

**The Role and Optimal Timing of Flexible  
Bronchoscopy and Broncho-alveolar Lavage  
Chemokine Measurement in Severely  
Immunocompromised Febrile Neutropenic  
Patients**

**Chien-Li Liew: 1042406**

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**Supervisors: Professor L B To, A/Professor P N Reynolds**

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# **The Role and Optimal Timing of Flexible Bronchoscopy and Bronchoalveolar Lavage Chemokine Measurement in Severely Immunocompromised Febrile Neutropenic Patients**

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## **Statement of Originality**

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Witnessed \_\_\_\_\_ Name \_\_\_\_\_ Date \_\_\_\_\_

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1. Royal Adelaide Hospital and Institute of Medical and Veterinary Science, Department of Haematology
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3. Royal Adelaide Hospital and Institute of Medical and Veterinary Science, Lung Research Laboratory
4. St Vincent's Hospital Department of Thoracic Medicine

## 1. ABSTRACT:

Respiratory infection remains a leading cause of morbidity and death in severely immunocompromised febrile neutropenic haematology patients, despite the introduction of numerous prophylactic strategies and advances in diagnosis and treatment. Prognosis is improved if an organism can be isolated and specific therapy commenced as soon as possible. Current practice in this population group is to commence empirical antibiotics and perform flexible bronchoscopy (FB) if temperature does not settle or *after* patients develop clinical or radiological features suggesting a respiratory source. This delay may result in a lower procedural diagnostic yield due to prior or prolonged anti-microbial treatment, and increased risk of respiratory compromise and procedural complications due to advanced respiratory infections. We hypothesised that proceeding to FB as early as possible after developing febrile neutropenia would improve treatment outcomes. With this randomised, prospective trial, we aim to further define the role of FB with reference to optimal timing of the procedure and its impact on diagnostic yield, future management and complication rate. We also aim to analyse the impact of proven infection on the cytokine profile of immunocompromised patients.

**Methods:** Patients with acute leukaemia, allogeneic bone marrow transplantation or chronic lymphocytic leukaemia (CLL) being treated with Fludarabine/ Mabthera without an obvious non-respiratory source of infection were prospectively randomised into early bronchoscopy or conventional management groups at onset of febrile neutropenia. Bronchoalveolar lavage (BAL) fluid chemokine levels (IP-10, RANTES, MIG, IL-8, MCP-1) were measured using a human Chemokine cytometric bead array (CBA) kit.

**Results:** Thirty-one episodes of febrile neutropenia in 29 patients were analysed; 17 conventional and 14 early. There was an increased yield in fungal growth in the early bronchoscopy group, which was not predicted by prior clinical or radiological changes. However, this had no impact on clinical management in the short-term due to the delayed growth. Overall diagnostic yield was not significantly different between the two groups. Procedural complication rate was negligible overall and there was no difference associated with either group. IP-10 and MIG were significantly lower in those patients who had a fungal pathogen isolated, compared with those study patients who did not (175.17 vs 1157.8,  $p=0.03$ , 30.33 vs 247.8,  $p=0.03$  respectively). IP-10 levels were higher in the conventional than early group (1253.0 vs 261.14,  $p = 0.035$ ) and the study population had higher MCP-1 (734 vs 2.83,  $p=0.006$ ) and IL-8 levels (606.9 vs 14.25,  $p=0.00655$ ) than normal controls. Those cases with fungal infection had higher mean MCP-1, RANTES and IL-8 levels than in normal controls (844.0 vs 2.83,  $p=0.007$ ; 17.5 vs 2.1,  $p=0.03$ ; 156.0 vs 14.25,  $p=0.004$ ).

**Conclusions:** Early bronchoscopy as a component of the septic screen in febrile neutropenic patients was feasible and safe. A significant difference in fungal yield was seen in the early bronchoscopy group compared to conventional methods, with a negligible complication rate, but this did not result in a change in immediate clinical management or outcomes.