing the number of regulatory T cells, interfering with the maturation of antigen-presenting cells, and increasing the secretion of immunomodulatory molecules , including prostaglandin E2, transforming growth factor-β (TGF-β), Interleukin-10, and heme oxygenase
- **MSC can reduce the incidence of acute GvHD and decrease the severity of both acute and chronic GvHD after HSCT**

Turkish J Pediatr Dis/Türkiye Çocuk Hast Derg / 2024; 18: 203-210

- Homing Capacity
- Anti-Inflammatory effect
- Regulation of the immune system
- Tissue Regeneration
- Neo-angiogenesis
- Antimicrobial Effect
- Suppression of Apoptosis

Properties of MSCs Turkish J Pediatr Dis/Türkiye Çocuk Hast Derg / 2024; 18: 203-210.

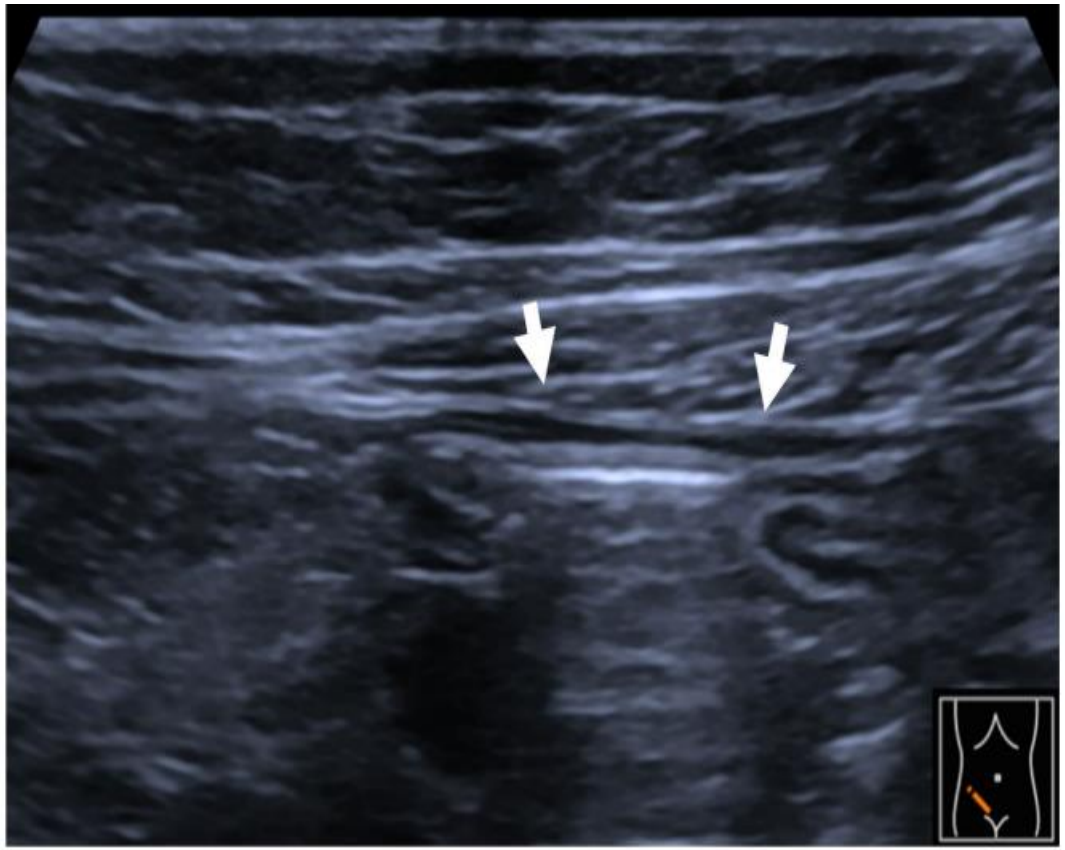


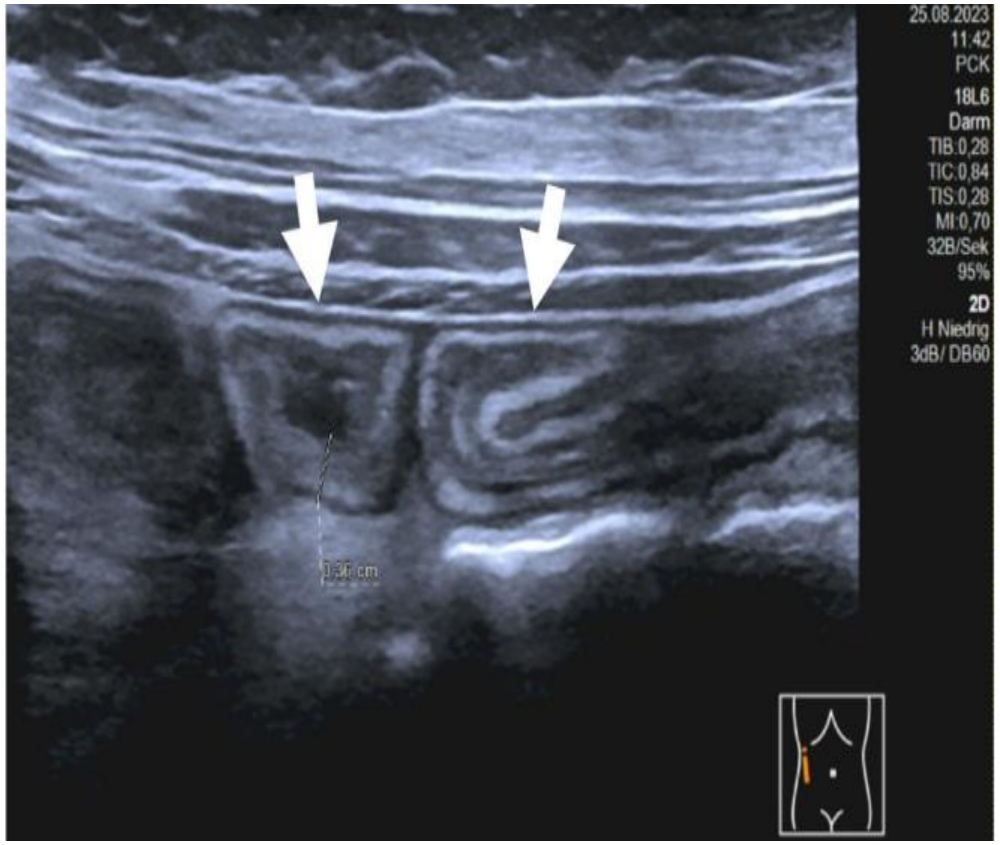
Successful treatment with mesenchymal stromal cells-Frankfurt am Main in a pediatric patient with steroid-refractory and ruxolitinibrefractory acute gastrointestinal graft-versus-host disease. Jana Ernst.Annals of Hematology (2025) 104:4237–4243.Germany.

- **A 12-year-old male ,** HR AML, severe GI aGVHD after allo-HSCT
- Grade IV aGVHD of the intestine : no improvement under **triple IS with CS, cyclosporine A and ruxolitinib.**
- **4 weekly infusions of human allogeneic (MSCFFM),** intestinal inflammation finally improved, as reflected by ameliorated symptoms, normalized intestinal wall thickness (ultrasonography) and decreasing calprotectin levels.
- **Intestinal mucosal healing was further supported by a strict, formula-based modular diet.**

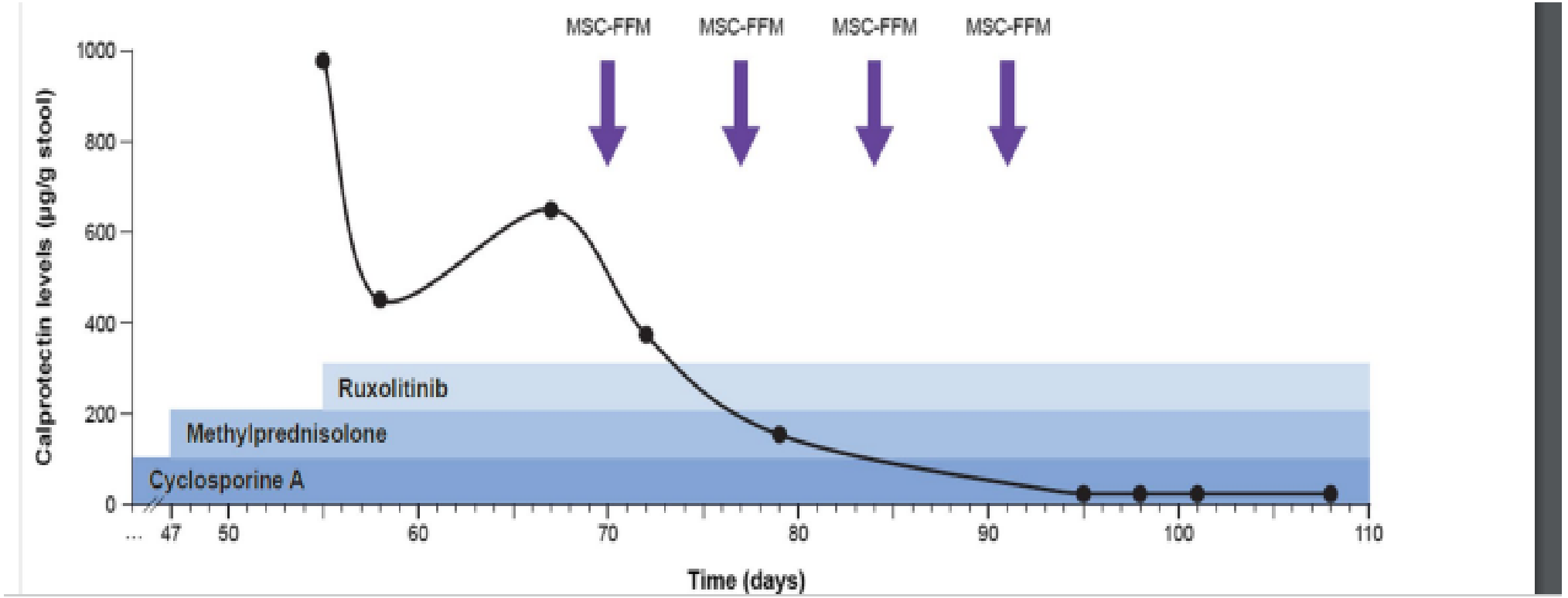
- B-mode image showing blurred bowel and thickened wall structure (arrows) in the right middle abdomen

  B-mode image showing normalized bowel wall structure (arrows) in the right middle abdomen





Calprotectin levels significantly decreased during treatment with MSC-FFM. Annals of Hematology (2025) 104:4237–4243



Mesenchymal stromal cells in the prophylaxis of graft vs host disease: A meta analysis Tejaswini Mariappan, Blood 2025

67th ASH Annual Meeting

- (GVHD) is a major complication following allogeneic (HSCT), causing morbidity and mortality.
- (MSCs) show potential benets in GVHD prophylaxis through immunomodulatory properties.
- The meta-analysis reveals that prophylactic mesenchymal stem cell (MSC) infusion significantly decreases acute (GVHD), severe acute GVHD, chronic GVHD, and severe chronic GVHD incidence, while enhancing GVHD-free relapse-free survival in allogeneic (HSCT) recipients compared to standard care.
- Although improved survival, reduced relapse, and mortality rates were observed in the MSC group, these did not reach statistical significance.
- **MSC infusion did not increase adverse events or viral infections and significantly reduced also hemorrhagic cystitis occurrence.**

Thank you