Introduction:
ICU-acquired weakness has shown to persist beyond the ICU stay and to associate with long-term functional impairment of ICU survivors. Underlying mechanisms remain unclear, but illness-induced aberrant DNA methylation could be involved due to its potential long-lasting impact on gene expression. Recently, DNA methylation alterations have been identified in peripheral blood of pediatric ICU patients, which were found to explain part of their long-term developmental impairment (1). Whether DNA methylation in muscle is altered by critical illness is unknown.

Methods:
We extracted DNA from skeletal muscle biopsies collected on day 8±1 in ICU from patients included in the EPaNIC trial (n=188) and from 20 matched healthy controls. Genome-wide DNA methylation was determined with Infinium® HumanMethylation EPIC-BeadChips, which interrogate more than 850000 CpG sites. Methylation status of individual CpG sites and of DNA regions of patients and controls were compared, using stringent corrections for multiple comparisons.

Results:
In DNA extracted from ICU patients, 565 CpG sites, associated with 400 unique genes, were differentially methylated as compared with controls, with an average difference in methylation of 3.2% (SEM 0.07%, P<0.00005). Many of the associated genes were identified as highly relevant for muscle structure, function and/or weakness. In addition, in patients as compared with controls, we identified two hypomethylated regions (family-wise error rate<0.05), spanning 18 and 3 CpG sites in the promoter regions of the HIC1 and NADK2 genes, respectively. HIC1 and NADK2 play important roles in muscle regeneration and postsynaptic acetylcholine receptor regulation, and in mitochondrial processes, respectively.

Conclusion:
The DNA methylation signature in skeletal muscle is altered by critical illness, which may provide a biological basis for the long-term persistence of weakness in ICU survivors.

References: