Reply to Patel et al .: Tempering the Clinical Effects of Early Myeloid-derived Suppressor Cell Expansion in Severe Sepsis and Septic Shock

Fabrice Uhel, Christophe Camus, Arnaud Gacouin, Jean-Marc Tadié, Yves Le Tulzo, Mikael Roussel, Karin Tarte

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Fabrice Uhel[1,2,3], Christophe Camus[1,2], Arnaud Gacouin[1,2], Jean-Marc Tadié[1,2,3], Yves Le Tulzo[1,2,3], Mikael Roussel[3], and Karin Tarte[3], on behalf of all the authors.

[1] Centre Hospitalier Universitaire de Rennes, Maladies Infectieuses et Réanimation Médicale, Rennes, France
[2] Institut National de la Santé et de la Recherche Médicale, Centre d'Investigation Clinique-1414, Rennes, France
[3] Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche U917, Université Rennes1, Etablissement Français du Sang Bretagne, Centre Hospitalier Universitaire de Rennes, Laboratoire Suivi Immunologique des Thérapeutiques Innovantes, Rennes, France

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Authors' contribution
Wrote the paper: FU, KT. Critically revised the manuscript: all authors.

We are grateful to Dr. Patel and colleagues for their interest in our study on the phenotype, suppressive activity, origin, and clinical impact of myeloid-derived suppressor cells (MDSCs) in septic patients (1). If evidence for a causal relationship between expansion of granulocytic (G-)MDSCs and development of secondary infections in sepsis is inherently hampered by the observational nature of our study, our work provides new insights supporting a role of MDSC expansion in sepsis-associated immune dysfunction.

Dr. Patel and colleagues raise concerns about the sample size of our study, which may result in insufficient power, thereby challenging our conclusions on the impact G-MDSC expansion on clinical outcome. The hazard ratio for the development of nosocomial infection in septic patients with >36% G-MDSCs was 2.83 (95% confidence interval 1.18 – 8.11), representing a statistically significant result, which has the limitation of type-I error (α risk = 5%), but not type-II error. In addition, a post hoc analysis confirmed that the size of our population (94 septic patients) allowed us to demonstrate a significant difference between patients developing or not nosocomial infections (alpha risk set at 5%) with a power of 97%. Finally, the size of our cohort is consistent with previous studies that could demonstrate a link between sepsis-induced immunologic impairments and the development of nosocomial infections (2, 3). Moreover, a recent study reporting a similar association between expansion of G-MDSCs and an increased incidence of nosocomial infections in 74 surgical patients admitted to the ICU for sepsis is in line with our results and strengthens our conclusions (4). Therefore, we believe that our study is methodologically robust.

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Given their lack of any specific pattern, we have not detailed in our leading study the causative pathogens involved in nosocomial infections. However, a rapid overview of responsible organisms (Table 1) confirms that they correspond to pathogens classically involved in nosocomial infection, as recently described in a large cohort of ICU patients (5).

Finally, Dr. Patel and colleagues challenge the clinical characteristics of our septic and non-septic ICU patient cohorts. We agree that mortality of septic patients was lower than expected from previous large epidemiological studies. However, our results are in agreement with the regular decrease in sepsis mortality observed in the past two decades, mainly explained by an earlier sepsis recognition and a widespread integration of best clinical practices (5). Moreover, because MDSCs have been initially described in patients with malignancies, and because we wanted to study their suppressive properties, we decided to exclude patients with cancer and preexisting immune suppression from our cohort. In many studies, malignancies and immunosuppression have been shown to be major risk factors of mortality during sepsis (6, 7). Finally, a large epidemiological study recently underlined that ICU-acquired infections contributed only modestly to overall mortality in septic patients (8). Thus, mortality and secondary infections should be considered as different outcome endpoints regarding the clinical impact of MDSCs. In agreement, as discussed by Dr. Patel, we found no difference in MDSC subsets between septic shock and severe sepsis patients, despite huge differences in clinical outcome. Of note, no clinical conclusion has been proposed based on our very small non-septic ICU patient cohort but their high mortality rate further exclude that the G-MDSC expansion specifically observed in septic patients could be related to a worse prognosis.

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To conclude, our study paves the way for investigations in large patient cohorts to further ascertain the relationship between MDSCs and nosocomial infection in sepsis. Our findings provide first mechanistic insights into the roles of MDSCs during sepsis and their potential as a therapeutic target.

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Table

Table 1. Causative pathogens of hospital-acquired infections in patients admitted for sepsis

Gram negative bacteria		**11 (47.8%)**
	Pseudomonas aeruginosa	4
	Escherichia coli	2
	Enterobacter cloacae	1
	Stenotrophomonas matophilia	1
	Klebsiella pneumoniae	1
	Serratia marcescens	1
	Bacteroides species	1
Gram positive bacteria		**8 (34.8%)**
	Coagulase negative staphylococcus	3
	Enterococcus faecalis	2
	Staphylococcus aureus	1
	Corynebacterium species	1
	Clostridium difficile	1
Fungi		**3 (13.0%)**
	Candida albicans	3
Virus		**1 (4.3%)**
	Varicella zoster virus	1

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