



**Karolinska  
Institutet**

**Institutionen för Medicin, Solna**

# **Aetiology and infection susceptibility in neutropaenic patients**

## **AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Welandersalen, B2:00,  
Karolinska Universitetsjukhuset, Solna

**Fredagen den 4 maj, 2012, kl 09.00**

av

**Michelle Wong**

*Huvudhandledare:*

Doktor Thomas Tolfvenstam  
Karolinska Institutet  
Institutionen för Medicin, Solna

*Bihandledare:*

Professor Kristina Brolden  
Karolinska Institutet  
Institutionen för Medicine, Solna

*Fakultetsopponent:*

Docent Ali Mirazimi  
Karolinska Institutet  
Institutionen för mikrobiologi, tumör- och  
cellbiologi

*Betygsnämnd:*

Docent Maria Brytting  
Karolinska Institutet  
Institutionen för mikrobiologi, tumör- och  
cellbiologi

Docent Jonas Hedlund

Karolinska Institutet  
Institutionen för Medicin, Solna

Docent Marianne Jansson

Lunds Universitet  
Institutionen för Laboratoriemedicin

**Stockholm 2012**

## ABSTRACT

Increasingly intensive antineoplastic regimes have been effective in the treatment for haematological malignancies, but as effective as it is in limiting neoplasm of the malignant cells, bystander damage occurs equally to cells of the immune system and epithelial cells of the mucosa. Infectious complications following chemotherapy reflect this situation.

The relationship between leukocytopaenia and infection risk, in the form of bacteraemia and fungaemia was first suggested by Bodey and colleagues and since then, many studies have followed establishing the breadth of pathogens in relation to neutropaenia. However, lymphocytes are also concurrently, markedly reduced suggesting that viraemia should also be considered in the repertoire of infectious complications with these iatrogenic neutropaenic patients. Reactivation of latent DNA viruses, for example, members of the *herpesviridae* family, and respiratory viruses have been reported in severely immunosuppressed patients after haematopoiesis stem cell transplantation (HSCT) but less so in patients that have been administered comparatively less aggressive chemotherapeutic treatment used against hematological malignancies. Since fever in these patients is sometimes the only indication of infection due to their immunosuppressed state, we not only determined the prevalence of viral infections in the iatrogenic neutropaenic adult patient we also related our findings to fever manifestation. Indeed, an association between virus detection and fever was observed, suggesting viral contribution to 30% of neutropaenic febrile episodes in our study cohort.

In addition to immune cell depletion, disruption of the gastrointestinal mucosa is another major side-effect since it can lead to microbial translocation from the large reservoir of bacterial microflora we harbour in our bowels. Elevated plasma endotoxins and sCD14 was observed in the bacteraemic episodes as well as in the episodes with fever of unknown origin (FUO). So, together with the 33% of the febrile episodes attributed to clinically documented bacteraemia and 30% attributed to viruses, we propose that aside from drug and tumour fever, a part of the remaining 37% of febrile neutropaenic episodes could be attributed to microbial translocation of bacterial products from the gut.

Acellular components of the immune system, such as the acute phase protein, mannose-binding lectin (MBL) have been suggested to be important in a similar cohort and that the use of replacement MBL therapy could be administered to reduce duration of febrile neutropaenic episodes. We however, did not observe any associations between MBL and infection type or frequency and add to the reports casting doubts on the benefit of recombinant therapy in the iatrogenic neutropaenic adult.

In conclusion, we have added to the panorama of infectious agents and bacterial products implicated during febrile neutropaenic episodes in the adult iatrogenic patient and have further discouraged suggestions for MBL replacement therapy.