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# INFECTION

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## Abstracts
## Weimar Sepsis Update 2017 – Facing the Challenges
## September 6–8, 2017, Weimar, Germany

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# Abstracts

## 8th International Congress "Sepsis and Multiorgan Dysfunction"

## *Weimar Sepsis Update 2017– Facing the Challenges*

**September 6–8, 2017**
**Weimar**

**Organizer**
H. Gerlach
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F. M. Brunkhorst

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Drug-resistant pathogen challenges of Seraph 200 by Battelle used a swine model. Bacteria were infused continuously at concentrations between 400 and 3100 CFU/mL into a prototype extracorporeal hemoperfusion circuit. Blood samples were collected contemporaneously before and after Seraph to quantify bacteria removal by the device.

**Results:** In vitro results demonstrated efficient single-pass removal of drug-resistant bacteria strains: MRSA (92%), MRSE (66%), CRE *E. coli* (99.9%), CRE *K. pneumoniae* (99.9%), VRE *E. faecalis* (91%), and ESBL *K. pneumoniae* (39%). The Battelle porcine model demonstrated that Seraph 200 could continuously remove MRSA (78–88%), MDR (79%), MDR *P. aeruginosa* (83%), and MDR *K. pneumoniae* (35%).

**Conclusions:** In vivo pre-clinical feasibility studies have been confirmed in an ongoing German clinical trial using Seraph in a 4-h therapy during hemodialysis. Human and pre-clinical animal testing support the use of Seraph therapy as an adjunctive tool to improve the therapeutic efficiency of currently available drugs, or when no effective antimicrobial drugs are available.

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## 066
**Infection 2017**

### Survival and function in rats with genetic predisposition for high or low exercise capacity

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**Introduction:** Sepsis may lead to multiple organ failure and death. Sepsis-induced cardiac dysfunction represents one of several possible complications and is co-responsible for the high mortality typical for sepsis. It is accepted that physical fitness as well as high intrinsic exercise capacity positively influences cardiovascular health. However, less is known about the impact of these factors on cardiac performance and metabolism in sepsis.

**Objectives:** We aimed to identify the effect of sepsis on cardiac function, metabolism and insulin responsiveness in rats differing in their genetic predisposition for either high or low inborn exercise capacity.

**Methods:** Sepsis was induced in 15-week old rats with high (HCR) or low (LCR) intrinsic running capacity by intraperitoneal injection of a human fecal suspension. The Clinical Severity Score (CSS) was determined to assess sepsis severity 6 and 24 h later. At 1 and 5 weeks, hearts from sepsis survivors were excised and prepared as isolated working hearts. Cardiac function, substrate oxidation and response to insulin were measured using radioactive tracer technology.

**Results:** The two groups did not differ in their CSS scores at 6 and 24 h and survival was poor with 33% (HCR) and 38% (LCR) survivors at 72 h. After 5 weeks, septic animals displayed substantial reductions of cardiac power (Control vs 5w of sepsis: $45.6 \pm 2.9$ vs. $37.6 \pm 1.5$, $p < 0.05$ mW/g dry). This reduction in power was not associated with sepsis-induced alterations in glucose oxidation ($0.33 \pm 0.06$ vs. $0.30 \pm 0.05$ μmol/min/g dry, n.s.) or fatty acid oxidation ($0.67 \pm 0.08$ vs. $0.70 \pm 0.05$ μmol/min/g dry, n.s.). However, when relating substrate oxidation to cardiac power as a measure of substrate efficacy, there was an increase in substrate used per force. Insulin response was increased in HCR only (change of glucose oxidation: $+0.32 \pm 0.08$ vs. $+0.39 \pm 0.07$ and $+0.16 \pm 0.04$ vs. $+0.51 \pm 0.11$ μmol/min/g dry, $p < 0.05$).

**Conclusions:** The detrimental effects of sepsis on survival in rats are not affected by their genetically determined exercise capacity. Sepsis causes significant mortality and contractile dysfunction in survivors. This dysfunction was accompanied by maintained glucose and fatty acid oxidation suggesting significantly decreased efficiency of substrate use.

## 067
**Infection 2017**

### Microbiota of the albino rats ileum lumen under abdominal sepsis

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**Introduction:** Microflora of the distal part of ileum plays a separate role in formation of abdominal sepsis (AS) and is characterized by enhanced vascularization and localization of mucous-associated lymphoid clusters, which provides a significant ability to resorption of antigens in comparison with other parts of the gastrointestinal tract.

**Objectives:** To study the qualitative and quantitative composition of the microbiota of the ileum lumen of albino rats with AS.

**Methods:** A bacteriological method was used in 25 white rats (200–220 g). All animals were quarantined for 10–14 days. Ten rats with induced AS concluded the main group, 15 intact animals formed the control. Before the study all animals were examined for possible pathology. In sterile conditions, the abdominal cavity was opened, a portion (1.5–2 cm) of the distal part of ileum with its contents was taken. Pure cultures were identified by morphological, tinctorial, cultural and biochemical properties.

**Results:** In animals with experimental AS the dominant microflora of ileum lumen consists of obligate anaerobic bacteria of the genera Bacteroides, Bifidobacterium, Lactobacillus, Peptostreptococcus, facultative anaerobic and aerobic opportunistic enterobacteria: *E. coli* and Proteus; additional microflora is formed by the bacteria of the genus Enterococcus and accidental—by Peptococcus and Klebsiella. Also, it should be noticed the elimination of the genera Bifidobacterium and Lactobacillus from the iliac lumen in 20.0% of the animals and the contamination and colonization of the biotope with the conditionally pathogenic enterobacteria of the genera Klebsiella and Proteus. The results of the bacteriological study confirm the moderate deficiency of the most important for composition of the intestinal microbiocenosis and multifunctional role in maintaining the microecological homeostasis bacteria of the genus Bifidobacterium (reduction by 33.91%) and Lactobacillus (reduction by 27.53%), as well as a less significant decrease in the population level of bacteria of genera Bacteroides (19.85%), Peptostreptococcus (13.88%), Escherichia (8.97%), Enterococcus (8.97%) etc. The number of Proteus in the microbiocenosis is increased by 10.33%; Klebsiella reached a moderate population level. Changes of the population level of bacteria of different taxons lead to an imbalance of microbiocenosis of

the ileum lumen, which is more clearly indicated by other analytical indices. Thus, in Bifidobacterium the quantitative dominance is reduced by 44.88%, participation in the formation of microbiocenosis of the biotope by 50.98%; in Lactobacilli by 37.02 and 36.01% respectively, in Enterococci—by 3.5 times and 4.51 times respectively. The quantitative dominance and participation in the formation of the microbiocenosis of opportunistic enterobacteria increased by 32.37 and 57.96%.

**Conclusions:** AS leads to deficiency and in some cases (20.0%) to elimination of Bifidobacterium, Lactobacillus and contamination and colonization of the ileum lumen with opportunistic enterobacteria (Klebsiella, Proteus).

## 073
**Infection 2017**

### Role of AMPK in systemic inflammation

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**Introduction:** The systemic inflammatory response syndrome (SIRS) is characterised by endothelial and microvascular dysfunction resulting in decreased organ perfusion and subsequent development of organ failure. The energy-sensing enzyme AMP-activated kinase (AMPK), a crucial regulator of cell metabolism and homeostasis, is thought to play an important role in inflammatory processes. It exerts significant anti-inflammatory and antioxidant effects in a variety of cell types, in part by inhibiting the pro-inflammatory NFκB pathway.
**Objectives:** We hypothesised that AMPK may control SIRS and limit inflammatory responses of the endothelium thereby protecting against vascular dysfunction.
**Methods:** Experiments were performed in wild type (WT) mice and in mice, in which the catalytic subunit AMPKα1 was knocked out (KO). SIRS was induced by intraperitoneal injection of LPS (10 µg/g body weight). To investigate differences in WT and KO mice, plasma cytokine levels and markers of cellular damage as well as cytokine levels in the liver were analysed. To characterise the influence of AMPK on endothelial permeability in vivo, a vascular leakage assay employing Evans Blue was performed. In vitro experiments were performed in human umbilical vein endothelial cells, which were stimulated with cytokines (IL-1β, TNF-α) and/or LPS and analysed for permeability (ECIS) and adhesion molecule expression (flow cytometry). AICAR and A769662 were used to activate AMPK in these experiments.
**Results:** Female WT mice showed a higher survival compared to male WT mice in response to LPS. Knockout of AMPKα1 reduced survival in female mice but had no effect on mortality in male mice. In line with this, higher plasma cytokine levels (IL1β, TNFα) and increased plasma markers of cellular damage (lactate dehydrogenase) were observed in female AMPKα1 KO mice indicating protection from systemic inflammation by AMPKα1. 6 h after LPS injection, a significant vascular leakage as monitored with Evans Blue was seen in organs including liver. Here, no gender difference was observed. LPS-induced vascular leakage in liver was clearly higher in AMPKα1 KO mice compared to WT mice. In parallel, cytokine levels (IL-1β, TNF-α) in liver and plasma markers of hepatocellular damage (alanine aminotransferase, aspartate aminotransferase) were increased in AMPKα1 KO animals. These data indicate that AMPKα1 protects from vascular leakage and liver inflammation during SIRS. This may be in part due to endothelial barrier stabilisation and prevention of leukocyte immigration into the tissue. Accordingly, pharmacological activation of AMPK in cultured endothelial cells led to a significant decrease of cytokine-induced endothelial permeability and adhesion molecule expression.
**Conclusions:** Taken together, these data underline the importance of AMPK as an anti-inflammatory molecule in the context of systemic and local inflammation. AMPK may represent a pharmacological target to prevent or ameliorate inflammatory responses during SIRS.

## 079
**Infection 2017**

### TLR-expressing cells as biosensor for bacterial ligands

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**Introduction:** The early recognition of potentially pathogenic microorganisms is the essential step before mechanisms of innate and adaptive immune responses are initiated. The evolutionary battle between host and pathogens lead to the development of the Toll-like receptor system for the recognition of bacterial, fungal and viral components of very different chemical composition. Bacterial and fungal cell wall components, proteins, toxins and nucleic acids belong to those molecules and the binding of the so-called pathogen-associated molecular patterns (PAMPs) to Toll-like receptors (TLRs) provokes a signaling cascade resulting in recruitment of the transcription factor NF-κB. NF-κB binds to certain NF-κB response elements in the promotor region of genes involved in inflammation and immunity and activates their transcription. The recognition process takes place soon after microorganisms overcome the barriers of skin and mucosa by tissue resident immune cells carrying TLRs and also other immune receptors.
**Objectives:** We generated a TLR expression based cellular assay to detect bacterial ligands in liquid samples. Our intention is to use reporter cell lines to measure the activation and signalling of certain Toll-like receptors to evaluate blood plasma samples from septic patients.
**Methods:** We generated stable isogenic cell lines expressing single TLRs (e.g. TLR5) or combinations of TLRs and cofactors (e.g. TLR4). The cells are seeded in 96 well plates and stimulated after 14–16 h of adherence. The cells were stimulated with soluble ligands, heat-inactivated bacteria and more complex samples e.g. spiked plasma samples and blood plasma from septic patients.
**Results:** Cells expressing TLR2, TLR2/TLR1, TLR2/TLR6, TLR4-CD14-MD2 or TLR5 were dose-dependently activated by the according ligands lipoteichoic acid, Pam3Csk4, Fsl-1, LPS and Flagellin as well as by heat-inactivated bacteria and spiked human plasma samples. Septic plasma samples activated several TLR-expressing cell lines according to the causing microorganism.