



## Filgrastim Induced Severe Leukocytosis in Sepsis-Associated Leukopenia: A Case Report

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### ABSTRACT

Sepsis-induced leukopenia occurs in critically ill patients and associated with negative clinical outcomes. A sixty years old patient with respiratory failure, decreased level of consciousness and pneumonia transferred to the intensive care unit (ICU). During ICU stay patient developed late ventilator-associated pneumonia and severe neutropenia. Colony stimulating factor (filgrastim) was initiated for patient. Severe leukocytosis (leukocyte counts of 94000/mm<sup>3</sup>) with no source of new infection was detected. After filgrastim discontinuation serum leukocyte counts returned to the normal limits with no sequel or complication. Although hyperleukocytosis may increase the risk of thrombosis and pulmonary edema, most cases of iatrogenic hyperleukocytosis are well tolerated without complication.

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### Introduction

Systemic inflammatory response syndrome (SIRS) has been recommended for early assessment of patients' possible sepsis (1). However, SIRS didn't predict all cases with possible infections. Therefore, The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) recommends using quick sequential organ failure assessment score instead of SIRS for initial assessments (2). It's recommended that sepsis defined as life-threatening organ dysfunction as a response to infections (1). Sepsis accounts for more than 700,000 cases each year. Leukopenia defined as absolute white blood count less than 4000/mm<sup>3</sup> may occur in patients with sepsis (3). Colony-stimulating growth factors can increase neutrophil production and function (1).

### Case presentation

A 63 years old female was admitted to the intensive care unit with a decreased level of consciousness, speech

disorder, and unilateral weakness. Past medical history of the patient was significant for hypertension and diabetes mellitus. Patient past drug history was included losartan and metformin. Vital signs at presentation were as follow (BP 198/90 mmHg, Heart rate 100/min, respiratory rate 19/min, Temperature: 37.1 0C). Serum electrolytes were within normal limits. Serum creatinine and urea were 1.5 mg/dl, and 17mg/dl respectively. Serum concentration of Pro-calcitonin and lactate were 1.02 ng/ml and 27 mmol/l respectively. Patient's serum D-dimer was 1963 ng/ml. Other data were within normal ranges.

The patient was admitted to intensive care unit while intubated. Empiric antibiotic with a combination of ceftriaxone at a dose of 1000 mg /intravenous twice daily and clindamycin at a dose of 600 mg/ intravenous/ three times daily was initiated. Negative computed tomography angiography results were ruled out pulmonary thromboembolism.

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After a week, a new onset fever, increase in sputum volume, and consolidations were noted. Possible late ventilator-associated pneumonia was considered for patients. Sepsis workup was done and broad spectrum antibiotics including a combination of vancomycin (2000 mg/daily in divided dose) and meropenem (1000 mg/intravenous/ three times daily) were initiated for the patient. After 72 hours, drug-resistant *Acinetobacter baumannii* was isolated from respiratory secretions. The empiric antibiotic regimen was continued. Patient's level of consciousness and mode of ventilator remained unchanged. The patient didn't experience drop in mean arterial blood pressure.

On day-12 of admission, patient developed severe leukopenia

(WBC:400/mm<sup>3</sup>) (Figure1). Filgrastim, Granulocyte- colony-stimulating factor, at doses of 300 micrograms twice daily was initiated. Three days after filgrastim initiation white blood count began to rise and eight days after filgrastim initiation, WBC count increased to 94,000/mm<sup>3</sup>. However, the patient didn't experience acute new onset fever and no new end-organ dysfunction. Infectious disease service consult recommended addition of levofloxacin (750mg/daily) to the previous antibiotic regimen. No other complications including electrocardiogram changes, rise in troponin and thrombosis were detected. At this point, filgrastim was discontinued and WBC began to decrease and finally after six-day normalized and patient with an improved level of consciousness, and muscle forces discharged.

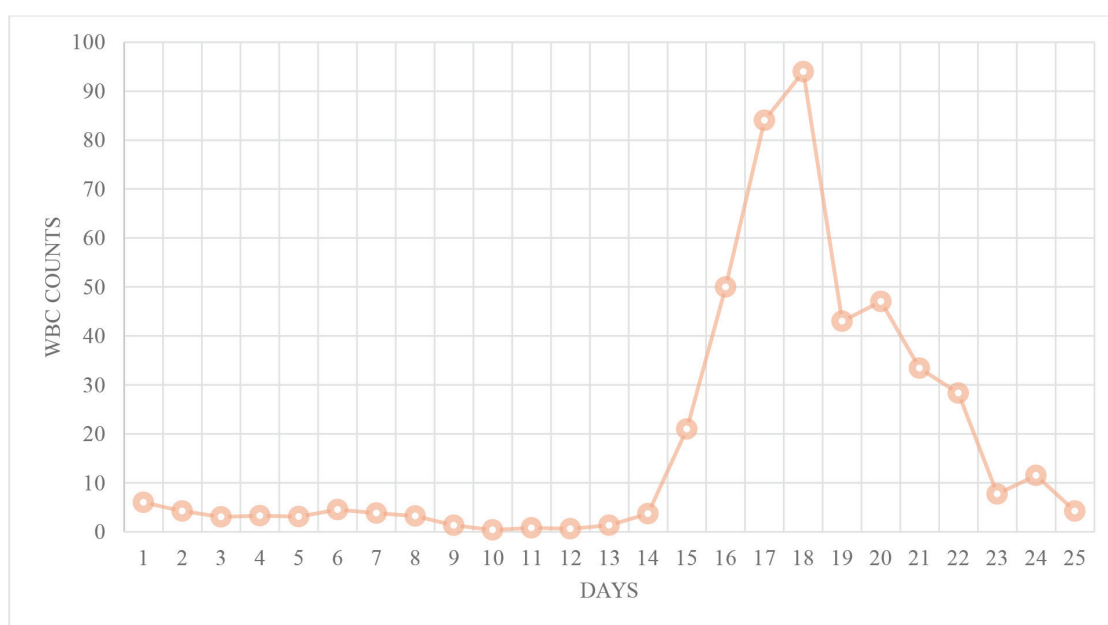


Figure 1. White Blood Counts of patients during intensive care unit stay.

## Discussion

Sepsis is a leading cause of death in critically ill patients, sepsis-induced neutropenia may occur in 13% of patients (4). Sepsis-related leukopenia increase risk of acute kidney injury (4). Root et al., evaluated effects of filgrastim administration on mortality and organ dysfunction. They used filgrastim dose of 300 micrograms daily for 5 days or until WBC >75.0 x10<sup>9</sup> cells/L (5). Filgrastim treatment significantly increased WBC but had no effects on mortality.

A systematic review of published studies showed no significant difference in 28-days mortality. However, the colony-stimulating factor may accelerate infection recovery with no significant adverse drug reaction (6).

Filgrastim administration is commonly well tolerated however, it's not without adverse effects. It is recommended filgrastim discontinued if the absolute neutrophil count is

more than 1000/mm<sup>3</sup> for three consecutive days (7).

Hyperleukocytosis, as defined WBC >100 x10<sup>9</sup>/L, may increase the risk of pulmonary edema, venous thrombosis, and signs of hyperviscosity, troponin rise, and ST-segment changes, intraocular flame hemorrhage. However, most of the patients are asymptomatic. Very few cases of growth factor associated with hyperleukocytosis induced complications have been reported (8, 9). Most cases of filgrastim associated hyperleukocytosis are iatrogenic (10). Usually, WBC count decreased by 50% after 48 hours and return to the pretreatment values after 1-7 days (8). In our case WBC counts decreased by 50% after 48 hours and returned to the normal range within a week. Although growth factor associated hyperleukocytosis is well tolerated, it is recommended to monitor neutrophil count for possible leukocytosis or a white blood cell count >100,000/mm<sup>3</sup> (7).

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