Introduction:
Clinical sepsis phenotypes are proposed at hospital presentation. These phenotypes, biomarker profiles, and outcomes are not yet reproduced in prospective data. Even less is known about the biologic mechanism that drives these distinct groups. Thus, we sought to validate clinical phenotypes and to determine markers of innate immunity, coagulation, tolerance and tissue damage in a prospective cohort.

Methods:
We prospectively studied patients with Sepsis-3 criteria within 6 hours of presentation at 12 hospitals in Pennsylvania (2018-2019) using automated electronic alerts. Using 29 clinical variables, we predicted phenotypes ($\alpha$, $\beta$, $\gamma$, $\delta$) for each patient using Euclidean distance anchored to published SENECA phenotype centroids. Discarded blood was analyzed in a subset (n=160) for markers of innate immunity (e.g. IL-6, IL-10), coagulation (e.g. antithrombin III, e-selectin), tolerance (e.g. HO-1, IGFBP7), and tissue damage (e.g. serum lactate, bicarbonate).

Results:
Among 549 patients, $\alpha$-type was present in 146 (27%), $\beta$-type in 140 (25%), $\gamma$-type in 168 (31%) and $\delta$-type in 95 (17%, Figure 1a). On average, $\beta$-type was older and more comorbid (mean 73, SD 9 yrs; mean Elixhauser 4.6, SD 2.2) with renal dysfunction (median creatinine 1.8 [IQR 1.1 – 2.9] mg/dL, p<0.01 all). The $\delta$-type had more acidosis (mean HCO3- 20.1, SD 4.7 mEq/L), higher serum lactate (median 1.8 [IQR 1.0-3.5] mmol/L, p <0.01 both) and inpatient mortality (13%, Figure 1b). The $\gamma$- and $\delta$-type had greater markers of innate immunity and abnormal coagulation (e.g IL-6, ICAM p<0.01 both), while markers of increased tissue damage (lactate) and poor tolerance (HO-1) were present in $\delta$-type, compared to $\alpha$-type (Figure 1c).

Conclusion:
The distribution and characteristics of clinical sepsis phenotypes were reproduced in a prospective validation cohort. Similar to the SENECA study, distinct biomarker profiles of tissue damage, innate immunity and poor tolerance were present for the $\delta$-type.
Figure 1: (A) Phenotype distribution (green: α-type, purple: β-type, red: γ-type, blue: δ-type) (B) Chord plot with ribbons connecting individual phenotype to an organ system if the group mean is greater or lesser than the overall mean for the entire cohort. (C) Heatmap showing the log of the fold change of the median biomarker value (column) per patient (row) for various markers of the septic host response grouped by those reflecting tissue damage, innate immunity and tolerance by phenotype. Red represents greater median biomarker value for that phenotype compared to the median of the entire study, while green represents lower values of the biomarker compared to the median of the entire study. White cells are those in which the biomarker was not measured.