ISBMT

Indian Society for Blood & Marrow Transplantation

BMT MASTERCLASS

ORGANISED BY ISBMT

2025

13th & 14th December 2025

Session 7: Supportive care during transplant

4.15 PM to 4.20 PM	**Case presentation 6**	Dr. Sinhal Gopal Nandkishor
4.20 PM to 4.35 PM	Mucositis and nutrition support	Dr. Sanjeevan Sharma

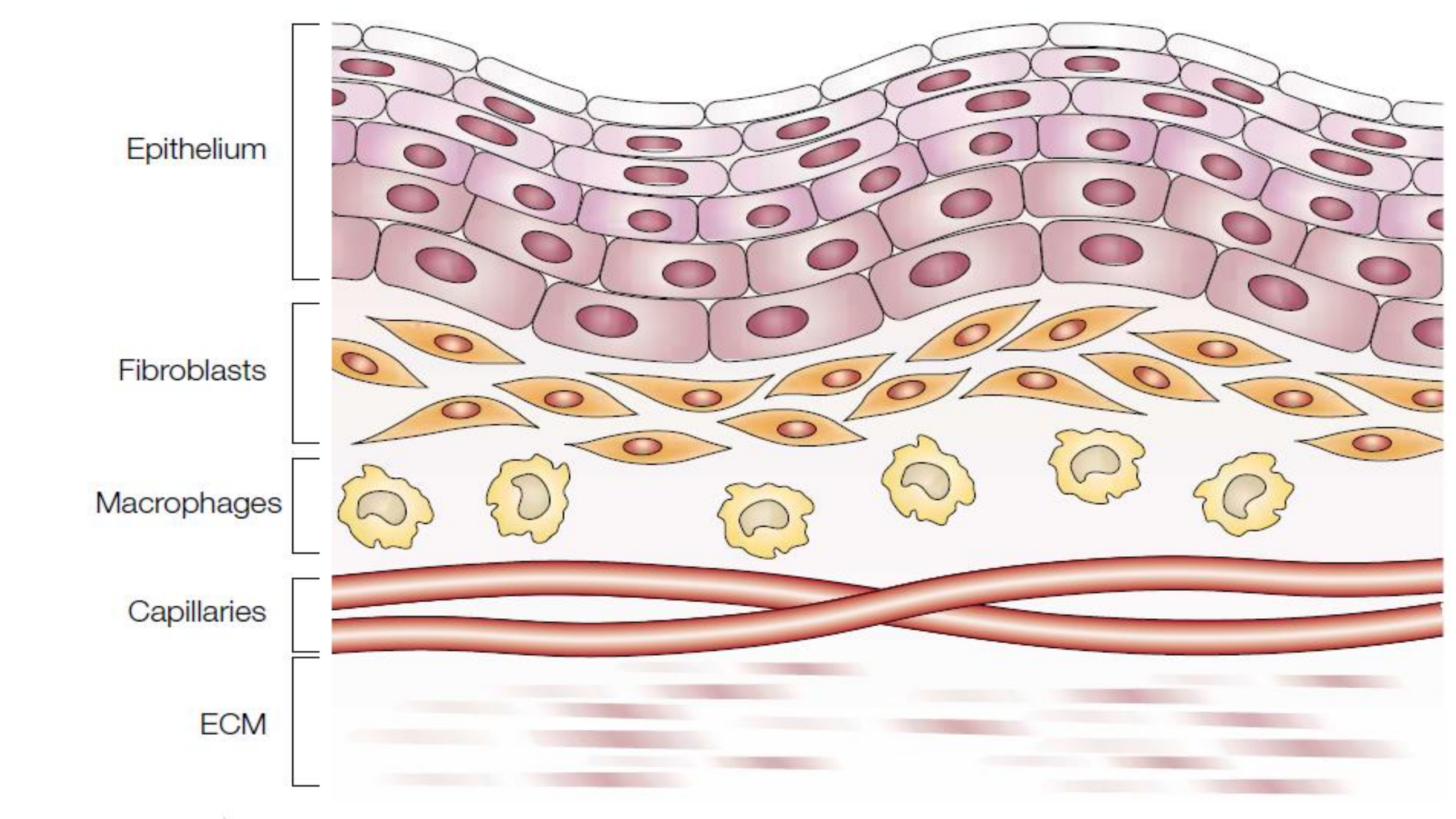
Importance of Mucositis

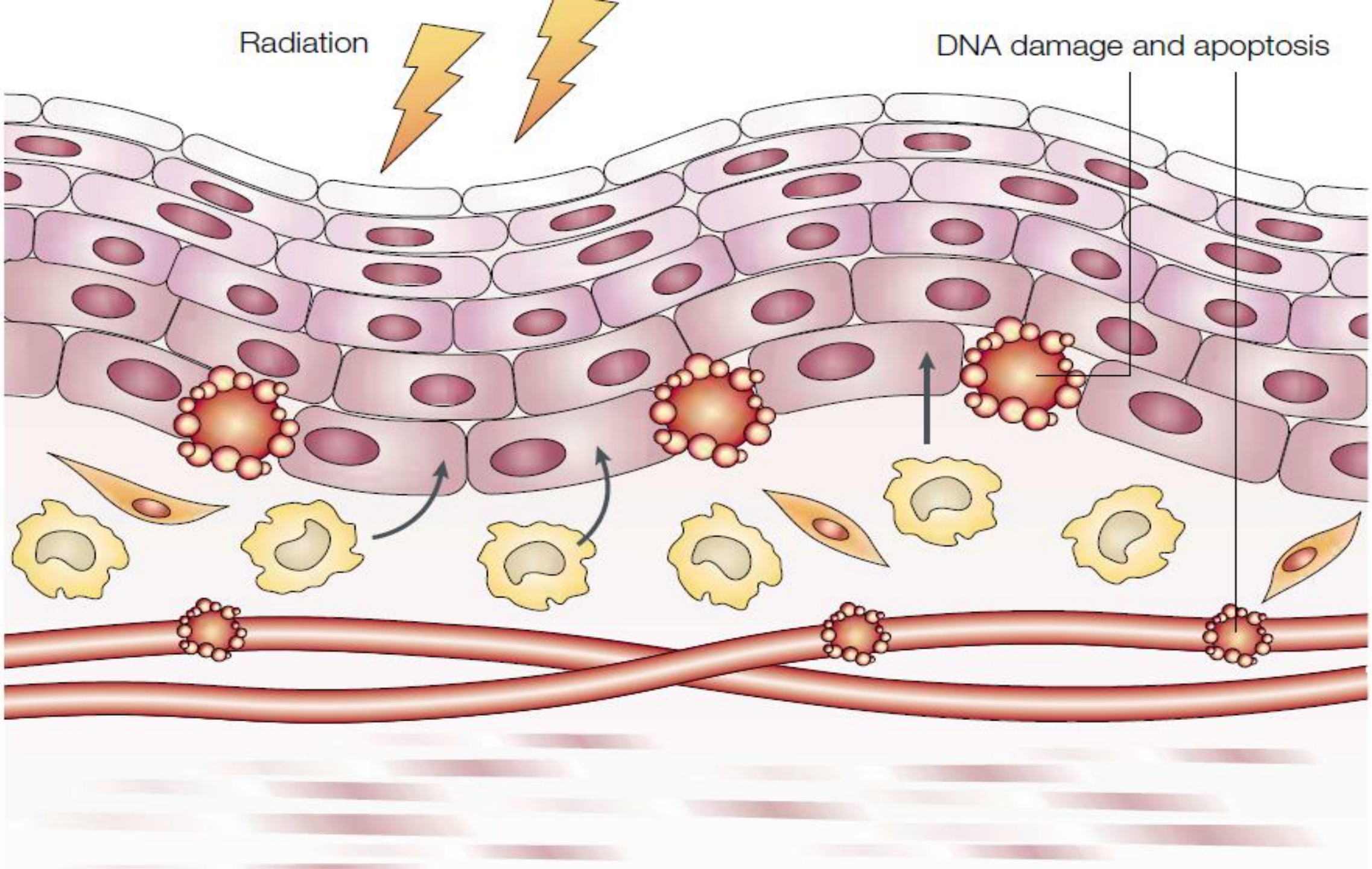
- Most frequent HSCT complication
- Impact on QoL inside the BMT unit
- Direct effect on probability of severe systemic infections
- Corelates with incidence & severity of subsequent aGVHD
  - Causal effect vs Predictive marker
- No major intervention strategies over past 50 years.

- 1 Why oral epithelium affected more than others?
- 2 Is grading of OM important?
- 3 Can severity of mucositis be predicted?
- 4 Role of microbiome
- 5 Role of Dental Care / Pallifermin
- 6 Optimal Nutrition support
- 7 Is TPN always necessary?

Basic Science

- The oral mucosa is comprised of stratified squamous epithelium that overlies the lamina propria, which consists of fibroblasts and connective tissue, small blood vessels (capillaries), inflammatory cells (macrophages) and extracellular matrix (ECM).
- The epithelium of the movable mucosa (which makes up the cheeks, inner aspects of the lips, ventral surface of the tongue, floor of the mouth and soft palate) is **not keratinized**, in contrast to the dorsal tongue, hard palate and gingiva.


Epithelium
Fibroblasts
Macrophages
Capillaries
ECM


Radiation
DNA damage and apoptosis

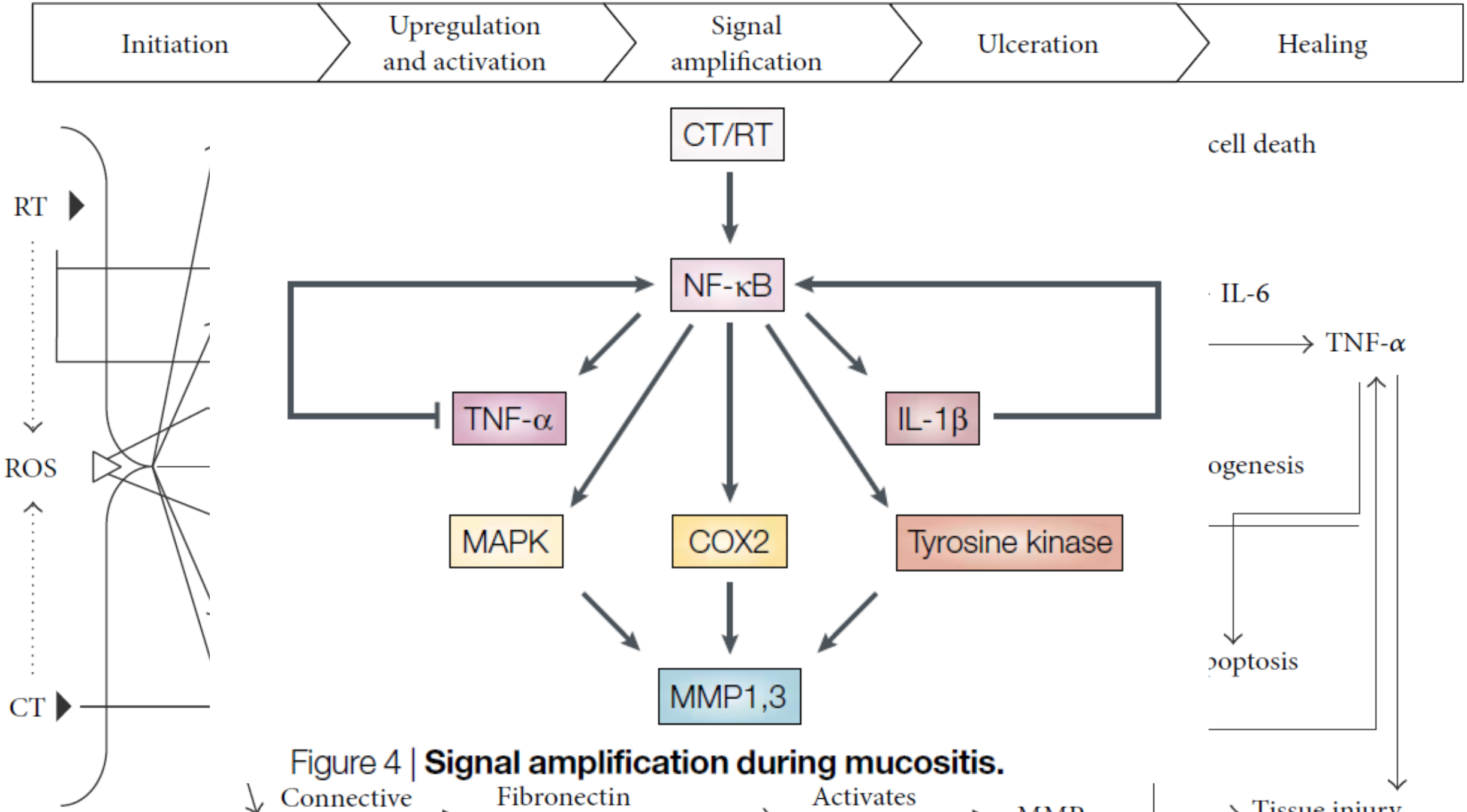
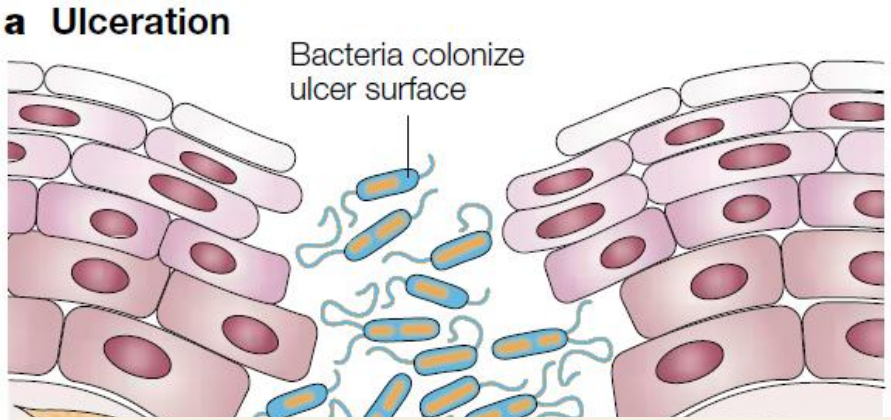


Figure 4 | **Signal amplification during mucositis.**



Agent	Potential mechanism of action
L-glutamine	Counteracts treatment-induced metabolic deficiencies
Amifostine	Free-radical scavenger; reduces pro-inflammatory-cytokine production
Benzydamine HCl	Reduces pro-inflammatory-cytokine production; scavenges reactive oxygen species; membrane stabilization; antimicrobial
N-acetylcysteine	Antioxidant; suppresses NF-κB activation
Keratinocyte growth factor	Epithelial mitogen; reduces levels of reactive oxygen species by activating NRF2
Sphingomyelinase and ceramide synthase	Inhibit ceramide-pathway-induced apoptosis inhibitors
Manganese superoxide dismutase	Detoxifies reactive oxygen species.
COX2 inhibitors	Suppress NF-κB; reduce pro-inflammatory-cytokine production; inhibit angiogenesis

Why post hsct mucositis is mostly in oral cavity

- The non-keratinized oral mucosa is uniquely vulnerable to cytotoxic injury,
- It has intense inflammatory amplification,
- It is continuously traumatized and colonized by dense microbiota,
- It is richly innervated; exposure of subepithelial nerve endings in ulcers causes severe nociceptive and contact pain,
- Lesser density of epithelial stem cells as compared to intestines.

Grading Scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NCI CTCAE [14]	Absence of other criteria*	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet intake	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention	Death
WHO [15]	Absence of other criteria*	Oral soreness, erythema	Ulcers but able to eat solids	Oral ulcers and able to take liquids only	Oral alimentation impossible	N/A
Bearman et al. (1988) criteria on regimen-related toxicity [16]	Absence of other criteria*	Pain and/or ulceration not requiring continuous i.v. narcotic drug	Pain and/or ulceration requiring a continuous i.v. narcotic drug (morphine drip)	Severe ulceration requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation	N/A	N/A
Modified OMAS [17]	OMAS assessed for erythema (none, mild, moderate, severe) and ulcers or pseudomembranes in the oral cavity; scale ranges from 0 to 2 and those with a score of ≥.5 are considered to have severe mucositis; assessments performed 3 times a week from admission to the day of discharge; maximum OMAS score recorded during the transplantation admission defined the severity of mucositis for a patient					
SWOG criteria [18]	None	Painless ulcers, erythema or mild soreness	Painful erythema, edema, or ulcers, but can eat	Painful erythema, edema, or ulcers, and cannot eat	Requires parenteral or enteral support	N/A
OMI [19]	Assess clinically evident oral mucosal changes (atrophy, erythema, ulceration, pseudomembranous ulcerations, and edematous changes) and consists of 34 items, each scaled from 0 to 3 (normal to severe). In the Robien et al. (2004) study, "each HCT patient at the FHCRC is examined for oral mucositis every 2 to 3 days during the early post-transplant period by a trained examiner. Results are recorded on a standardized machine-readable form, from which the OMI is computed."					
ECOG scale [20]	None	Mild: soreness	Moderate: ulcers—can eat	Severe: ulcers—cannot eat	Life-threatening	Lethal
DMS [21]	Score: 0	Mild mucositis; score 1-7	Moderate mucositis: score, 8-14	Severe mucositis, score: ≥15	N/A	N/A
	Daily monitoring for mucositis by lesions, erythema, edema, pain, bleeding, dryness, and the production of viscous mucous Each item allocated a score of 0 (normal) to 3 (severe) with values summed to yield a daily oral mucositis score DMS grade II is comparable with WHO grade III					

OMAS indicates Oral Mucositis Assessment Scale; SWOG, Southwest Oncology Group; OMI, Oral Mucositis Index; ECOG, Eastern Cooperative Oncology Group; FHCRC, Fred Hutchinson Cancer Research Center; DMS, Daily Mucositis Score.

DAILY PATIENT ORAL ASSESSMENT RECORD		WHO Mucositis Grading Scale							Patient's label						
		0	None												
		1	Soreness +/- erythema, no ulceration												
		2	Erythema, ulcers, can swallow solids												
		3	Ulcers, can swallow liquid/ puree only												
		4	Alimentation not possible												
	Date														
	Time														
Patient reported data	Diet: (S) solids, (L) liquids, NBM														
	Pain (Y/N)														
	Dry mucosa (Y/N)														
	Taste dysfunction (Y/N)														
	Saliva: (E) excess, (T) thick, (A) absent														
Physical assessment (-) no abnormality (E) erythema +/- (U) ulceration	Presence of bleeding (Y/N)														
	Tongue changes (Y/N)														
	Upper inside lip														
	Lower inside lip														
	Right buccal mucosa														
	Left baccal mucosa														
	Right lateral& ventral tongue														
	Left lateral& ventral tongue														
	Soft Palate														
	Floor of mouth														
	OM grade														
	Initials														
** When assigning an OM grade, consider the patients oral intake related to mucositis only (not other morbidities)															

cancers

MDPI

Systematic Review

Elevated Likeliho
Mucositis After H
A Systematic Rev
Risk Factors

s Related to Oral
plantation:
tcomes and

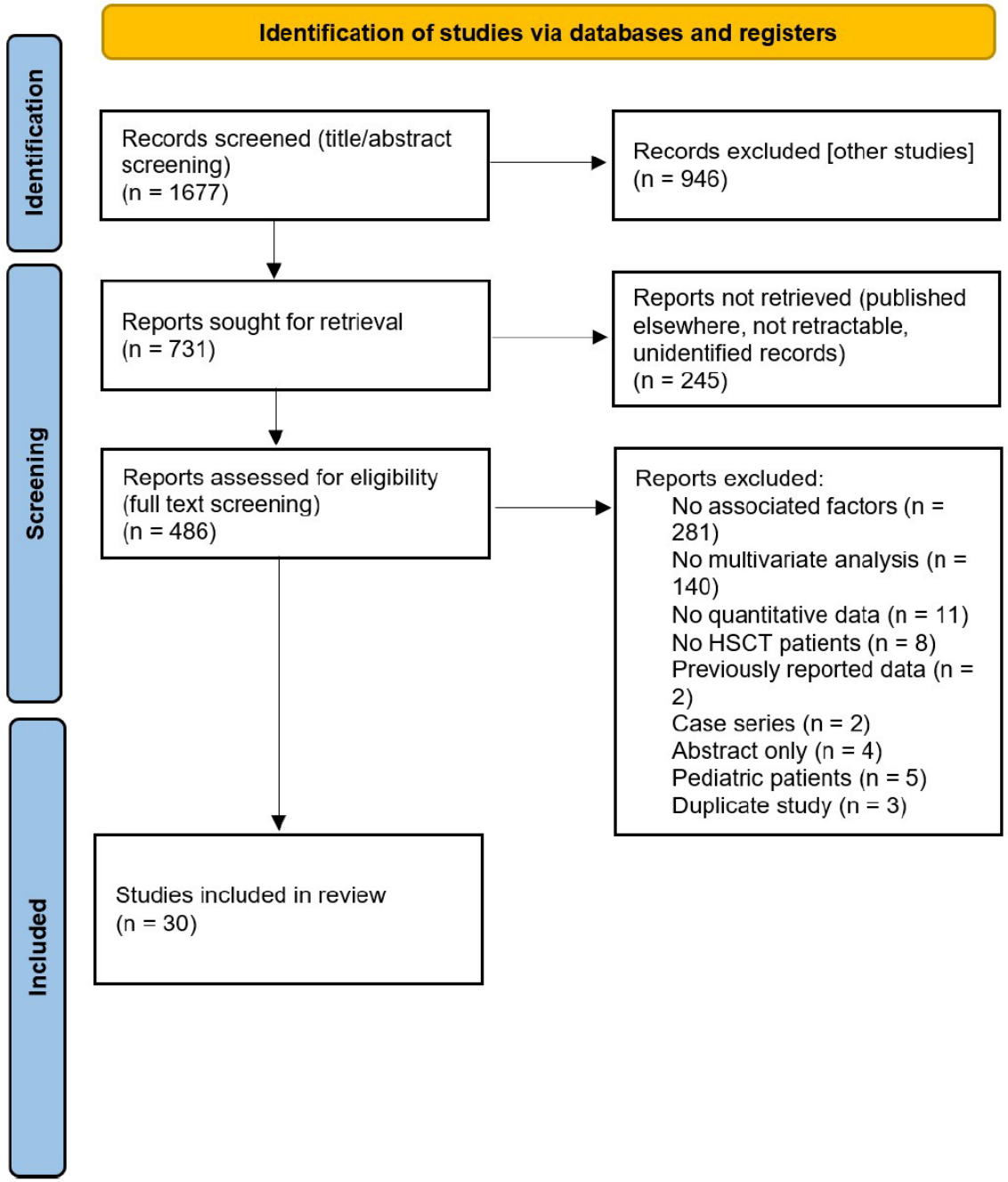


Figure 1. PRISMA flow chart for OM risk factor analysis [23].

Risk Factors

Patient Characteristics

- Age< 40y
- Female Sex
- HSV-1 infection in past
- Malnutrition

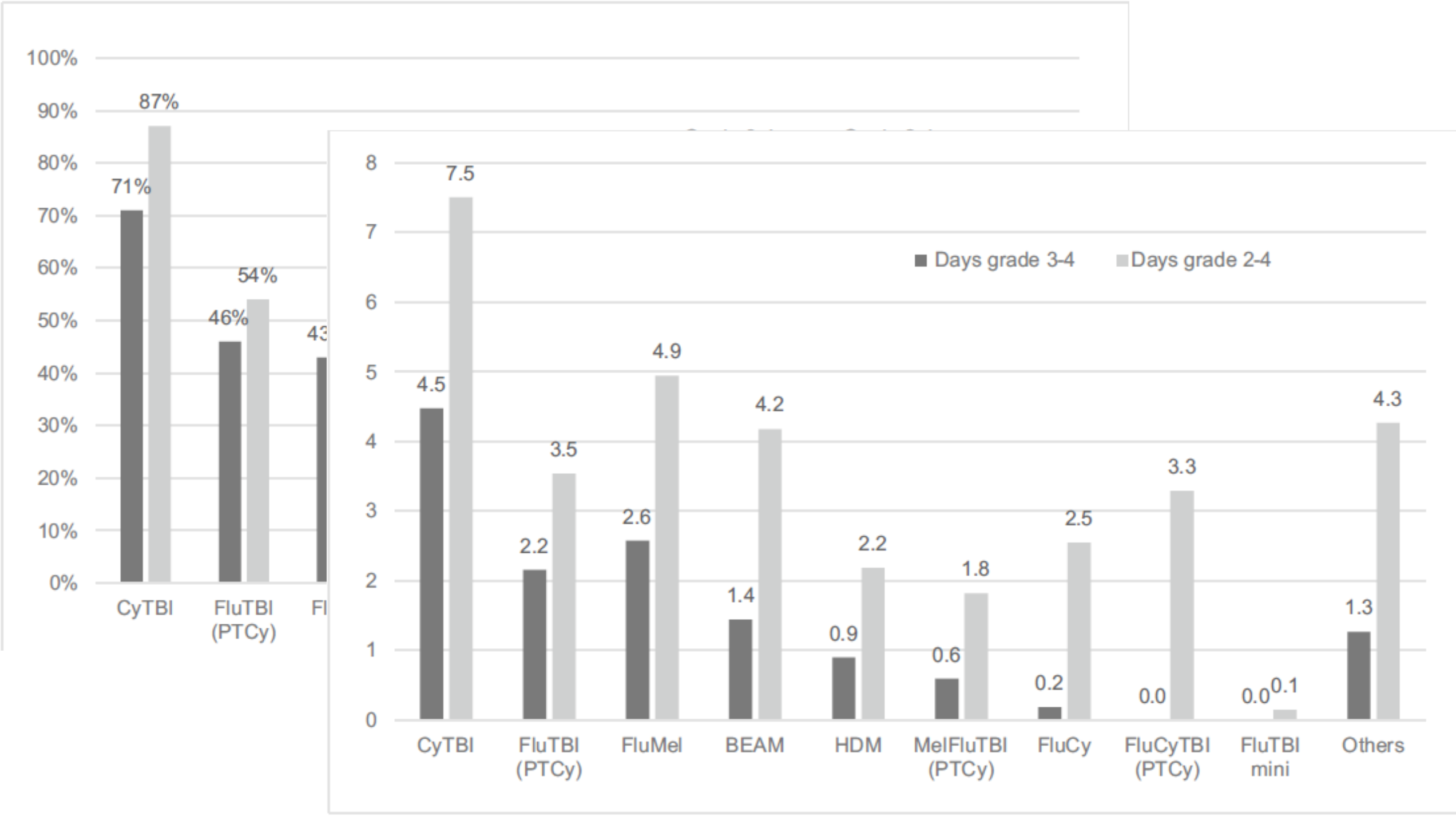
Transplant Related Factors

- Conditioning regimen
- GvHD prophylaxis
- Indication for Tx

Laboratory Values peri-engraftment

- Ferritin
- IL6
- Serum Magnesium

Oral Microbiota


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
87%
71%
54%
46%
CyTBI
FluTBI (PTCy)
8
7
6
5
4
3
2
1
0
Days grade 3-4
Days grade 2-4
7.5
4.5
4.9
3.5
4.2
2.2
2.6
1.4
2.2
0.9
1.8
0.6
2.5
0.2
3.3
0.0
0.1
0.0
4.3
1.3
CyTBI
FluTBI (PTCy)
FluMel
BEAM
HDM
MelFluTBI (PTCy)
FluCy
FluCyTBI (PTCy)
FluTBI mini
Others

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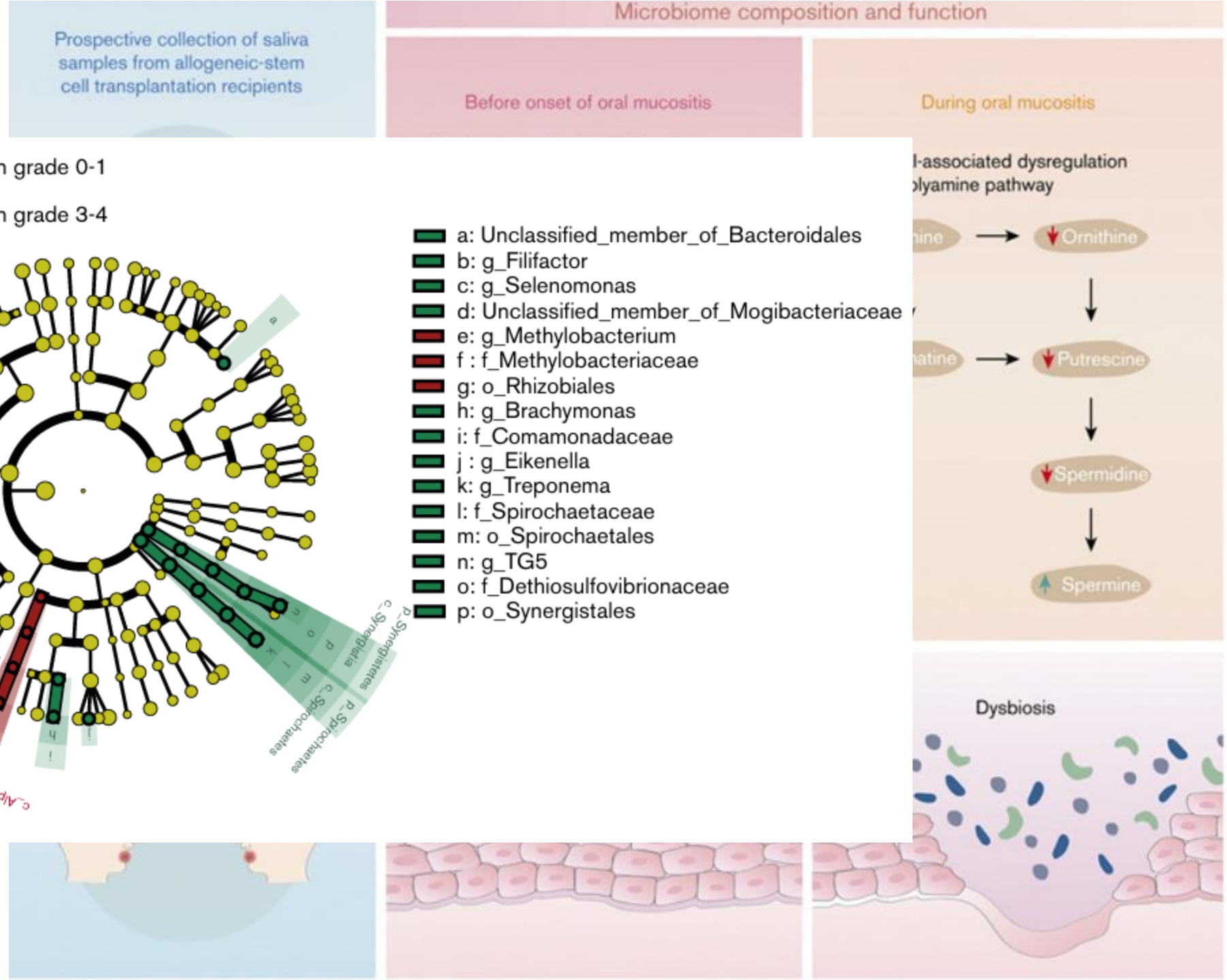
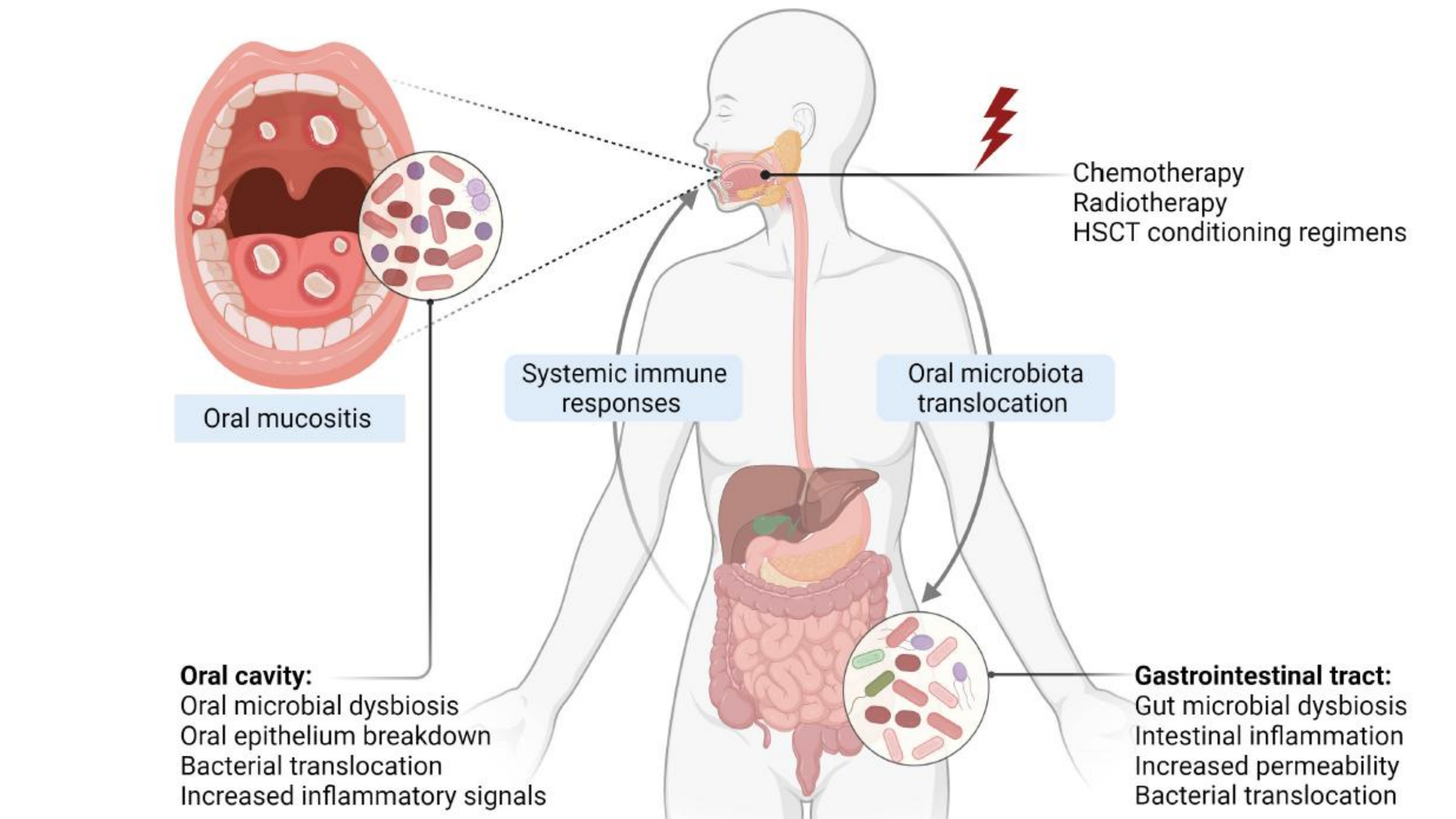
Statistical Analysis of Groups Using the Random Effect and Standard Logistics Models

Comparison	Total Group 1	Percent OM in Group 1	Total Group 2 or 0	Percent OM in Group 2 or 0	OR from RE Model	OR from Standard Logistic Model	*P* Value for RE
MA (=1) versus RIC (=2) grade 2-4	241	.79668	214	.71495	3.021 (1.475-6.185)	1.562 (1.013-2.409)	<.01
MA (=1) versus RIC (=2) any OM	395	0.73165	245	.86531	4.478 (1.225-16.369)	.424 (.276-0.652)	.05
TBI (=1) versus Non-TBI (=0) any OM	181	.96685	418	.69139	4.49 (.195-103.261)	13.019 (5.612-30.202)	.34
MTX (=1) versus non MTX (=0) any OM	649	.83359	130	.55385	26 (.903-748.774)	4.035 (2.696-6.041)	.06
MTX std (=1) versus MTX red (=2) any OM	342	.84211	307	.82410	1.123 (.12-10.494)	1.138 (.752-1.722)	.92
Flu/Bu (=1) versus Flu/Mel (=2) grade 2-4	28	.50000	93	.66667	.47 (.038-5.816)	.5 (.21-1.189)	.12
TBI/Cy (=1) versus Bu/Cy grade 2-4	88	.96591	112	.70536	12.181 (1.902-78.025)	11.835 (3.465-40.429)	.09
MA (=1) versus RIC (=2) grade 1-4	215*	.6325†	195*	.5744†	1.694 (1.001-2.865)	1.322 (.878-1.989)	<.01

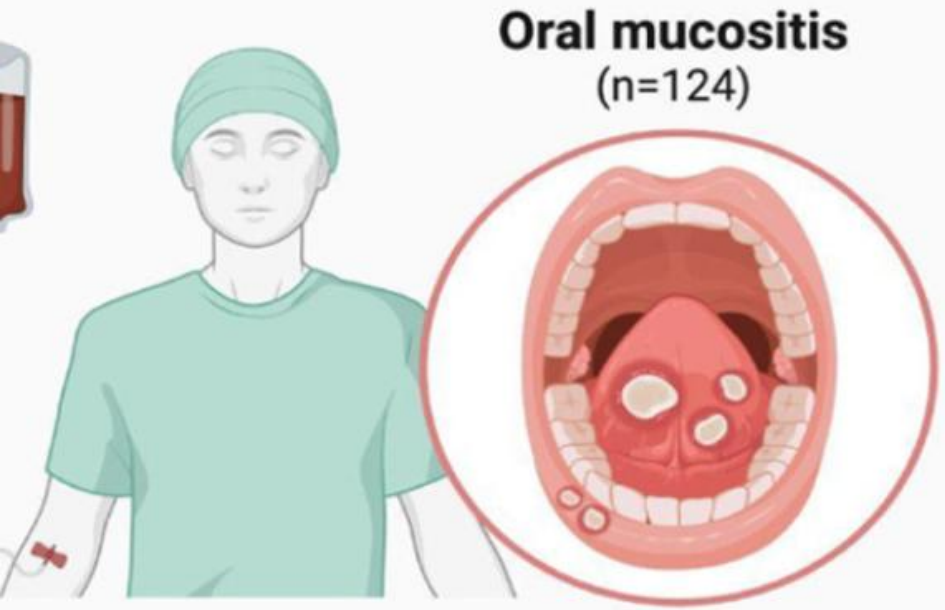
OR indicates odds ratio; Std, standard; red, reduced.

Groups 0, 1, and 2 were arbitrarily assigned to the treatment groups shown.


Prospective collection of saliva samples from allogeneic-stem cell transplantation recipients
Microbiome composition and function
Before onset of oral mucositis
During oral mucositis
Enriched in grade 0-1
Enriched in grade 3-4
a: Unclassified_member_of_Bacteroidales
b: g_Filifactor
c: g_Selenomonas
d: Unclassified_member_of_Mogibacteriaceae
e: g_Methylobacterium
f : f_Methylobacteriaceae
g: o_Rhizobiales
h: g_Brachymonas
i: f_Comamonadaceae
j : g_Eikenella
k: g_Treponema
l: f_Spirochaetaceae
m: o_Spirochaetales
n: g_TG5
o: f_Dethiosulfovibrionaceae
p: o_Synergistales
c_Alphaproteobacteria
c_Spirochaetes
c_Synergistia
p_Spirochaetes
p_Synergistetes
-associated dysregulation
lyamine pathway
Ornithine
Putrescine
Spermidine
Spermine
Dysbiosis


Chemotherapy
Radiotherapy
HSCT conditioning regimens
Oral mucositis
Systemic immune responses
Oral microbiota translocation
Oral cavity:
Oral microbial dysbiosis
Oral epithelium breakdown
Bacterial translocation
Increased inflammatory signals
Gastrointestinal tract:
Gut microbial dysbiosis
Intestinal inflammation
Increased permeability
Bacterial translocation

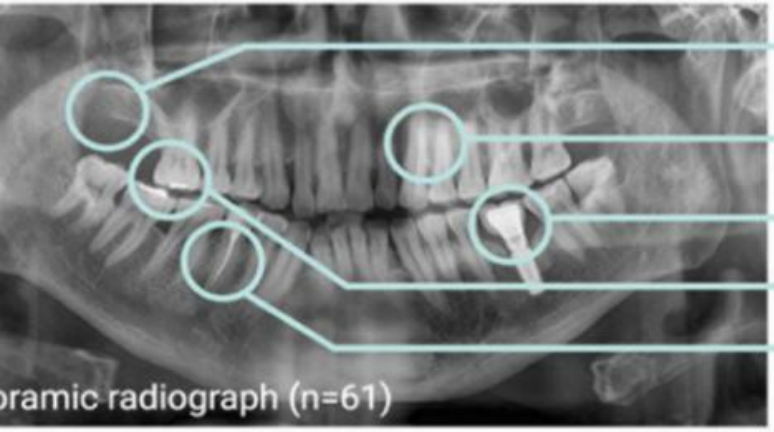
Study	Subjects	Therapy	Sampling/analysis method	Key findings
Laheij et al. [6]	Adult patients with hematological malignancies ($n = 49$)	Myeloablative or reduced intensity-conditioning + HSCT	Oral rinsing samples/real-time PCR	The presence and load of *P. gingivalis* were associated with a higher risk of ulcerative OM in non-keratinized and keratinized oral mucosa Percentage (in relation to total load) of *P. gingivalis, P. micra, F. nucleatum,* and *T. denticola* was associated with ulcerative OM in non-keratinized oral mucosa
Laheij et al. [46]	Patients with multiple myeloma ($n = 51$)	High dose melphalan + autologous HSCT	Oral rinse samples/16S rRNA gene sequencing	Significant alteration in oral microbiota post- autoSCT which recovered within three months More pronounced changes in oral microbial diversity in patients who developed ulcerative OM Distinctive pre-autoSCT taxa discriminate between patients who developed OM and those who did not Pre-autoSCT, patients who developed OM had increased abundance of in *Veillonella, Enterococcus faecalis*, *Streptococcus*, *Staphylococcus spp.*, *Fusobacterium*, *Prevotella oris*, and *Prevotella veroralis*, and reduced abundance of *Actinomyces graevenitzii* and *Streptococcus constellatus* Patients who did not develop ulcerative OM had a more resilient microbial community
Shouval et al. [49]	Patients with hematological conditions ($n = 184$) Healthy controls ($n = 19$)	High intensity/ myeloablative conditioning + allogeneic HSCT	Saliva/16S rRNA gene sequencing	HSCT was associated with a decrease in oral alpha diversity Pre-HSCT: an increased abundance of *Kingella* and *Atopobium* correlated to a higher risk of developing severe OM (grade 3-4) Post-HSCT: *Methylobacterium spp*. were enriched in patients with severe OM, while *Treponema* and *TG5* were increased in grade 0-1 OM A more pronounced change in the salivary microbial diversity and metabolites post-HSCT in those developed grade 3-4 OM
Takahashi et al. [50]	Patients with hematological malignancies ($n = 19$) Healthy controls ($n = 3$)	Cyclophosphamide + total body irradiation OR fludarabine and melphalan + HSCT	Tongue, buccal mucosa, and teeth swabs/16S rRNA gene-based terminal restriction fragment length polymorphism (T-RFLP)	Patients with severe OM had larger changes in the oral bacterial community post-HSCT than patients with mild OM Faster recovery of the microbial diversity and abundance in patients with mild/moderate OM compared to patients with severe OM



Oral mucositis
(n=124)

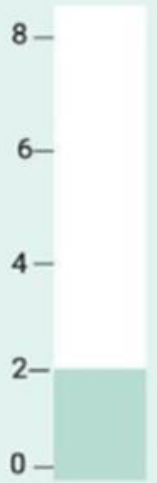
allo-HSCT (n=242)

Dental health score



- Gaps
- Bone level
- Implants
- Restorations
- Root canal treatments

Mild (Grade I-II)



Low Dental score

Severe (Grade III-IV)

High Dental score

Oral Hygiene assessment pre SCT

Dental Biofilm control –

- Brushing with soft toothbrush
- Use of Fluoride based toothpaste

Oral Microbial Control

- Non Alcohol based mouth rinses after each food intake / q 8h
- Chlorhexidine digluconate gels

Table 1 Palifermin phase II and III clinical trials: published randomized, double-blind, placebo-controlled studies

Disease	Treatment	Palifermin dose/Schedule	Endpoints/Observations*	Side effects
Autologous transplant (HDT-ASCT)				
Hematologic cancer (Phase III)	TBI (12 Gy) CT: etoposide: 60 mcg/kg × 1 day cyclophosphamide: 100 mg/kg × 1 day	60 mcg/kg/day × 3 days pre & × 3 days post transplant	Incidence, grade 3 or 4 OM: 63% *versus* 98%, $P < 0.001$ Incidence, grade 4 OM: 20% *versus* 62% Duration, severe OM (median): 3.0 days *versus* 9.0 days, $P < 0.001$ TPN: 31% *versus* 55%, $P < 0.001$ Morphine equivalents (median): 212 mg *versus* 535 mg, $P < 0.001$ Better PRO with palifermin	Skin: rash, pruritis erythema Mouth: taste alteration, white film, thick tongue Edema
Multiple myeloma (Phase III)	CT: High dose melphalan 200 mg/m^2 × 1 day, if CC ≥ 30 ml/min.; 140 mg/m^2 × 1 day, if CC < 30 ml/min.)	60 mcg/kg/day × 3 day pre only, or × 3 days pre & × 3 days post transplant	Incidence, grade 3 or 4 OM: 24% *versus* 38% *versus* 37%, P = NS Duration, Severe OM (mean): 1.9 days *versus* 2.7 days *versus* 2.4 days, P = NS Similar PRO in all groups	Skin, mouth and edema: as above

Palifermin

60 mcg/kg IV bolus 3 consecutive days before and 3 consecutive days after myelotoxic therapy (6 doses total)

Dosage schedule

- **Premyelotoxic therapy**
  - Administer the first 3 doses prior to myelotoxic therapy
  - Administer the third dose 24–48 hr prior to beginning myelotoxic therapy
- **Postmyelotoxic therapy**
  - Administer the last 3 doses after myelotoxic therapy is complete
  - Administer the first of these doses on the day of hematopoietic stem cell infusion after the infusion is completed, and at least 7 days after the most recent administration of palifermin (ie, 3rd premyelotoxic dose)

Dosage Modification

Renal or hepatic impairment: Dose adjustment not necessary

Limitation of Use

The safety and efficacy of not established in patients with non-hematologic malignancies

Not effective in decreasing incidence of severe mucositis in patients with hematologic malignancies receiving myelotoxic therapy in the setting of allogeneic hematopoietic stem cell support

Nutrition Support

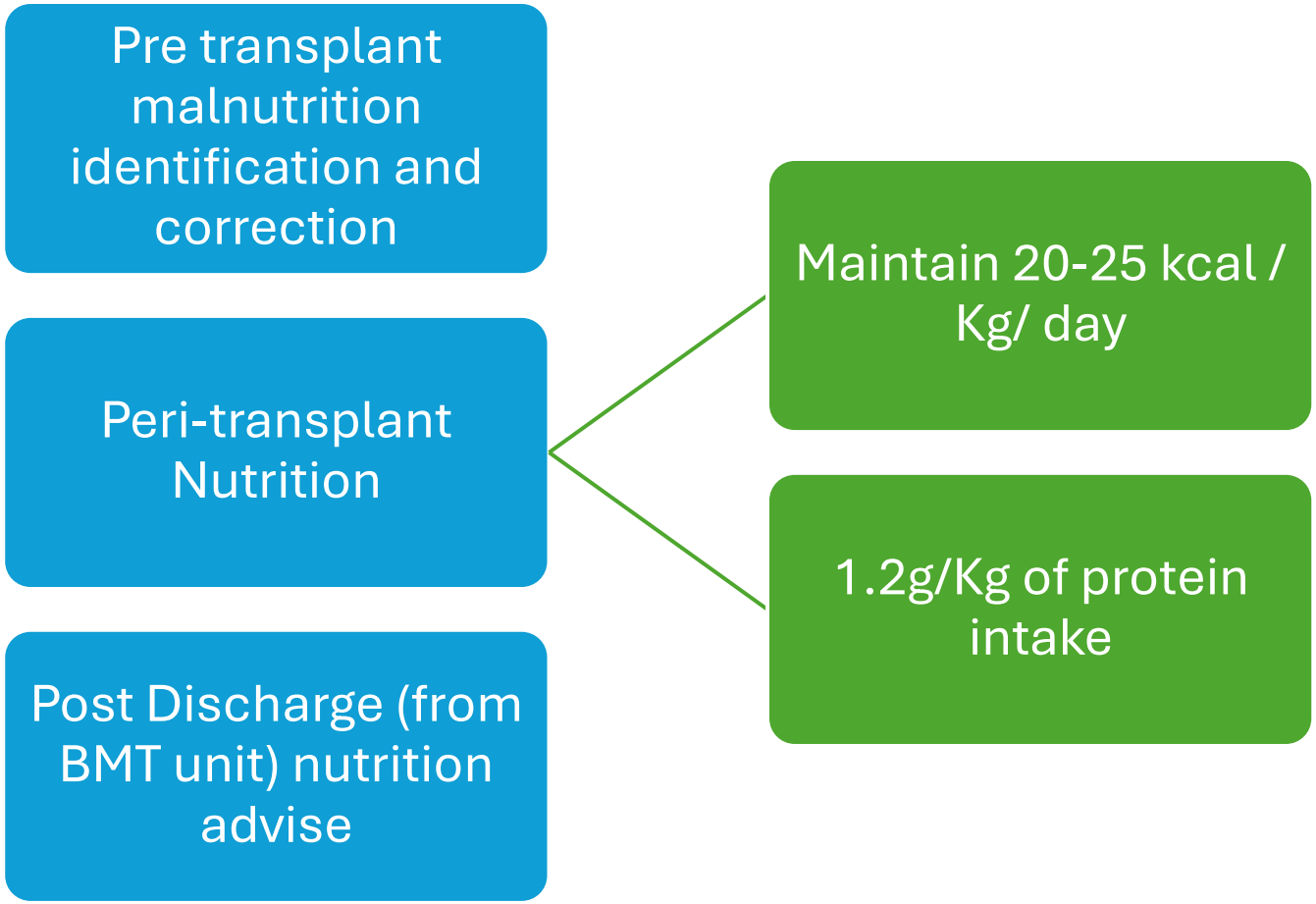


Table 5. Nutritional Screening Tools.

Tool/Acronym/Year	Features/Aspects	Patients Group
Instant nutritional assessment (INA, 1979)	Serum albumin levels and total lymphocyte counts	Cancer surgery, liver, and pancreatic diseases
Prognostic nutritional index (PNI, 1979)	Serum albumin, TSF, TFN, DH	Surgical patients
Prognostic inflammatory and nutritional index (PINI, 1985)	C-reactive protein, orosomucoid, albumin, and transthyretin	Cancer patients, surgery, liver diseases, trauma, burn
Nutritional screening initiative checklist (DETERMINE, 1994)	Questionary about nutritional well being	Elderly people
Nutritional Risk Index (NRI, 1988)	Serum albumin, current/usual body weight ratio.	All inpatients
Malnutrition screening tool (MST, 1999)	Data about recent appetite status and weight loss	All inpatients
Risk Evaluation for Eating and Nutrition (SCREEN, 2000).	Factors affecting food intake, access to food, social factors, anthropometry, dietary intake	Elderly people
Malnutrition inflammatory score (MIS, 2001)	SGA method combined with BMI, serum albumin, and serum TIBC	Dialysis patients

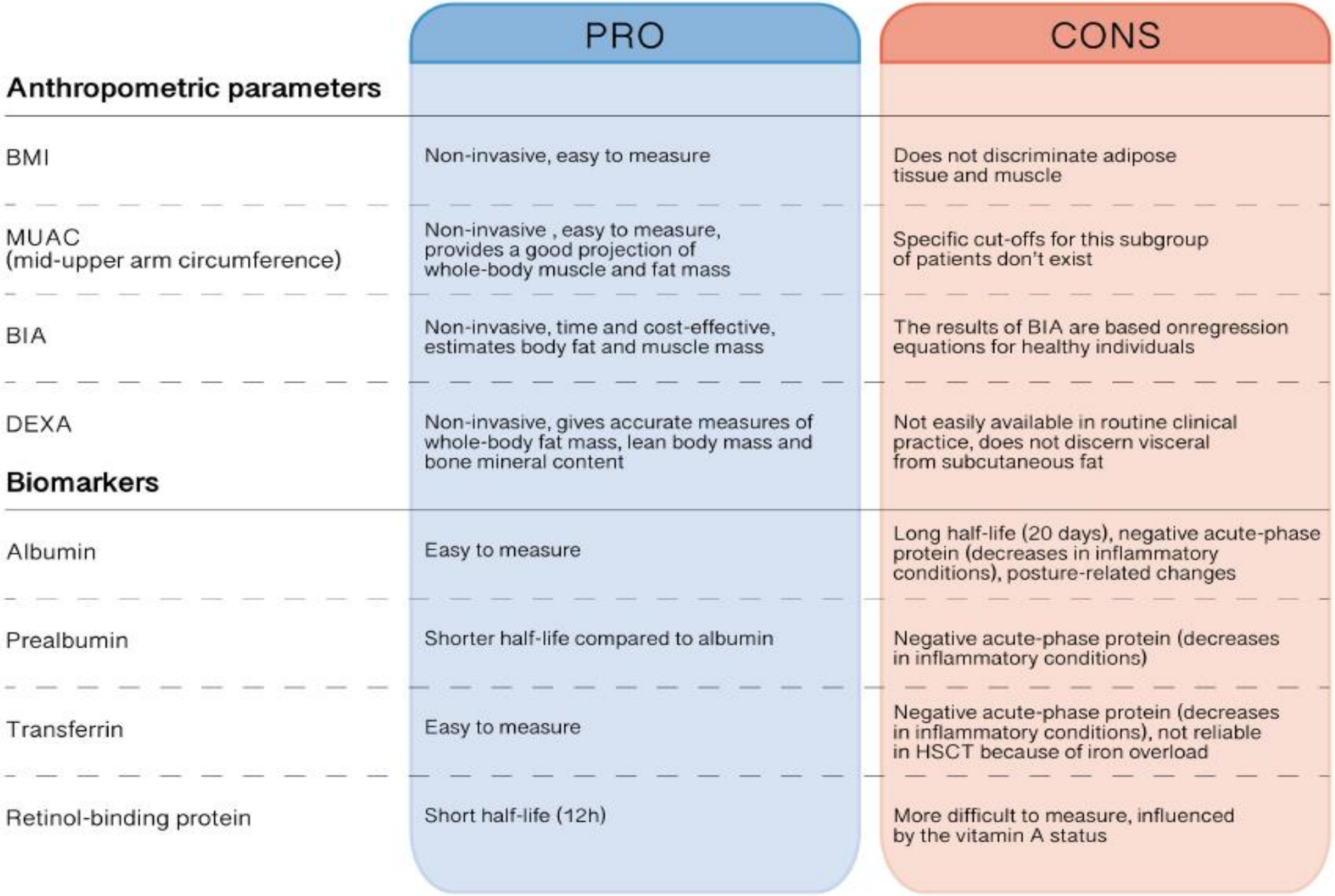


FIGURE 1
Advantages and disadvantages of anthropometric and biochemical parameter used to assess the nutritional status in pediatric HSCT recipients.

Rapid and Severe Caloric Deficit

- Poor Oral nutrition due to
  - The side effects of the conditioning regimen, mainly vomiting, anorexia, diarrhea and mucositis.
  - Bacterial Sepsis
  - VOD / SOS
- Increased Catabolic load
- Artificial nutrition is usually indicated if oral caloric intake falls below 60% to 70% of basic requirements for 3 consecutive days

Artificial Nutrition

Enteral

- NG tube
- Seems invasive and cumbersome
- Inconvenient to patient

Parenteral

- Convenient
- Traditionally used in most BMT units

Transplantation and Cellular Therapy 27 (2021) 180.e1–180.e8

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

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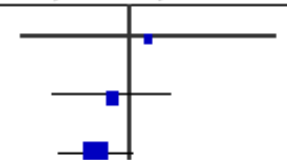
Supportive Care

Enteral versus Parenteral Nutrition as Nutritional Support after Allogeneic Hematopoietic Stem Cell Transplantation: a Systematic Review and Meta-Analysis

Daniele Zama[1], Davide Gori[2], Edoardo Muratore[1,*], Davide Leardini[1], Flavia Rallo[2], Silvia Turroni[3], Arcangelo Prete[1], Patrizia Brigidi[4], Andrea Pession[1], Riccardo Masetti[1]

A: aGvHD

Study or Subgroup	Enteral Nutrition Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andersen 2015	3	5	2	4	2.0%	1.20 [0.36, 4.04]
Andersen 2020	10	20	13	22	10.9%	0.85 [0.48, 1.48]

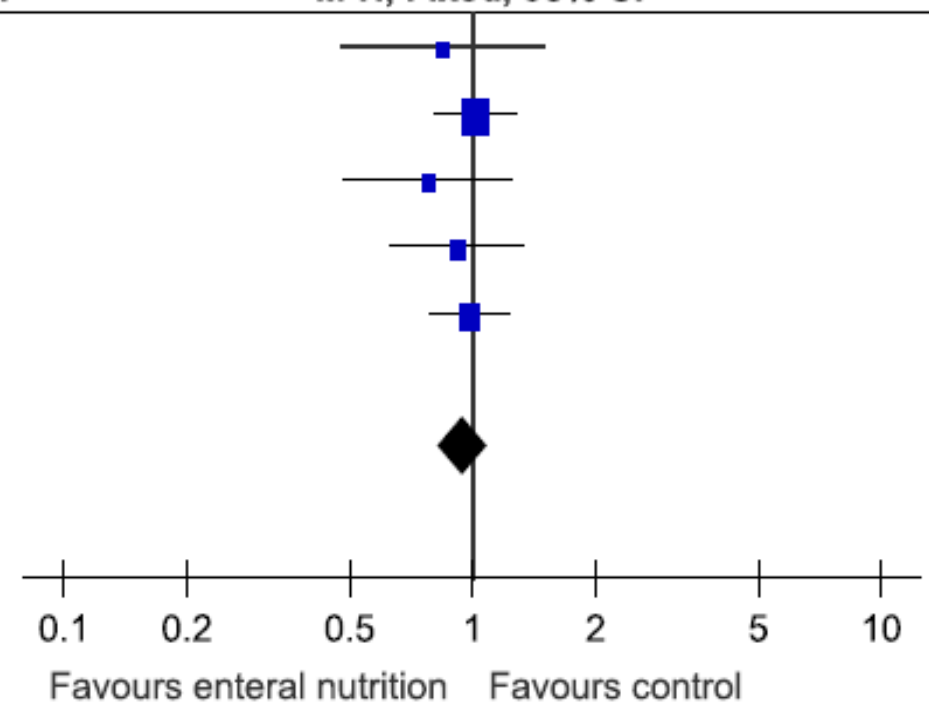


Mucositis grade III-IV

Study or Subgroup	Enteral Nutrition Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andersen 2020	10	20	13	22	7.8%	0.85 [0.48, 1.48]
Gonzales 2018	61	97	60	97	37.7%	1.02 [0.82, 1.27]
Guieze 2015	14	28	18	28	11.3%	0.78 [0.49, 1.23]
Seguy 2012	51	94	16	27	15.6%	0.92 [0.64, 1.32]
Skaarud 2018	42	57	45	60	27.6%	0.98 [0.79, 1.22]
Total (95% CI)		**296**		**234**	**100.0%**	**0.95 [0.83, 1.09]**
Total events	178		152			

Heterogeneity: Chi² = 1.38, df = 4 (P = 0.85); I² = 0%

Test for overall effect: Z = 0.73 (P = 0.46)



Enteral Nutrition vs Parenteral

No Statistical difference in

- OS
- Engraftment
- Mucositis
- Infection Rates

EN had favourable effect in

- Reducing aGVHD incidence
- Gut Microbiota Diversity
- CVC related morbidities

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frontiers in Oral Health

MINI REVIEW
published: 28 March 2022
doi: 10.3389/froh.2022.881949

Oral-Gut Microbiome Axis in the Pathogenesis of Cancer Treatment-Induced Oral Mucositis

REGULAR ARTICLE

blood advances

Patterns of salivary microbiota injury and oral mucositis in recipients of allogeneic hematopoietic stem cell transplantation

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Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Review Articles

The Incidence and Severity of Oral Mucositis among Allogeneic Hematopoietic Stem Cell Transplantation Patients: A Systematic Review

ORIGINAL ARTICLE

The incidence of severe oral mucositis in patients undergoing different conditioning regimens in haematopoietic stem cell transplantation

Midori Nakagaki[1,2] · Glen A. Kennedy[3,4] · Nicole C. Gavin[3,4,5,6] · Alexandra Clavarino[7] · Karen Whitfield[1,2]

Received: 31 January 2022 / Accepted: 9 August 2022 / Published online: 26 August 2022

NATURE REVIEWS | CANCER VOLUME 4 | APRIL 2004 | 277

cancers

Cancers 2025, 17, 2657

MDPI

Systematic Review

Elevated Likelihood of Infectious Complications Related to Oral Mucositis After Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis of Outcomes and Risk Factors

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Supportive Care

Enteral versus Parenteral Nutrition as Nutritional Support after Allogeneic Hematopoietic Stem Cell Transplantation: a Systematic Review and Meta-Analysis

Q1

- The central initiating event post conditioning regime toxicity which starts the cascade of mucositis is the activation of
  - A : IL-6 and TNF alfa
  - B : NF-kB
  - C : Pro- apoptotic pathway
  - D : Anti- apoptotic pathway

Q2

- Use of enteral feeding over parenteral feeding post SCT has max benefit in
  - A : Reducing bacterial sepsis
  - B : Early engraftment
  - C : Lower incidence of Mucositis
  - D : Lower incidence of aGVHD