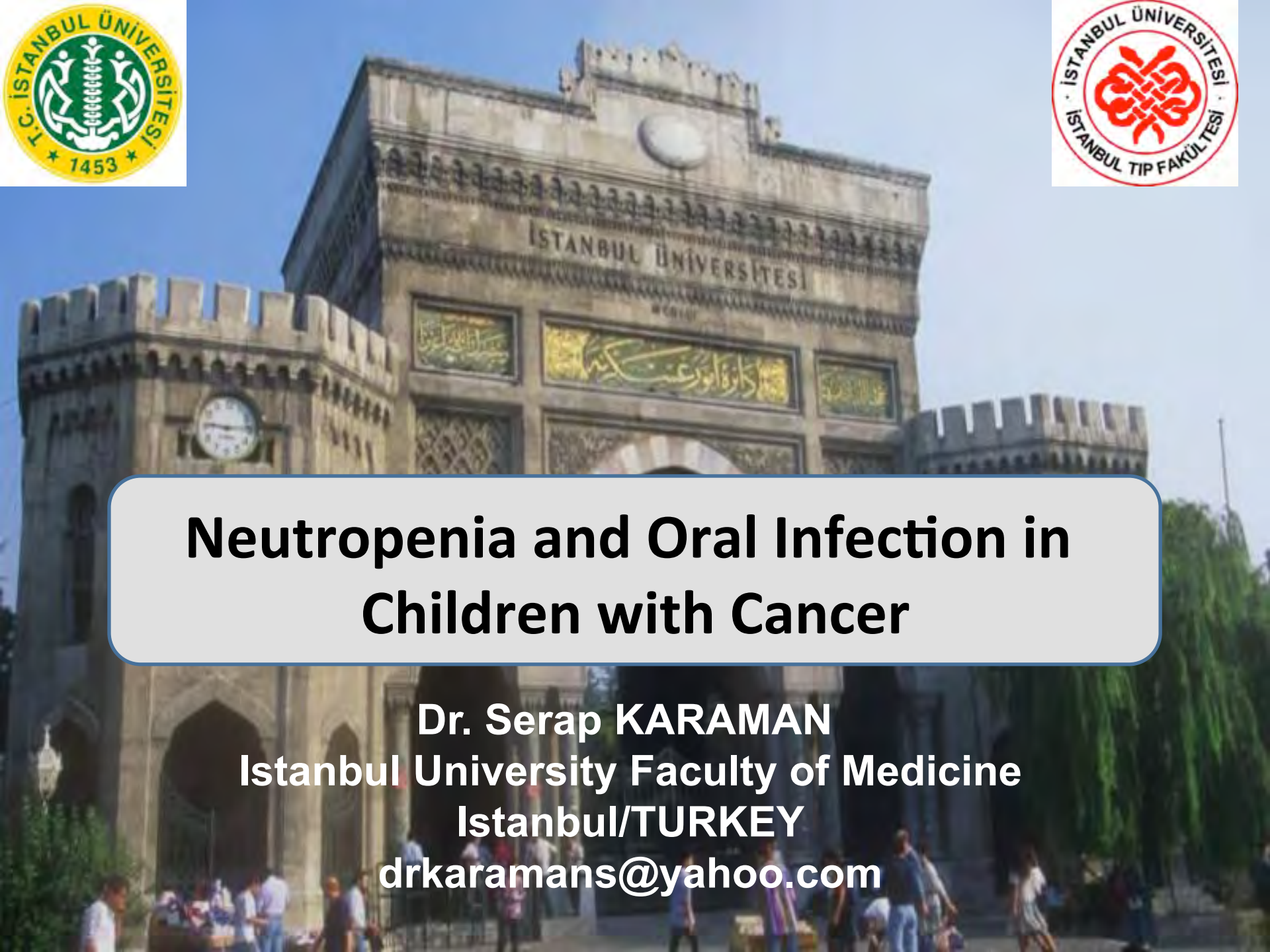

Neutropenia and Oral Infection in Children with Cancer

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Presentation overview

- Childhood cancer and neutropenia
- Oral complications during neutopenia
- Approaching oral infections during cancer therapy
- Cases

Childhood cancers differ from adults

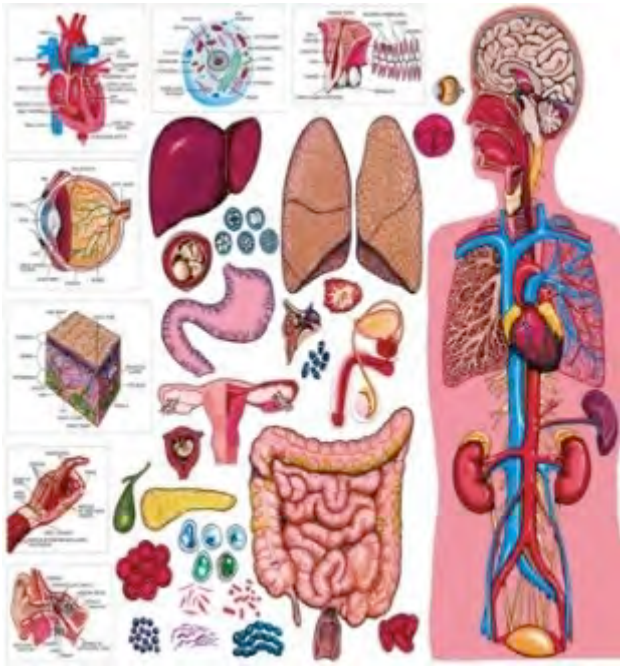
- Rapid tumor growth with shorter doubling time
- Shorter duration of symptoms with usually “little” time for diagnosis and start of therapy

- More intensive and multimodal treatment protocols
- Much more severe and frequent disease or therapy related side effects

- Significantly **higher survival rates**

Complications of the therapy

- Cancer therapy affects all body
- Especially systems and tissues with rapid renewal rate are affected seriously, such as
  - –Oral and intestinal mucosa
  - –Bone marrow
  - –Skin



Cancer and gastrointestinal system

- Both cancer itself and treatment derange the immune system and also induce inflammation and damage to the gastrointestinal mucosa
- Oral cavity is the most common site affected throughout the GI system

- Children experience 3 x more oral complications than adults do because:
  - Tissue sensitivity to radiation in children is 30% greater than adults
  - Higher mitotic index of normal tissues of the growing child (increased cell turnover)

Oral complications in patients with cancer

- They develop in 40-90 % of child patients during cancer therapy and,

- They are still one of the the leading causes of systemic infections, therapy related morbidity and mortality

Allen et al. 2010 Kitap

Oral complications in patients with cancer

- Mucositis/stomatitis
- **Oral infections**

Most common and serious, especially in neutropenic patients

- Dental demineralization
- Hypersensitive teeth
- Periodontal problems
- Xerostomia/salivary gland dysfunction
- Dysphagia and gingival bleeding

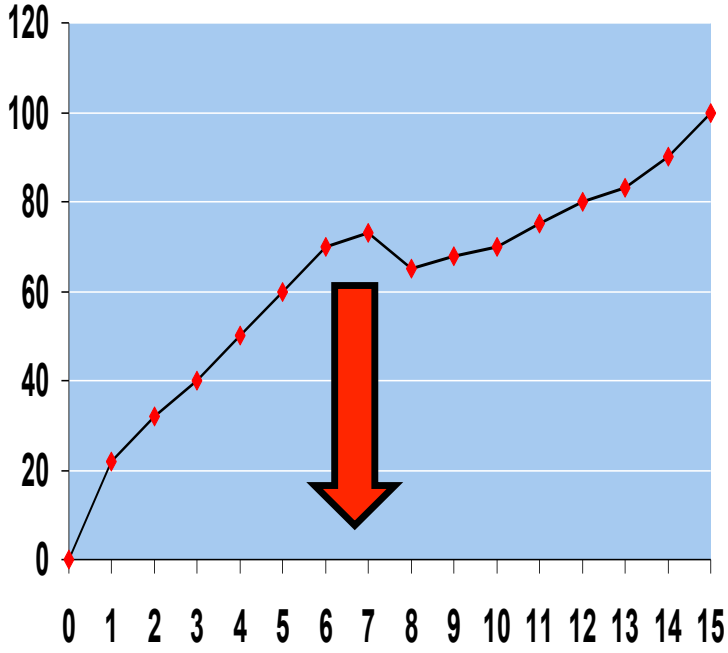
Elad S. Et al. Support Care Cancer;2015:23:223–236

Risk factors associated with oral infections

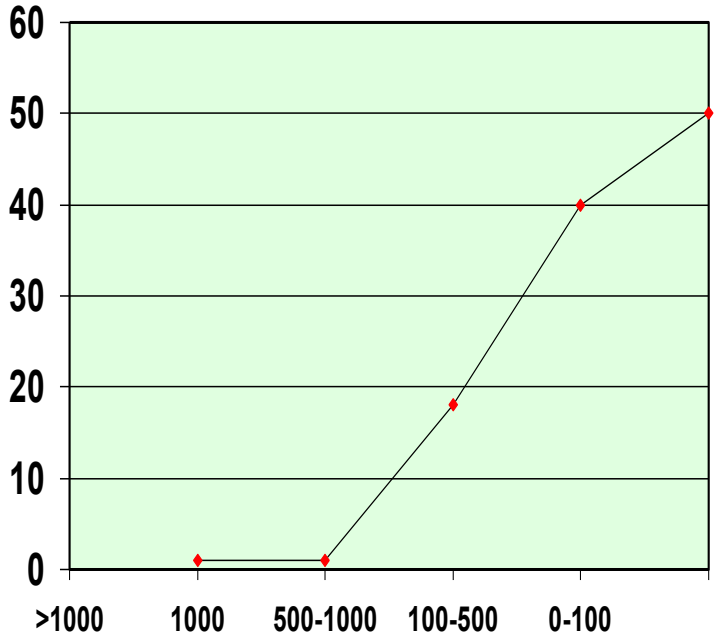
- **Neutropenia/Impairment of neutrophil functions**
- Lenfopenia/ Impairment of lymphocyte functions
- Mucositis, Xerostomia
- Poor nutritional status, oral health and hygiene
- Cancer type, stage and treatment protocol
- Prior history of oral and non-oral infections
- History of pulpal, periodontal disease, pericoronitis and endodontic therapy

Lerman MA, et al. Dent Clin N Am 2008,129-53

The risk of infections is related to **duration of neutropenia** and absolute **neutrophil count**



Duration of neutropenia in days



Absolute neutrophil count /mm3

The risk of infections is positively correlated with absolute neutrophil count and duration of neutropenia

Neutropenia and Infections

- Bacteriemia
- Skin- soft tissue infections
- Respiratory infections
- GI system infections
- Urinary tract infecitons
- **Oral-pharyngeal infections: 10-50 %**

Wilberg P, et al. Support Care Cancer 2012;20:3115-3122

Oral Bacterial Infections

- The most frequent documented source of **sepsis** in the immunocompromised cancer patient is the **mouth**

- The oral mucositis is a major risk factor for bacteremia

Allen G, et al. Clin J Oncol Nurs 14:481–490

Effect of multimodal treatment on oral complications

- The patients received **combination of chemotherapy and radiotherapy** have the highest incidence of oral infection

- Radiotherapy also induce mucositis, xerostomia and mucosal damage which aggravates the oral manifestations and infection in addition to effects of chemotherapy

Sonalika WG, et al. Oral Oncol. 2012;48:881-886.

Cancer type associated with oral infections

- Oral complications including infections are most commonly seen in children with **hematologic malignancies** such as,
  - Leukemia
  - Lymphoma

Otmani N, et al. Int J Pediatr Dent 2011;21.211-16

Clinical outcome of oral complications

- It is often very painful for a child with gross changes on the quality of life
  - Oral feeding becomes difficult
  - Need for nasogastric tube feedings or TPN
  - More days in hospita l!!

- Disruption of mucosal physical barrier producing a gate for bacterial invasion
  - Increased risk of local and subsequent systemic infection, even sepsis
- Resulting in the reduction of chemotherapy doses or postponing the therapy

Feushner C. Supportive Care in Pediatric Oncology 2015

Oral infections

Bacterial (25%)

- Gram (-):15%
- Gram (+):10%

Viral

- Herpes (25%)

Fungal (35%)

Candida albicans
Candida Non albicans

Allen G, et al. Clin J Oncol Nurs 2010;14:481–490

Oral bacteriel infections

Clinical spectrum
Odontogenic infections
Infections related to caries and nonvital teeth
Periodontal infections and pericoronitis
Parotitis
Bacteremia

Agents
Streptococcus viridans
Stomatococcus muciliaginosus
Coagulase negative staphylococci
Klebsiella pneumoniae
Pseudomonas aeruginosa
Echericia coli

Allen G, et al. Clin J Oncol Nurs 2010;14:481–490

Oral fungal infections

Clinical spectrum
Oropharingeal candidiasis
Deep fungal infections

Agents
Candida albicans
Non-candida albicans
Aspergilloz
Fusarium
Mukormikozis
Rhizopus

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Oral viral infections

Agents
Herpes Simpleks Virus
Human Papilloma Virus
Ebstein Barr Virus
Cytomegalovirus

Clinical spectrum
Herpetic gingivostomatit
Intaroral zoster
Oral hairy leukoplakia
Oral condyloma
Oral papilloma

James H. Feusner (Eds). Supportive Care in Pediatric Oncology 2015

Case-1

- A 7-year-old-boy with acute leukemia
- Phase-1 induction, ALL BFM 2000 protocol
- At day 21 of treatment, febrile neutropenia with ANC zero/µL
- On physical examination just a mild oral mucositis

- Broad-spectrum antibiotic was started,
- At the 5th day of antimicrobial treatment, worsening mucositis with persistant fever, caspofungin was added

Case-1

Case-1

- On the 3rd days of treatment with caspofungin, she became afebrile.
- **Candida kefyr** was isolated from both central catheter and peripheral venous cultures and then catheter was removed.

- Antifungal therapy was stopped after 14 days with total recovery of the oral lesions and negative cultures.
- We questioned the mother again and learned that she gave regularly kefyr to our patient off the record!

Case-2

- 11 years-old-male, High Risk ALL
- Bad oral and dental hygiene at diagnosis, but to start treatment rapidly, we do not have the time for dental treatment.

- After the HR block including high dose MTX, steroid, cytarabine; grade 3 mucositis with fever was appeared during the neutropenia, despite routine mouthcare
- In addition to blood, culture was taken from white plaque on the palate and antifungal therapy was started.

Case-2

Case-2

- His was severely neutropenic for about 14 days
- Blood culture was positive **Candida albicans**
- At 14 days of treatment, antifungal therapy was stopped with 2 negative blood cultures.

- He had repeated atttacks of febrile neutropenia and bacteremia during the subsequent therapy
- Significant delay in chemotherapy for several times

Clinic spectrum of oral candidiasis

- Pseudomembranous candidiasis (thrush)
- Erythematous candidiasis (red appearance)
- Hyperplastic candidiasis (white tissue overgrowth)
- Angular cheilitis (redness at corners of mouth).

- **Oral candidasis** is the most common oral mucosal infection in cancer patients (%7.2-50)
    - Pre-treatment:7.5%; during treatment:39.1%, after the end of treatment 32.6%
- The majority of infections are due to **C. Albicans**

Lalla RV, et al. Support Care Cancer 2010;18:985–992

Prevention of oral fungal infections

Topical antifungal agents

- There is inconsistency in the efficacy of topical antifungal agents as antifungal prophylaxis for patients receiving cancer therapy. No recommendation possible

Systemic antifungal agents

- Systemic antifungals are effective in preventing oral fungal infection

Oral Care Study Group, MASCC/ISOO

Case-3

- 8 years-old-boy
- ALL, high risk
- During deep neutropenia, a progressive white/ yellowish lesion on the hard palate
- Local and systemic cultures were taken
- Broad spectrum antibiotics and antifungal therapy was scheduled

Case-3

- Despite treatment, the lesion progressed
- On imaging infiltration of hard palate, soft palate, gingival arch, nasal cavity till pterygoid fossa and infraorbital area
- Severel, consequtive surgical excisions and debridements with wide curetage of necrotic tissues
- Culture of debridement material was positive for **Mucor spp.**
- **He was diagnosed as mucormycosis**

Case 3-Palatal Prothesis

Mucormycosis

- Rapidly progressive, invasive fungal infection
- Mostly hard palate involvement with bone and soft tissue infiltration
  - If the infection is localised to oral cavity, the necrotic lesion may be white in color, in contrast to usual “black lesion”.

- If any fungal lesions was suspicious for infiltration of deep tissue or unresponsive to standart teatment, depending on the clinical features
  - Imaging – CT, MRI
  - Antigen specific fungal tests and biopsy for patohologic and microbiologic evaluation

Case-4

- 11 years-old-girl
- Hodgkin lymphoma, Stage 4A
- Oral ulcers and vesicular lesions on the upper lip during neutropenia
- Herpetic gingivostomatitis was the diagnosis
- Systemic acyclovir was started

Herpes Simplex Virus (HSV)

- **HSV type 1** is the most common viral pathogen isolated from mucosal lesions in immunocompromised patients
- It is a latent virus and may reactivate with several predisposing factors resulting in immundysfunction or suppression

- 60-90% **of healty population** meet HSV-1 in their lifetime with **only 1 %** of them present with herpetic gingivostomatitis
- But repeated herpetic infections is seen about **20-40%** of **immuncompromised population**

- Acute painful oral ulcers in cancer patients, regardless of clinical appearance, must be considered to be recrudescent HSV until proven otherwise

Mark A. Lerman , et al. Dent Clin N Am;2008:52:129–153

Prevention and treatment HSV

- Acyclovir and valacyclovir have been found effective for both the prevention and treatment or reactivation of HSV infections in cancer patients

Oral Oral Care Study Group, MASCC/ISOO

Case-5

- 11 years-old-boy
- Medulloblastoma
- Radiotherapy and comcomitant chemotherapy
- 5 days after the completion of chemo-radiotherapy, painful oral ulcers developed
- As he was deeply neutropenic, systemic acyclovir was started
- He had also fever and broad spectrum antibotic was scheduled

Case-5

In patients who have cancer, recrudescent HSV may lead to potentially life-threatening disseminated disease

Varicella-zoster virus (VZV)

- VZV causes primary varicella and the recurrent infection
- Vesicles and/or ulcers involving the skin or oral mucosa along one nerve dermatome
- In immunosuppressed individuals, complications may be severe and may include dissemination, bacterial superinfection, scarring, and death

Glenny AM, et al. Cochrane Database Syst Rev 1 (2009) :CD006706

Rare oral viral infections

- **Ebstein- Barr Virus:** Even not so commonly we can see also EBV related lesions in children with cancer usually as coenfected with candida

- **Cytomegalovirus:** Oral lesions appears as non specific painful ulcers and may persist for weeks even months on mucosal surfaces

- **Human Papilloma virus:** Infections are not so common in pediatric population but it should be suspected in the presence of pink, painless papillary lesions on mucosal surfaces.

James H. Feusner (Eds). Supportive Care in Pediatric Oncology 2015

Case-6

- 5 years-old-male
- Primary HLH, with prolonged immunosuppression
- After multi drug chemotherapy, white, papillary lesions was developed during neutropenia
- Local swab culture was positive for S. maltophilia

Stenotrophomonas maltophilia

- Gram negative bacil
- Immuncompromised individuals are at a significant risk for infection by S. Maltophilia

- Risk factors for S. Maltophilia **infection-associated mortality** include malignancy, severe septic shock and organ failure

Oral Bacterial Infections

- Most bacterial infections arise from the patient's endogenous normal oral micro-flora
- A small proportion of bacterial infections comes from exogenous sources or environmental exposure

- The incidence of gram positive cocci has been increasingly reported in neutropenic cancer patients
- It is independent risk factor for anaerobic bacteremia after Hematopeatic Stem Cell Transplantation

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What we do in our daily practice for dental care ?

- Pre-treatment consultation to dentist

- If there is enough time to start therapy, dental (filling, extraction etc) and periodontal interventions are performed
- But this is not always possible in practice!

Routine mouth care in our daily practice

- Regular brush teeth with a soft brush or oral sponges designed for oral care, 2-3 times daily (is possible after each meal)
- Normal saline mouth-wash 3-4 times/day
- Bicorbanate mouth-wash, if there is xerostomia or thick saliva
- Clorhexidine rinse is not routinely performed
- Floride gel might be used as clinical preference
- Dietary regulations with eating soft easy-to-chew foods avoidance of too hot, spicy, sticky or acidic foods

Conclusion

- In children with cancer, oral infections are an important cause of morbidity and mortality

- Dental assesment should be a part of pre-treatment evaluation of all children with cancer

- If possible, with enough “safe” time to treatment, dental and periodontal critical interventions should be performed as soon as possible

Take home message

- Dentist should be an active member of the pediatric oncology team

- Good oral hygiene and dental care should be applied before and during treatment to reduce the risk of oral infections and related morbidity and mortality

- Oral hygiene advices and education for routine mouthcare should be given to patients and parents

Take home message

- In addition to pre-treatment evaluation, a regular dental, oral assessment by dentist should be included into the treatment programme

- Close monitoring of the oral cavity allows for timely diagnosis and treatment of oral infections.

- Oral cultures and/or biopsies of all suspicious lesions should be performed and prophylactic medications should be initiated until more specific therapy can be prescribed

THANK YOU

THANK YOU


Prof. Dr. Welke