# Complement System Targets and Models

## Clinical Impact of Early Complement Activation in Combat Casualties with Blast Injury

The complement system plays a role in the early response to injury and is involved in the pathogenesis of subsequent organ failure. Researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, TX) investigated the relationship between the complement system and clinical variables in combat casualties with blast injury. Service members sustaining blast trauma during Operation Iraqi Freedom (OIF) were included in the study (n = 54). Levels of complement factors were measured in sera from samples drawn at admission and 8 and 24 hours later. Results were compared to levels of complement factors in healthy controls (n = 10).

Levels of complement factors C5b-9, Bb, and C4d were significantly higher in the injured group than in controls at all time points, while levels of C5a were significantly higher in the injured group than in controls initially and 8 hours after admission (Figure 1). Complement factors were significantly correlated with multiple clinical variables including injury severity score, Glasgow Coma Scale, and infusion of crystalloids and colloids. C5a and C5b-9 were positively correlated with Bb but not C4d at admission and 8 hours later, suggesting that the alternative complement pathway, but not the classic or lectin complement pathways, contributed to early complement activation (Figure 2). However, C4d was inversely correlated with mortality, suggesting that the classical or lectin complement pathway may play a protective role in this setting.

These data demonstrated that acute complement and inflammatory responses were present in military blast trauma patients and correlated with clinical variables of importance. They reinforce previous findings that early therapeutic modulation of the complement system may reduce morbidity and mortality in trauma patients.

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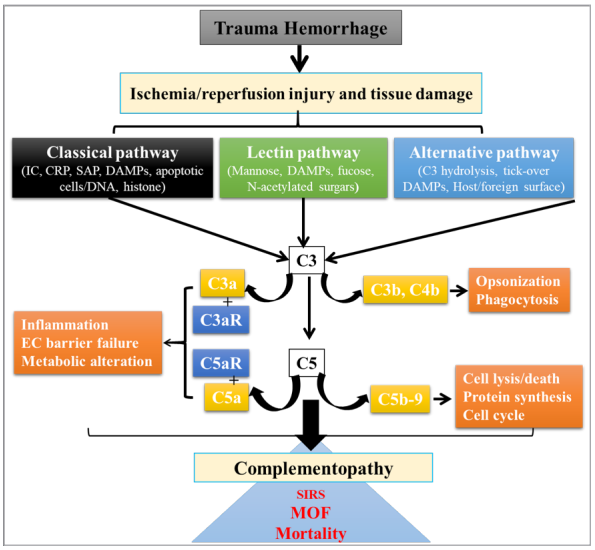


**FIGURE 1:** Schematic model and proposed roles of complement activation in traumatic hemorrhage. C3aR, C3a receptor; C5aR, C5a receptor; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; EC, endothelial cell; IC, immune complex; MOF, multiple organ failure, SAP, serum amyloid P; SIRS, systemic inflammatory response syndrome.

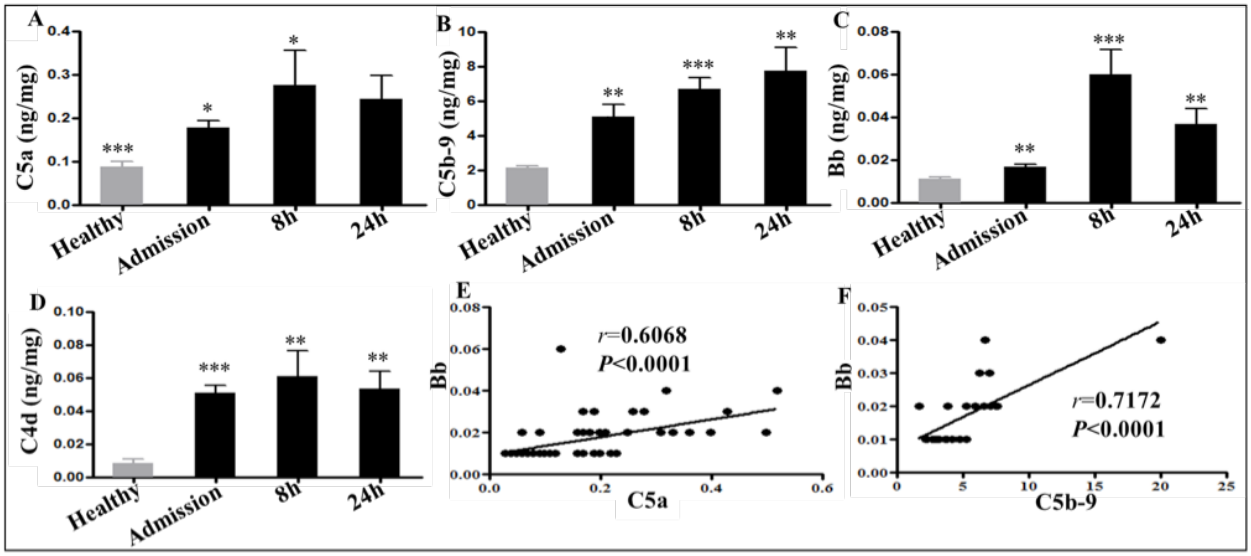


**FIGURE 2:** Systemic activation of complement and alternative complement pathways in military casualties with blast injury. A-D, Plasma levels of C factors of C5a, C5b-9, Bb and C4d were measured by ELISA in healthy donors (*n*=10) and trauma patients at admission (*n*=54), 8 hr (*n*=23)and 24 hr (*n*=9) after admission. E-F, correlation between alternative pathway (Bb) and C5b-9 in the injured patients at admission. The data were expressed as nanogram per milligram plasma protein and presented as mean ± SEM, * $p<0.05$. ** $p<0.01$, *** $p<0.001$ vs. healthy.