

# Deficiency of mannose-binding lectin-associated serine protease-2 (MASP-2) is associated with an increased risk of chemotherapy-related infections in pediatric cancer patients

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## Introduction

Fever in neutropenia (FN) is a frequent complication in pediatric oncology. Deficiencies of the lectin pathway of complement activation, a mainstay of innate immunity, are frequent due to polymorphisms and may influence individual susceptibility to infection. Both mannose-binding lectin (MBL) and ficolins activate MBL-associated serine protease-2 (MASP-2), leading to bacterial killing by complement activation (Fig. 1). In contrast to MBL, the impact of MASP-2 deficiency on susceptibility to infections is largely unknown.

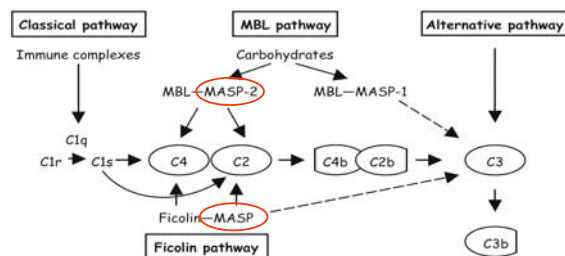


Fig. 1: MASP-2 represents the final pathway of complement activation for MBL and ficolins. (Sorensen. Springer Sem Immunopath 2005)

## Conclusions

In children treated with chemotherapy for cancer, MASP-2-deficiency was significantly associated with an increased risk of fever in neutropenia.

MASP-2 deficiency thus represents a novel risk factor for chemotherapy-related infections. Determining MASP-2 concentration at cancer diagnosis may help to identify children at elevated risk for fever in neutropenia.

## Methods

### Design:

- Retrospective single-center study
- 94 pediatric oncology patients (<16yrs at diagnosis)
- Measurement of MASP-2 serum levels at cancer diagnosis using a commercially available EIA assay (HyCult Biotechnology, NL)
- Assessment of frequency, duration and cause of FN episodes
- Statistics: multivariate Poisson regression stratified for chemotherapy intensity, with chemotherapy duration as exposure time

### Definitions:

- fever in neutropenia (FN): T  $\geq$ 38.5°C  $\geq$  2 hrs or single T  $\geq$ 39°C and severe chemotherapy-induced neutropenia (ANC  $\leq$ 500/ $\mu$ L)
- MASP-2 deficiency: MASP-2 serum concentrations < 200 ng/ml
- This cut-off was chosen since patients homo- or heterozygous for the polymorphism D105G in the MASP2/MAP19 gene usually have levels <200 ng/ml (Steengard-Petersen. NEJM 2003)

## Results

In 94 children (32 ALL, 9 AML, 14 lymphoma, 15 brain tumor, 14 sarcoma, 10 various tumors), 177 FN episodes were recorded during a cumulative chemotherapy time of 81.7 years (Table 1).

Table 1: Etiologies and frequencies of FN episodes.

|  |           |
|--|-----------|
| bacteremia   | 35 (20%)  |
| severe bacterial infection (bacteremia and/or pneumonia) | 49 (28%)  |
| viral infection (microbiologically confirmed)            | 14 (8%)   |
| invasive fungal infection                                | 6 (3%)    |
| no microbiologically proven etiology                     | 114 (64%) |

Median MASP-2 level was 527 ng/mL and nine (10%) children were MASP-2 deficient (<200 ng/mL), see Fig. 2.

MASP-2 deficient children had a significantly increased risk to develop FN (Table 2, Fig. 3), translating into significantly prolonged cumulative duration of hospitalization and of intravenous antimicrobial therapy. They experienced significantly more episodes of FN without a microbiologically defined etiology, while there was a trend towards more episodes of FN with bacteremia. No clear relationship between the type of bacteremia (gram-positive versus gram-negative) and MASP-2 serum level was observed ( $p = 0.28$ ).

Fig. 2 (right): Distribution of MASP-2 serum concentrations.

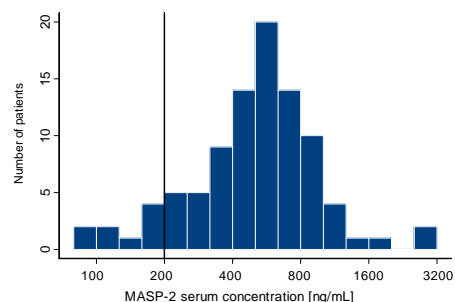


Table 2, Fig. 3 (below): Risk ratios and 95%-CI for MASP-2 deficient children\*

| Outcome measure                             | Multivariate analysis† |        | Risk ratios (95% CI) |
|---|------------------------|--------|----------------------|
|   | Risk ratio (95% CI)    | P      |                      |
| Total number of FN episodes                 | 2.08 (1.31 to 3.21)    | 0.002  |                      |
| Duration of hospitalization due to FN‡      | 1.67 (1.42 to 1.95)    | <0.001 |                      |
| Duration of i.v. antimicrobial therapy‡     | 1.84 (1.58 to 2.15)    | <0.001 |                      |
| FN episodes with bacteremia                 | 2.46 (0.84 to 6.35)    | 0.10   |                      |
| FN episodes with severe bacterial infection | 1.63 (0.56 to 4.11)    | 0.40   |                      |
| FN episodes with confirmed viral infection  | 0.46 (0.00 to 2.77)    | 0.47   |                      |
| FN episodes with no identified etiology     | 2.47 (1.44 to 4.05)    | 0.001  |                      |

\*9 (10%) patients with MASP-2 deficiency (< 200 ng/mL) compared with 85 (90%) patients with normal level  
 † Results of exact Poisson regression stratified on chemotherapy intensity  
 ‡ Cumulative duration; results of asymptotic (not exact) Poisson regression  
 FN, fever and neutropenia