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### Prediction and prevention of infectious complications in children with cancer

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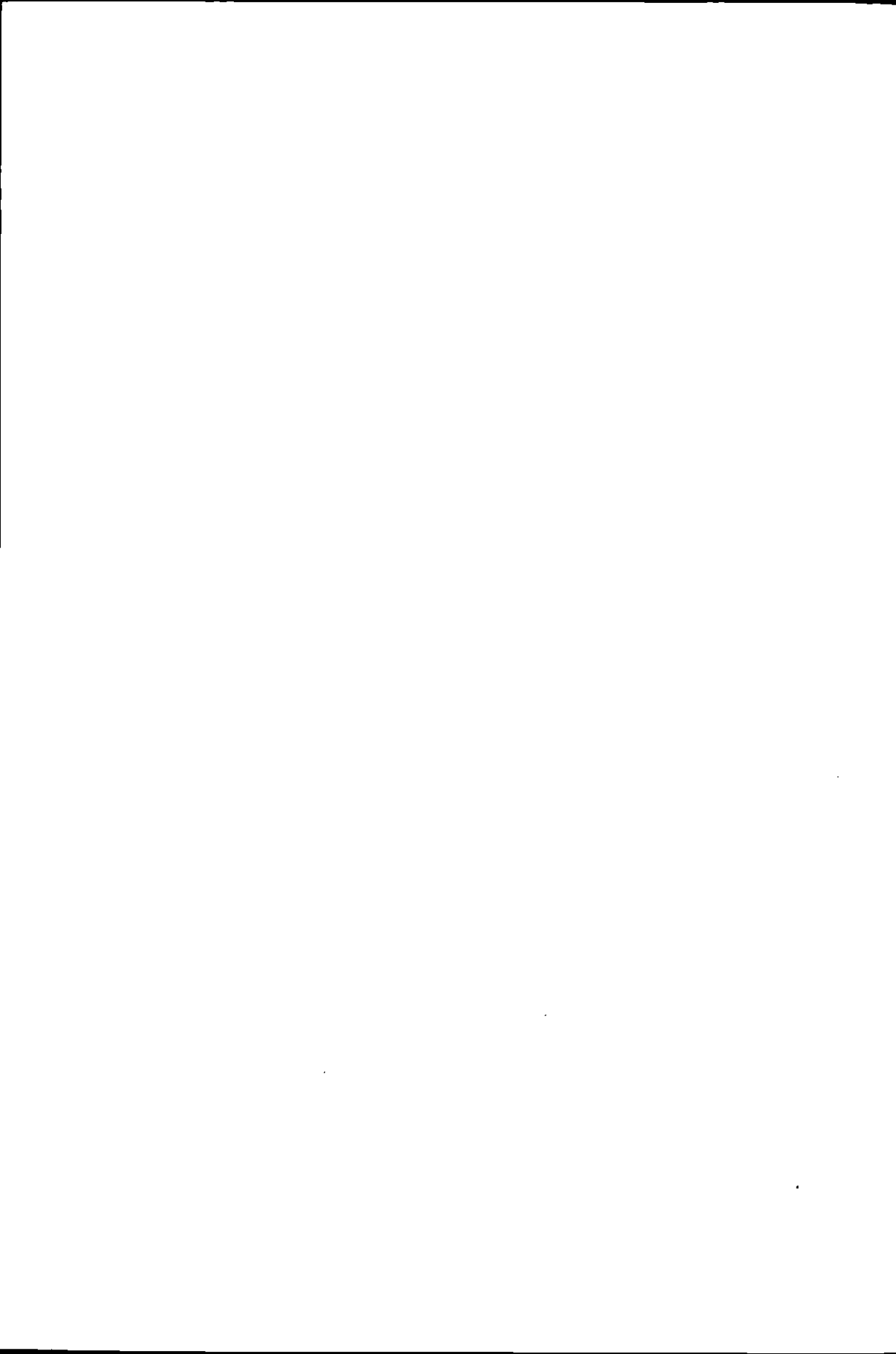
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Ntwana umngane wami omkhulu  
"the child is my best friend"

# Chapter

## Summary



## General overview

Infections in patients with cancer remain an important problem. Therefore this thesis focused on prediction and prevention of infectious complications in patients with cancer.

The first part of this thesis focusses on immunological parameters as possible **predictors of severity** of infection, such as the significance of mannose-binding lectin in infectious complications, and the role of cytokines in predicting the severity of the clinical course of neutropenic enterocolitis.

The second part of the thesis focuses on **prevention of infections**. Three aspects will be discussed: 1) prevention of Gram-positive catheter-related infections; 2) prevention of bacteremia during episodes of neutropenia using selective decontamination of the digestive tract (SDD) 3) prevention of varicella in varicella-zoster virus (VZV) IgG-negative children with cancer.

By gaining more insight in predicting and preventing infectious complications during the treatment of cancer patients, care and management of infections in this group of patients will improve.

In **Chapter 1** a general overview is presented on epidemiological aspects, causes and complications of infections in oncology patients. Two infections which can cause serious complications are discussed in more detail. These are neutropenic enterocolitis, bowel wall inflammation during deep neutropenia, and varicella zoster (VZV) infection which can lead to serious complications in patients who are neutropenic and not protected against VZV.

In **Chapter 2** a retrospective study is presented on risk-factors for infection in a single oncology unit in South-Africa. Limited data are available on infectious complications in pediatric oncology patients in countries, where most patients come from rural area's. Most children are admitted in an advanced stage of their disease. The poor housing circumstances, the long travel distances and therefore the long duration of hospitalization might influence the risk for infection. Between 1991 and 1995 all data on positive blood-cultures in pediatric oncology patients were collected, after which the medical records were studied. 200 separate episodes of bacteremia were recorded in 83 patients. Of these 200 episodes 83 were first bacteremic episodes. Of the 83 first bacteremic episodes 8 ended in death of the patient. Mainly Gram-negative organisms were seen, resistant *Acinetobacter Baumannii* played a major role. In the following bacteremic episodes fungal organisms were more important, mainly *Candida parapsilosis*. A risk-factor for infection was the presence of a tunnelled central venous catheter (CVC). The mean incidence of catheter related infections was 3.3 episodes per 1000 catheter days. Of all fungal infections 64% were reported in children with a CVC. Striking finding was the high incidence of Gram-negative organisms and a relative low incidence of Gram-positive organisms. Cause of the increased incidence of resistant *Acinetobacter Baumannii* and fungal organisms is most likely the long hospital-stay of these patients (mean 83 days) which could lead to higher rates of

colonization and indirect transmission between patients. Gaining insight in infectious complications in this group of patients allows us to consider intervention trials to reduce Gram-negative and fungal infections.

### **Chapter 3 and 4 focus on prediction of the severity of the course of the infection**

In **Chapter 3** a pilot study is presented evaluating the role of mannan-binding lectin deficiency (MBL) in pediatric oncology patients with neutropenic fever. MBL is a serum protein produced in the liver that plays a critical role in the innate immune response. 25% of the normal population is MBL deficient. This deficiency is recognized clinically in patients with co-existing immune-defects. Possibilities are now available to start replacement therapy with MBL. A prospective study needs to gain insight in the patients who will benefit most from replacement therapy with MBL. Over a period of 8 months all pediatric oncology patients who were expected to become neutropenic were considered for inclusion. From these patients MBL genotyping and MBL serum levels were performed. The clinical outcome parameters looked at were duration of fever, duration of neutropenia, signs of septicemia, intensive care admission and mortality due to infection. Forty patients were genotyped of which 24 (60%) had a febrile neutropenic episode. The incidence of *MBL* exon-1 gene mutations was found to be 32.5% and the incidence of MBL-deficiency (<800  $\mu\text{g/L}$ ) was 32.5%. No correlation was found with either the severity or frequency of the infections, although a trend was found towards a longer duration of neutropenia in the MBL-deficient group of patients. Most of the included patients were not "newly diagnosed" patients but had been on chemotherapy at least several months (median 8 months, range 0-59 months). 70% of all patients presented with a severe neutropenia (<100x10<sup>9</sup>/L). Because of the severe neutropenia the effect of MBL deficiency might be completely overshadowed. We will extend this cohort with "newly diagnosed" patients to identify the subset of patients who might benefit from mannan-binding lectin substitution.

In **Chapter 4a** a case-report is presented describing 2 patients with an enterocolitis. In the first patient this was caused by *Clostridium difficile* and in the second patient no organism was found, but the pathological severity resembled a typhlitis-like picture. In **Chapter 4b** a prospective study is presented of 25 pediatric oncology patients admitted between 1998 and 2002 with the clinical suspicion of neutropenic enterocolitis. Inclusion criteria were fever, neutropenia, abdominal pain and diarrhea. 8 of these children were admitted to ICU. On day 1, 3 and 7 clinical parameters and laboratory parameters were done, this also included a rectoscopy on day 1 and immunological parameters (CRP, IL-8, IL-6 and IL-10) on day 1, 3 and 7. The main findings of the study showed that clinical parameters, rectoscopy, and blood or stool-cultures did not predict the severity of the course of neutropenic enterocolitis. Immunological parameters were better predictors. If CRP on day 1 >150 mg/L then the chance of admittance to ICU was 6.4x higher than in children with the same complaints and a lower CRP. For IL-8 this difference

was even more significant. The chance of ICU admission was 11.3 x higher if IL-8>1000 pg/mL, 6 out of 7 ICU admissions had a level>1000 pg/mL, compared to 2 out of 16 non-ICU patients. In this cohort of patients IL-8 was considered the best predictor of severity of the clinical course of neutropenic enterocolitis. Future trials will be directed at intervention of the high risk patients, possibly by starting inotropics early, or giving granulocyte-transfusions.

## **Chapter 5, 6 and 7 focus on prevention of infection**

In **Chapter 5** a systematic review is presented on the use of prophylactic antibiotics to prevent Gram-positive catheter-related infections. One of the main complications of a tunnelled central venous catheter is the risk for infection. Most catheter-related infections are caused by Gram-positive organisms. There is no consensus on the use of prophylactic antibiotics to prevent Gram-positive catheter-related infections. Therefore this review was done. All randomized trials on both adult and pediatric oncology patients between 1966 and 2003 were searched. 33 trials were identified and 9 could be included. 4 trials reported on vancomycin or teicoplanin before insertion of the catheter, and 5 trials reported on flushing the catheter with a combination of vancomycin and heparin. In the 4 trials reporting on antibiotics before insertion of the catheter, there were 17 patients with a Gram-positive catheter related sepsis in the group receiving antibiotics (n=95) and 30 patients in the control group (n=92). The Odds ratio found was 0.46 (95 % CI 0.24-0.91). In the 5 trials reporting on flushing the catheter with vancomycin and heparin, there were 13 patients with a Gram-positive catheter related sepsis in the group receiving the flushing method of vancomycin and heparin (n=153) and 31 patients in the control group (n=189). The Odds ratio found was 0.43 (95% CI 0.21-0.87). The conclusion is that both interventions in a high-risk patient are beneficial. To apply the above strategies will depend on the base-line infection risk of the patient. Patients with hematological malignancies and bone-marrow transplant patients will benefit from prophylactic antibiotics prior to insertion of the catheter or flushing the catheter with the combination of vancomycin and heparin to prevent Gram-positive catheter-related infections.

In **Chapter 6** a systematic review is presented on the efficacy of the use of selective gut decontamination in oncology patients. This strategy has been known since the early 70's. Gram-negative bacteremia's are decreased with effective use of the SDD.

No consensus on it's use has been achieved, mainly because the effect on decreasing infection-related mortality was not known, and the fear for creating resistant strains.

A systematic review was performed including all randomized trials between 1966 and 2002. A total of 21 trials met the inclusion criteria. Seventeen trials compared SDD (quinolones or Trimethoprim/sulfamethoxazole (TMP/SMZ)) to no SDD, and 4 trials compared quinolones to TMP/SMZ. The incidence of Gram-negative bacteremia's significantly decreased. There were 59 patients in the control group with a Gram-negative bacteremia (n=517) and in the SDD group

25 patients (n=530). The OR was 0.39 (95% CI 0.24-0.63). Quinolone-based regimens showed a stronger reduction in Gram-negative bacteremia's, and TMP/SMZ based regimens showed a stronger reduction in Gram-positive bacteremia's. Infection related mortality due to bacterial causes decreased with the use of SDD. There were 23 patients who died of an infectious cause in the SDD group (n=564) and 39 patients in the control group (n=551). An OR of 0.49 was found (95% CI 0.27-0.88).

From our results we consider that TMP/SMZ or quinolone prophylaxis should be administered to cancer patients with a high baseline risk for infections, such as patients with hematological malignancies, autologous and allogenic bone-marrow transplant patients and solid tumor patients who have an expected neutropenia of at least 7 days.

In **Chapter 7** the focus is on prevention of varicella zoster infection in pediatric oncology patients. One patient is presented in **Chapter 7a**. Until now many trials have been performed on administering live attenuated varicella vaccine to this group of patients. In the trials performed chemotherapy was stopped one week before and two weeks after the vaccination. Seroconversion occurred in 95% of vaccinees after 2 doses of vaccination. In **Chapter 7b** a prospective pilot-study is presented. This is the first cohort of pediatric oncology patients who received the attenuated live varicella zoster vaccine in a relative early phase of the chemotherapy without interrupting the chemotherapy. Eleven patients with either a hematological malignancy (n=8) or a solid tumor (n=3) were vaccinated with VZV vaccine during chemotherapy. Seroconversion occurred in 8 of the 11 patients (72.7%). The only adverse effects consisted of a mild rash (50-200 lesions). In none of the patients chemotherapy needed interruption. This study demonstrates that it is feasible to administer VZV-vaccine in an early stage of chemotherapy without interruption of the chemotherapy. This will largely reduce the incidence of severe varicella during the complete course of chemotherapy. Larger cohorts of pediatric oncology patients will be required to determine the benefit of this strategy compared to the strategies studied so far.

In the closing **Chapter 8** all the results found on predicting the course of severity of infection and preventing infections are further discussed and proposals for future trials are given;

- mannan-binding lectin substitution in MBL-deficient oncology patients,
- intervention trials on high risk neutropenic enterocolitis patients such as the administration of granulocyte transfusions or substitution of endothelial growth factor.

- Trials on VZV vaccine achieving a higher conversion-rate in oncology patients without stopping chemotherapy, determining the time to boost these patients, and gaining more insight in response to household contacts after vaccination.

- Implementation of systematic reviews in clinical practice