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Incontri di aggiornamento del Dipartimento Oncologico

La tossicità gastrointestinale: Mucosite e Diarrea

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Negrar, 7 Luglio 2015

mucosite

- “mucositis is defined as infiammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract”

Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. - Ann Oncol 2011 -

- “mucositis refers to mucosal damage secondary to cancer therapy occurring in the oral cavity, faryngeal, laryngeal and other areas of the gastrointestinal tract”

MASCC/ISOO Clinical Practice Guidelines for the management of mucositis secondary to cancer therapy . - Cancer 2014 –

Sedi di infiammazione

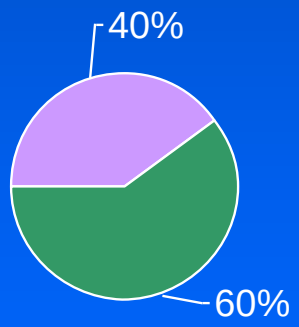
- La mucosa orale é la sede più frequente di tossicità
- Si può verificare in tutto il tratto gastrointestinale:
  - Esofago
  - Stomaco
  - duodeno
  - digiuno/ileo
  - colon
  - retto
- I meccanismi patogenetici appaiono sovrapponibili indipendentemente dal tratto interessato sebbene il danno si manifesti clinicamente con severità ed intensità diverse.
- Frequenza maggiore nei fumatori, alcolisti, diabetici,

  pz anziani o malnutriti

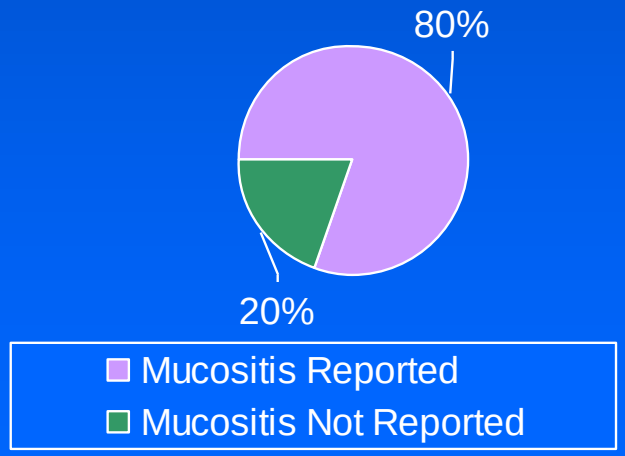
Epidemiologia

- 40% dei patienti sottoposti a “standard-dose chemotherapy”
- Oltre il 80% dei patienti sottoposti a Radioterapia del distretto cervico-facciale
- Oltre 75% dei pazienti sottoposti a BMT/HDCT

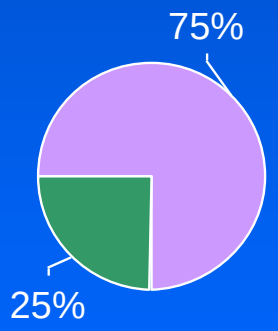
Mucositis Frequency: Standard-Dose Chemotherapy



Mucositis Frequency: Radiation for Head and Neck Cancer



Mucositis Frequency: BMT with High-Dose Chemotherapy and/or Radiation Pre-Conditioning



Trotti et al Radiother Oncol 2003

Mucosite : eventi clinici correlati

- Eritema e/o ulcerazione della mucosa
- Nausea, vomito e diarrea
- Dolore
- Disfagia
- Calo ponderale
- Nutrizione parenterale
- Utilizzo di oppiacei
- Ospedalizzazione
- Terapia antibiotica

WHO scale for oral mucositis

Grade 0 = No oral mucositis
Grade 1 = Erythema and soreness
Grade 2 = Ulcers, able to eat solids
Grade 3 = Ulcers, requires liquid diet (due to mucositis)
Grade 4 = Ulcers, alimentation not possible (due to mucositis)

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

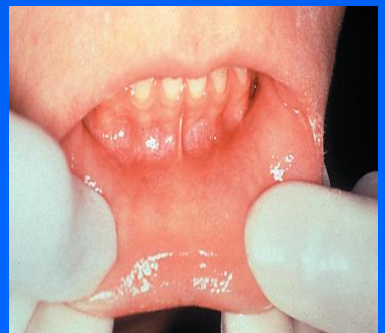
Grade 1 = Asymptomatic or mild symptoms; intervention not indicated.
Grade 2 = Moderate pain; not interfering with oral intake; modified diet indicated
Grade 3 = Severe pain; interfering with oral intake
Grade 4 = Life-threatening consequences; urgent intervention indicated
Grade 5 = Death

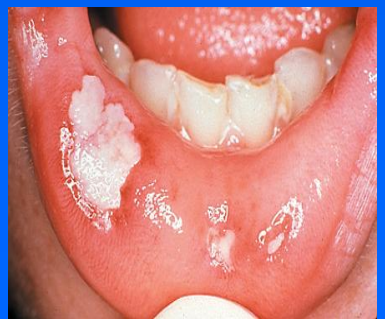
Soreness ± erythema

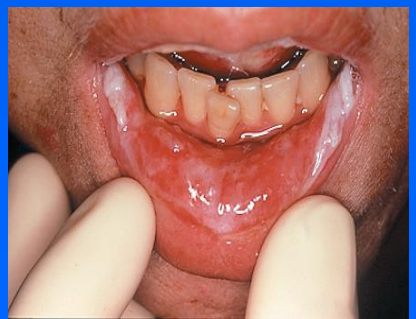
Erythema, ulcers; patient can swallow solid food

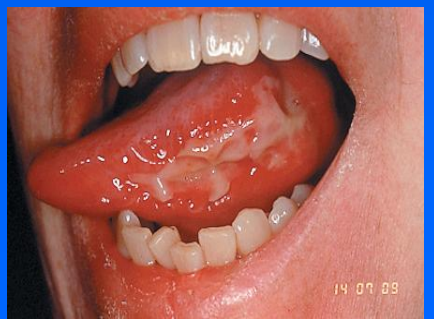
Ulcers with extensive erythema; patient cannot swallow food

Mucositis to the extent that alimentation is not possible









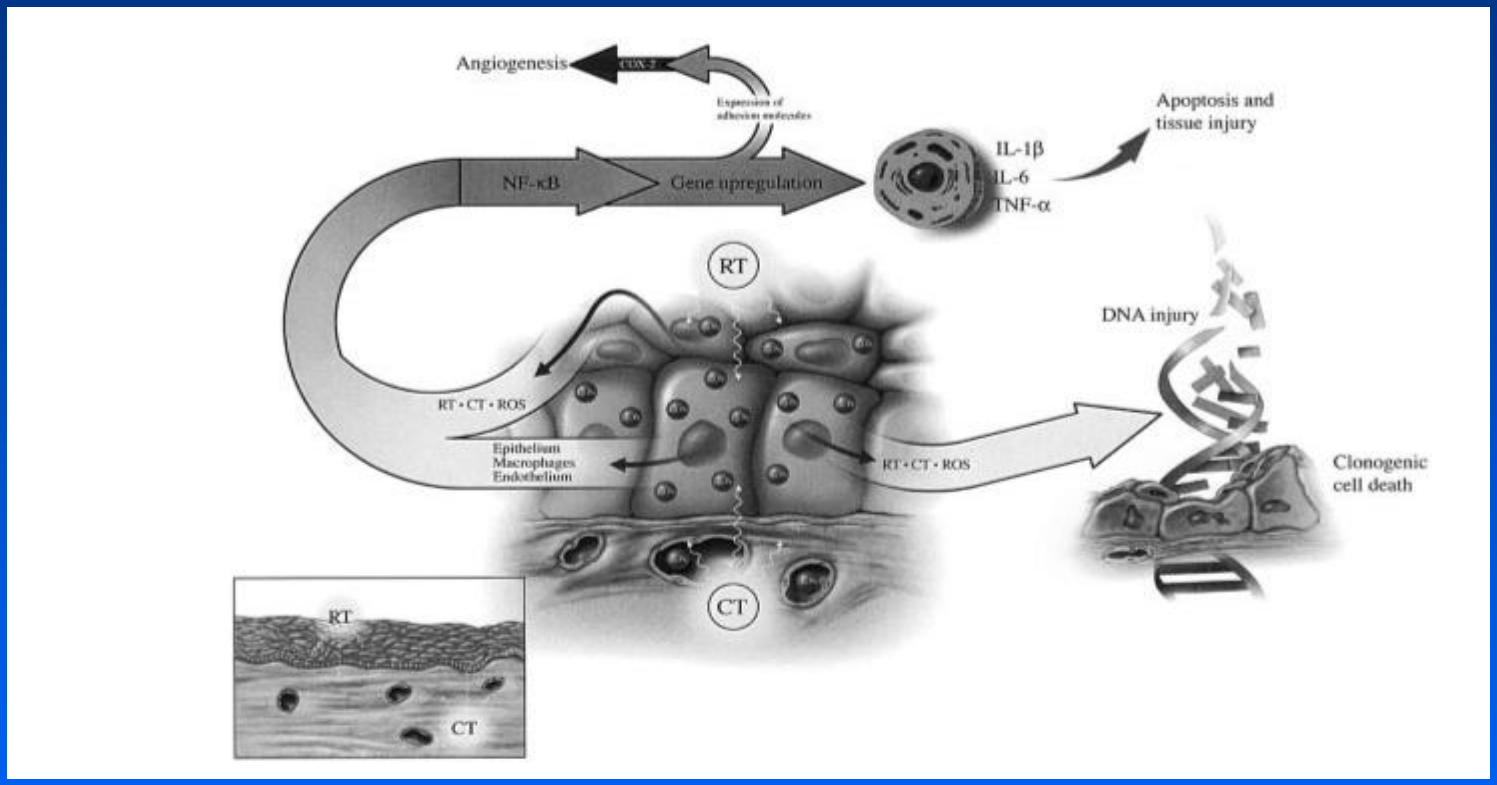
Relazione tra farmaci antiblastici e mucosite (G3-4)

regime	N° ptz	Rischio mucosite orale %	Rischio mucosite GI %
CPT11 + 5FU + AF	318	5	25
FAC/FEC	1382	3	1
Antraciclina + PTX	790	11	<1
Antraciclina + DCT	845	11	14
DCT + 5FU	303	46	5
DCT + CDDP + RT	346	60	2
PTX + CDDP + 5FU	225	27	18
CDDP + RT	309	11	11
CDDP + PTX + RT	329	64	2
CDDP + PTX/DCT	671	2	3
5FU/AF	3177	14	11
5FU + CDDP + RT	687	38	14

da :Sonis et al Cancer 2004 modificato

Patogenesi: non solo danno diretto all'epitelio di superficie

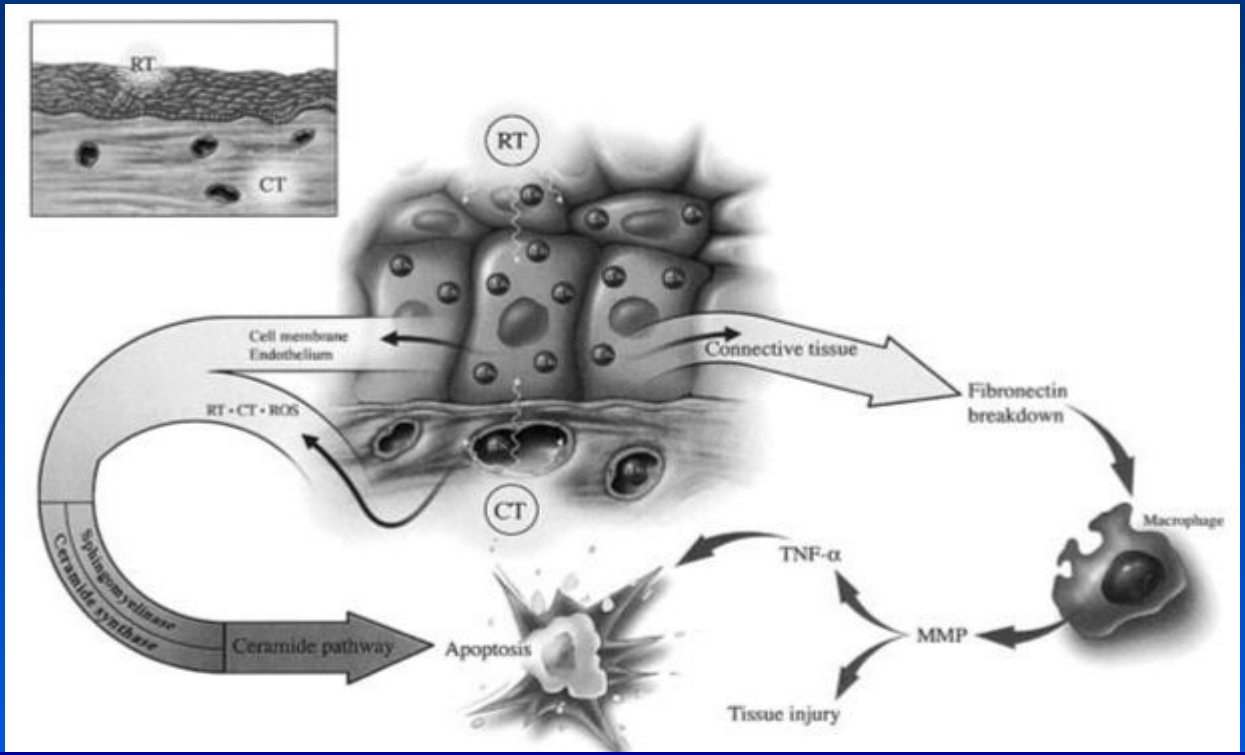
Fase I: INIZIAZIONE



CT o RT possono causare un danno diretto alla mucosa attraverso la formazione di agenti ossidanti (ROS) che modificano il DNA
La presenza di ROS stimola la trascrizione di NF-kB.

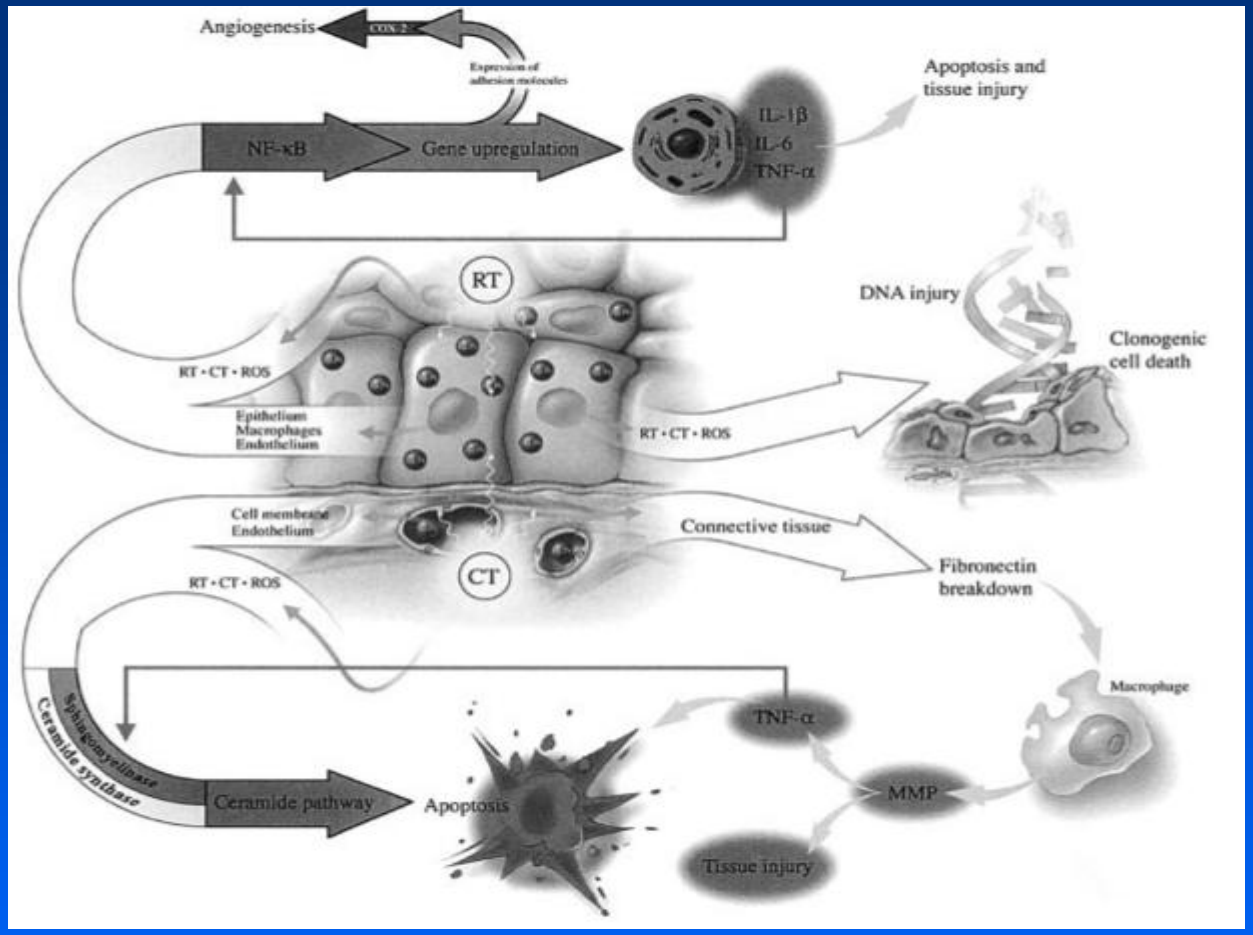
- Sonis ST Nat Rev Cancer 2004 -

Fase II: “up regulation”



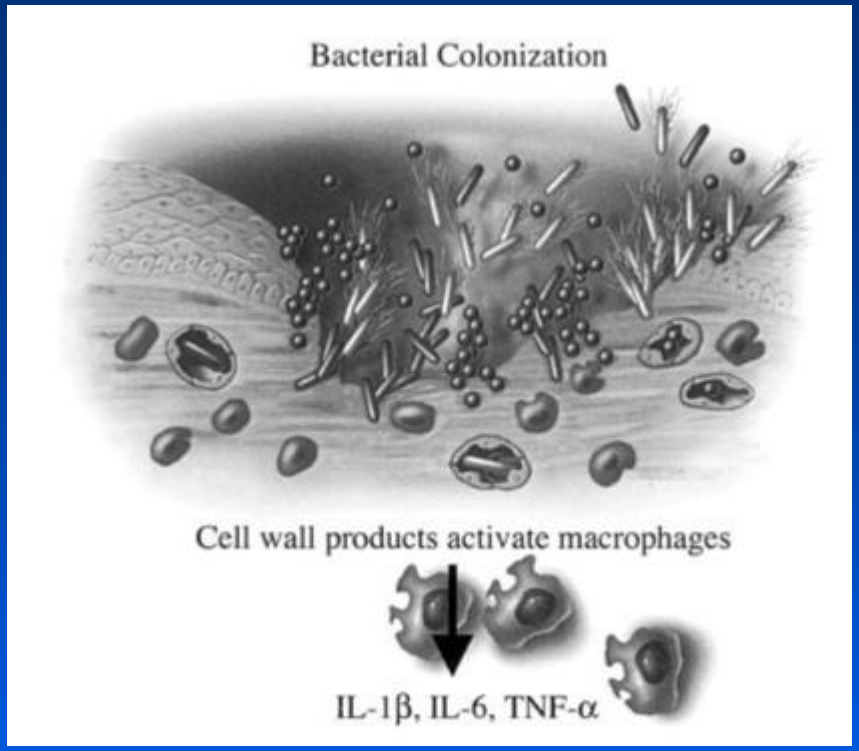
NF-kB stimola la attivazione di altri geni con produzione di TNF-a, IL-1B, IL-6 e conseguente danno tissutale (a livello della membrana basale).
attivazione di COX2 (stimolo angiogenetico) e produzione di Ceramide con apoptosi di cellule dello strato basale.
Alterazione del connettivo (fibronectina) ed attivazione di macrofagi con liberazione di MM proteinasi e danno tissutale

Fase III: amplificazione



Aumento ed amplificazione della produzione di citokine infiammatorie con meccanismi feed back.
Eventi localizzati prevalentemente nella sottomucosa con mucosa apparentemente normale ma biologicamente alterata

Fase IV: ulcerazione



Infiltrati tissutali costituiti da macrofagi come conseguenza dello stress ossidativo
Attivazione di linfociti T e produzione di molecole di adesione
Colonizzazione batterica con ulteriore attivazione di macrofagi e liberazione di citokine pro-infiammatorie.
Nel paziente neutropenico rischio di batteriemia

RV Lalla et al. Cancer 2014

MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy

ORAL MUCOSITIS

RECOMMENDATIONS **IN FAVOR** OF AN INTERVENTION
(i.e., strong evidence supports effectiveness in the treatment setting listed)

1. The panel *recommends* that 30 minutes of oral cryotherapy be used to prevent oral mucositis in patients receiving bolus 5-Fluorouracil chemotherapy (Level of Evidence II).

2. The panel *recommends* that recombinant human Keratinocyte Growth Factor-1 (KGF-1/palifermin) be used to prevent oral mucositis (at a dose of 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (Level of Evidence II).

3. The panel *recommends* that low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm2) be used to prevent oral mucositis in patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation (Level of Evidence II).

4. The panel *recommends* that patient-controlled analgesia with morphine be used to treat pain due to oral mucositis in patients undergoing hematopoietic stem cell transplantation (Level of Evidence II).

5. The panel *recommends* that benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (Level of Evidence I).

ORAL MUCOSITIS

RECOMMENDATIONS **AGAINST** AN INTERVENTION
(i.e., strong evidence indicates lack of effectiveness in the treatment setting listed)

1. The panel *recommends* that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste not be used to prevent oral mucositis in patients receiving radiation therapy for head and cancer (Level of evidence II).

2. The panel *recommends* that iseganan antimicrobial mouthwash not be used to prevent oral mucositis in patients receiving high dose chemotherapy, with or without total body irradiation, for hematopoietic stem cell transplantation (Level of Evidence II), or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer (Level of Evidence II).

3. The panel *recommends* that sucralfate mouthwash not be used to prevent oral mucositis in patients receiving chemotherapy for cancer (Level of Evidence I), or in patients receiving radiation therapy (Level of Evidence I) or concomitant chemoradiation (Level of Evidence II) for head and neck cancer.

4. The panel *recommends* that sucralfate mouthwash not be used to treat oral mucositis in patients receiving chemotherapy for cancer (Level of Evidence I), or in patients receiving radiation therapy (Level of Evidence II) for head and neck cancer.

ORAL MUCOSITIS

SUGGESTIONS **AGAINST** AN INTERVENTION
(i.e., weaker evidence indicates lack of effectiveness in the treatment setting listed)

1. The panel *suggests* that chlorhexidine mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (Level of Evidence III).

2. The panel *suggests* that granulocyte macrophage colony-stimulating factor (GM-CSF) mouthwash not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (Level of Evidence II).

3. The panel *suggests* that misoprostol mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (Level of Evidence III).

4. The panel *suggests* that systemic pentoxifylline, administered orally, not be used to prevent oral mucositis in patients undergoing bone marrow transplantation (Level of Evidence III).

5. The panel *suggests* that systemic pilocarpine, administered orally, not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (Level of evidence III), or in patients receiving high dose chemotherapy, with or without total body irradiation, for hematopoietic stem cell transplantation (Level of Evidence II).

GASTROINTESTINAL MUCOSITIS (other than the oral cavity)

RECOMMENDATIONS **IN FAVOR** OF AN INTERVENTION
(i.e. strong evidence supports effectiveness in the treatment setting listed)

1. The panel *recommends* that intravenous amifostine be used, at a dose of ≥340 mg/m2, to prevent radiation proctitis in patients receiving radiation therapy (Level of evidence II).

2. The panel *recommends* that octreotide, at a dose of ≥100 µg subcutaneously twice daily, be used to treat diarrhea induced by standard- or high-dose chemotherapy associated with hematopoietic stem cell transplant, if loperamide is ineffective (Level of evidence II).

SUGGESTIONS **IN FAVOR** OF AN INTERVENTION
(i.e., weaker evidence supports effectiveness in the treatment setting listed)

1. The panel *suggests* that intravenous amifostine be used to prevent esophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small-cell lung carcinoma (Level of evidence III).

2. The panel *suggests* that sucralfate enemas be used to treat chronic radiation-induced proctitis in patients with rectal bleeding (Level of evidence III).

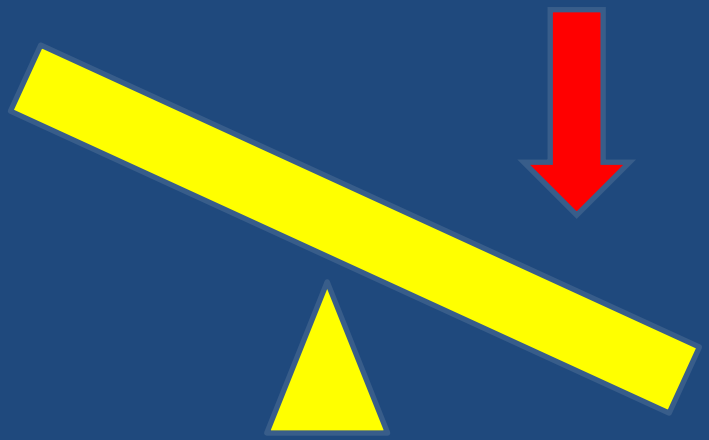
3. The panel *suggests* that systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to prevent radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (Level of evidence II).

4. The panel *suggests* that probiotics containing Lactobacillus species be used to prevent diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (Level of evidence III).

5. The panel *suggests* that hyperbaric oxygen be used to treat radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (Level of evidence IV).

“Diarrhea: a disorder characterized by frequent and watery bowel movements” *(CTC-AE v 4.0)*

50-70% dei pazienti (5-40% di grado severo)



	Regimen	Proportion with grade 3–4 diarrhoea (%)
Saltz et al, 2001[1]	Irinotecan	6%
	Irinotecan with infused fluorouracil or folinic acid	15%
O'Shaughnessy et al, 2002[2]	Docetaxel	5%
	Docetaxel with capecitabine	14%
Chau et al, 2005[3]	Bolus fluorouracil with folinic acid	16%
	Infused fluorouracil	5%
Falcone et al, 2007[4]	FOLFOXIRI	20%
	FOLFIRI	12%
Fuchs et al, 2007[5]	FOLFIRI	14%
	mIFL	19%
	capeIRI	47%
Van Cutsem et al, 2011[6]	FOLFIRI	11%
	FOLFIRI with cetuximab	16%
Tveit et al, 2012[7]	FLOX	10%
	FLOX with cetuximab	17%

FOLFOXIRI=oxaliplatin, irinotecan, fluorouracil, and folinic acid (leucovorin). FOLFIRI=folinic acid (leucovorin), fluorouracil, and irinotecan. mIFL=irinotecan with bolus fluorouracil. capeIRI=capecitabine and irinotecan. FLOX=folinic acid (leucovorin), oxaliplatin, and bolus fluorouracil.

Table 1: Randomised trial data of the frequency of grade 3–4 diarrhoea with different chemotherapy regimens

- Andreayev et al Lancet Oncol 2014 -

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.02: Sept. 15, 2009)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Fattori di rischio

Età > 65 anni

Sesso femminile

Polimorfismi genetici correlati al metabolismo del farmaco (DPD)

Ostruzione biliare/ S. di Gilbert

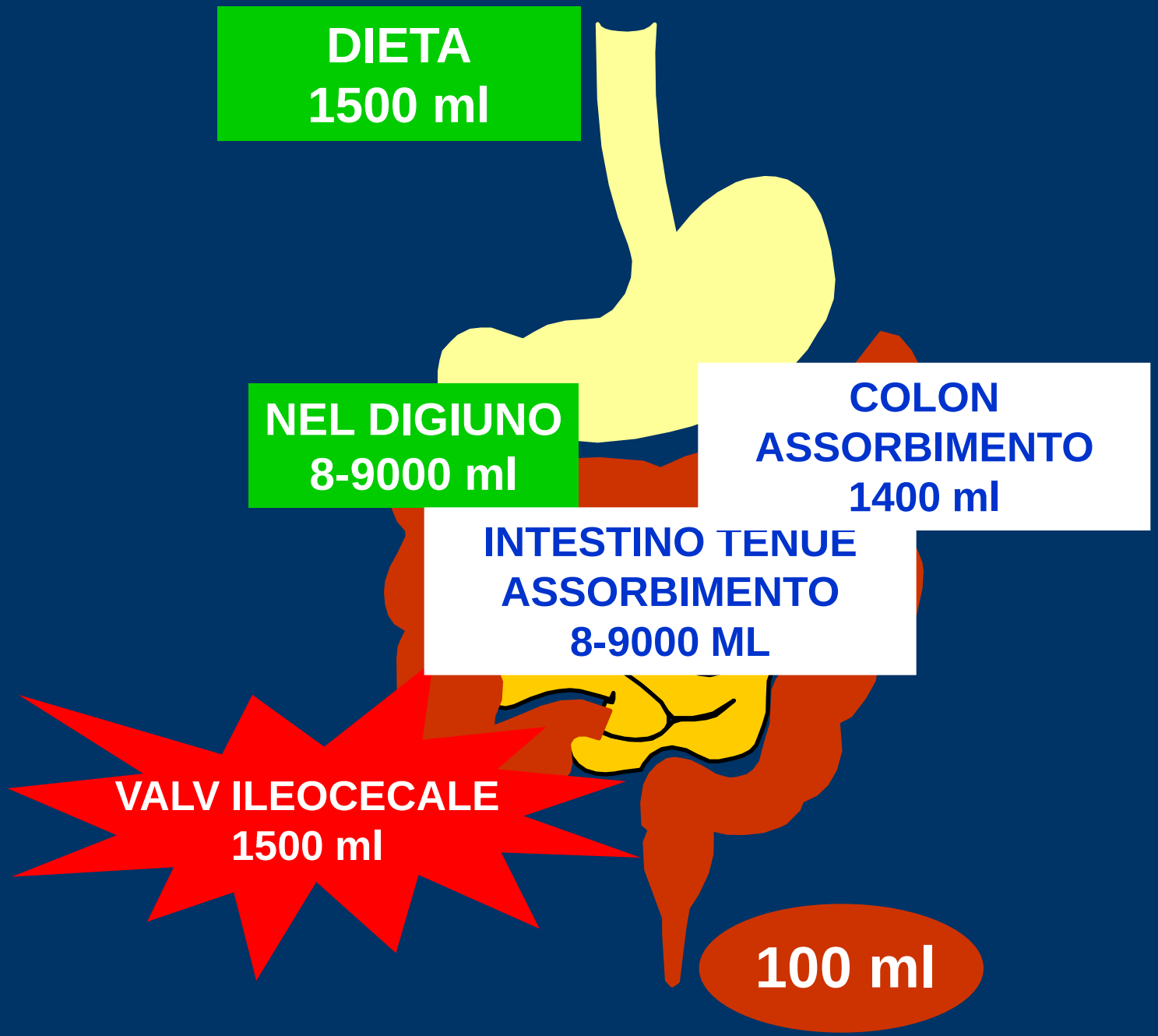
Patologie infiammatorie associate intestinali

Precedente storia di diarrea associata a CT

Precedente o concomitante RT

Famaco utilizzato

McQuade et al Int J Clin Med 2014


DIETA
1500 ml
NEL DIGIUNO
8-9000 ml
COLON
ASSORBIMENTO
1400 ml
INTESTINO TENUE
ASSORBIMENTO
8-9000 ML
VALV ILEOCECALE
1500 ml
100 ml

Patogenesi della diarrea da Chemioterapia

Danno endoteliale - Danno a cellule intestinali

Apoptosi e necrosi cellulare nelle cripte

Riduzione di goblet cells

Scomparsa dei villi e perdita della normale architettura

Aumentato stimolo secretivo (entro 24-96 h)

Alterata capacità di assorbimento

Perdita di enzimi : effetto osmotico intraluminale e minore riassorbimento di acqua

Rilascio di citochine, leucotrieni, prostaglandine, Infiltrati linfocitari T, ascessi criptici

Aumentata motilità

Alterazione della flora intestinale: infezioni opportunistiche

Chemioterapici associati a diarrea

Diarrea > 30%	Diarrea < 30%
• Capecitabine	• Carboplatino
• Docetaxel/Paclitaxel	• Ciclofosfamide
• Irinotecan	• Epirubicina
• Gefitinib/Erlotinib	• Gemcitabine
• Pemetrexed	• Methotrexate
• Busulfan	• Melphalan
• Sorafenib/Suntitinib	• Ibritumomab
• Everolimus	• Panitumumab/Cetuximab

Irinotecan

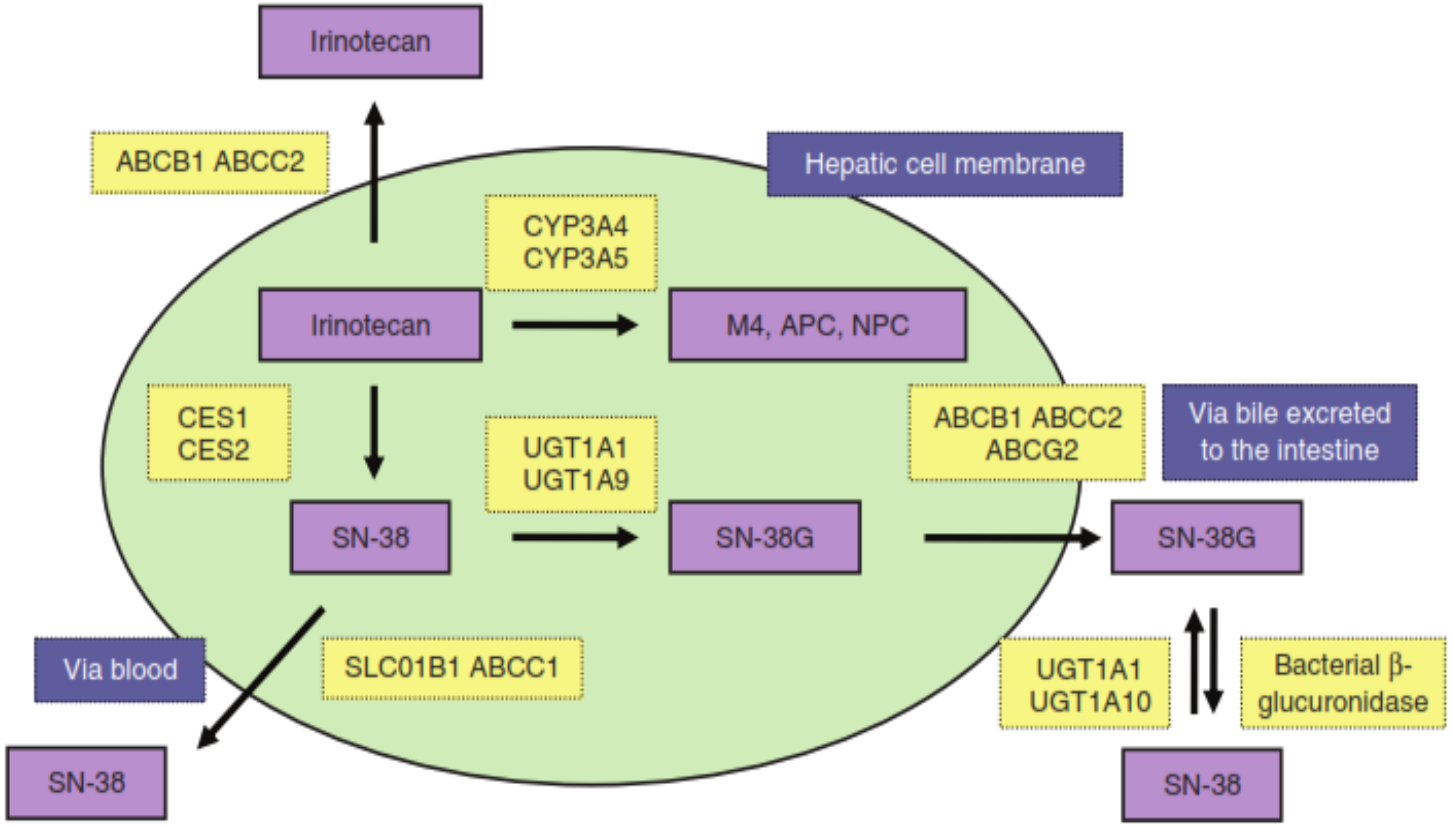


Figure 1. Metabolism of irinotecan. UGT, UDP glucuronosyltransferase; SN-38, 7-ethyl-10-hydroxycamptothecin;, CYP, cytochrome P450;, CES carboxylesterases; APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin; NPC, 7-ethyl-10-(4-amino-1-piperidino)carbonyloxy-camptothecin; M, oxidized metabolite; ABCB/C, ATP-binding cassette, sub-family B/C.

Stein A et al Ther Adv Med Oncol 2010

Diarrea da Irinotecan

Patogenesi verosimilmente secretoria ed essudativa

SN38 libero causa danno diretto alla mucosa intestinale con conseguente malassorbimento di acqua ed elettroliti

Manifestazioni evidenti già dopo 6 h a livello del digiuno (apoptosi cellulare delle cripte). A 48 h alterazione dei villi con perdita della normale architettura. A 72 h completa ablazione delle cripte. riduzione di goblet cell nel colon

aumentata secrezione di mucina a livello della mucosa colica e digiuno

Deplezione di glutamina

attività batterica di B-glucuronidasi che aumenta livelli intraluminale di SN38

Polimorfismi genetici: UTG1A1*28; ABCC2

Stein A et al Ther Adv Med Oncol 2010

Diarrea da Fluorouracile

Effetto tossico dose e schedula-dipendente

Maggiore tossicità con FU bolo o pro-farmaci (Capecitabine, S1)

Rischio aumentato con ac Folinico

Rischio aumentato con polmorfismi genetici (DPD, TS, MTHFR, Cytidine deaminasi)

Arresto mitotico delle cellule presenti nelle cripte, riduzione di enterociti con villi a funzione di riassorbimento e riduzione dell'area di riassorbimento

Aumento di MPO e citokine sieriche infiammatorie

Stein A et al Ther Adv Med Oncol 2010 ; Chang CT PLoS ONE 2012

Diarrea da Target therapy

Effetto tossico dose-dipendente

Il blocco di EGFR determina:

- alterato riassorbimento di Cloro

- danno mitotico su cellule intestinali

- alterazione microflora intestinale

Possibile meccanismo vasculitico nelle diarrea associate ad anti-VEGF

Danno alle cellule interstiziali di Cajal che hanno funzione di controllo sulla motilità intestinale

Stein A et al Ther Adv Med Oncol 2010

VOLUME 22 · NUMBER 14 · JULY 15 2004

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea

Al B. Benson III, Jaffer A. Ajani, Robert B. Catalano, Constance Engelking, Steven M. Kornblau, James A. Martenson Jr, Richard McCallum, Edith P. Mitchell, Thomas M. O'Dorisio, Everett E. Vokes, and Scott Wadler

Guidance on the management of diarrhoea during cancer chemotherapy

Lancet Oncol 2014

Jervoise Andreyev, Paul Ross, Clare Donnellan, Elaine Lennan, Pauline Leonard, Caroline Waters, Linda Wedlake, John Bridgewater, Rob Glynne-Jones, William Allum, Ian Chau, Richard Wilson, David Ferry

Diarrhoea induced by chemotherapy in cancer patients is common, causes notable morbidity and mortality, and is managed inconsistently. Previous management guidelines were based on poor evidence and neglect physiological causes of chemotherapy-induced diarrhoea. In the absence of level 1 evidence from randomised controlled trials, we developed practical guidance for clinicians based on a literature review by a multidisciplinary team of clinical oncologists, dietitians, gastroenterologists, medical oncologists, nurses, pharmacist, and a surgeon. Education of patients and their carers about the risks associated with, and management of, chemotherapy-induced diarrhoea is the foundation for optimum treatment of toxic effects. Adequate—and, if necessary, repeated—assessment, appropriate use of loperamide, and knowledge of fluid resuscitation requirements of affected patients is the second crucial step. Use of octreotide and seeking specialist advice early for patients who do not respond to treatment will reduce morbidity and mortality. In view of the burden of chemotherapy-induced diarrhoea, appropriate multidisciplinary research to assess meaningful endpoints is urgently required.

Trattamento

- **Idratazione** (perdite fino a 4-6 l/24 h)
- **Loperamide** dose iniziale di 4 mg seguita da 2 mg ogni 2 h fino a cessazione della diarrea. Dosi maggiori di 16 mg/die non sono indicate. Utile circa 30' prima dei pasti in modo da ridurre la motilità intestinale riflessa
- **Octreotide** indicato nella diarrea resistente a Loperamide. Diminuisce secrezione di VIP, riduce la motilità e la secrezione pancreatica, promuove l'assorbimento intestinale.
- **Atropina** utilizzato nella profilassi della diarrea da Irinotecan
- **Antibiotici** indicati nella diarrea G3-4 nei pz neutropenici (Ciprofloxacina, Norfloxacina, Rifaximina, Metronidazolo, Neomicina, Doxiciclina). Da escludere infezione da *Clostridium difficile*
- **Probiotici** utili formulazioni contenenti *Lactobacillus* nella prevenzione della diarrea associata a CT+RT

Andreyev J et al Lancet Oncol 2014; McQuade RM et al Int J Clin Med 2014

Trattamento

- **Codeina:** potrebbe rappresentare una alternativa alla Loperamide
- **Budesonide** è uno steroide ad azione topica sulla mucosa intestinale danneggiata. Agisce come antagonista di Prostaglandine. Risultati controversi nelle forme severe con aumento di rischio di infezione
- **Tiorfano** inibitore di Encefalinasi. Le Encefaline agiscono con effetto pro-assorbente ed aumentano l'assorbimento di Cl. Indicato nelle forme acute con componente infettiva.
- **Colestiramina** utile nelle forme associate a steatorrea da malassorbimento di acidi biliari. Utilizzo controverso.
- **Assorbenti (Diosmectite)** utili nelle forme non gravi. Aumentano la consistenza delle feci riducendo i dolori addominali e la frequenza delle evacuazioni. Accentuano la funzione protettiva sulla mucosa intestinale di glicoproteine di superficie; neutralizzano tossine batteriche

Andreyev J et al Lancet Oncol 2014; McQuade RM et al Int J Clin Med 2014

Diarrea non complicata

Diarrea G1-2

- Dieta adeguata
- Loperamide 4 mg poi 2 mg ogni 4 h fino a 12 h da arresto diarrea

La diarrea non si risolve in 24 h:
- Loperamide 2 mg ogni 2 h
- antibiotici orali (non raccomandati se diarrea associata a RT)

La diarrea non si risolve dopo altre 24 h:
- stop Loperamide ed inizia Octreotide
- esami colturali
- adeguata idratazione e controllo elettroliti

Diarrea complicata

Diarrea G3-4
Diarrea G1-2 con:
dolori addominali
febbre
neutropenia
sanguinamento
nausea/vomito > G2
Iniziale disidratazione

- Idratazione
- controllo elettroliti sierici
- Octretide con aumento di dosi sulla base della sintomatologia
- antibiotici ev
- meno efficace Loperamide
-Esami colturali
-Controindicatai esami endoscopici nel pz neutropenico

Grazie