Hi, this is Evan Khraisah, Editor-in-Chief of *Anesthesiology*, with some highlights from the August issue of the journal.

We begin this month with a clinical investigation of the technique of intranasal injection for local anesthesia. Intranasal injection deposits local anesthetic inside the epinarium and among the nerve fascicles, and can provide faster onset of block compared to extranasal injection, but the safety of intranasal injection remains not extensively investigated. The goal of this investigation was to determine the minimum effective volume of intranasal 1% ropivacaine needed to achieve complete sensory-motor macular nerve block in 90% of patients. A second goal was to evaluate the safety of intranasal injection, based on electrophysiological consequences. Dr. Gianluca Cappellini of the Arcispedale Sant’Anna Nova, Reggio Emilia, Italy, and colleagues there prospectively evaluated 208 patients who met the inclusion criteria. The starting volume was 15 ml. The investigators also performed baseline, 5-week, and 6-month electrophysiological tests to evaluate action potential amplitude, latency, and velocity. They also performed baseline, at 6 months from the time of nerve block. These results show that intranasal popliteal injection reduces the local anesthetic dose needed for sensory-motor block. However, persistent electrophysiological changes suggest possible axonal damage that could constitute a potential safety issue, and which will require further investigation.

Next we have an observational study that examined the hypothesis that ketamine-induced perioperative pyroptosis would be associated with worse intubation conditions and increase the risk of intubation failure. They also evaluated whether the incidence of complications was higher in the ICU with poor ketamine-induced pyroptosis compared with the operating room. The first-time intubation success rate was lower in the ICU compared with the operating room, with 85.6% vs. 99.6% (p<0.001) for successful intubation attempts. The authors concluded that tracheal intubations in the ICU were associated with worse intubation conditions and increased complications compared with tracheal intubations in the operating room and then again within 1 month in ICU. The investigators performed the investigation at the University Medical Center Groningen, Groningen, The Netherlands. They conducted the study in 311 patients with a history of malignant hyperthermia. The investigators developed a multi-compartmental pharmacokinetic model for starting therapy, with a central supply of dantrolene available within 30 minutes. Our next article uses a mouse model to look at the glyplasia, particularly neuroinflammation in the hippocampus, which presents traumatic brain injury. This neurogenesis is dependent on NMDA receptors, which are inhibited by ketamine. Dr. Aastum Peters of Oxford Brookes University, Health & Science, Oxford, UK, and colleagues there prospectively evaluated the hypothesis that ketamine administration after traumatic brain injury would reduce hippocampal cell proliferation, leading to worse behavioral outcomes in mice. The investigators induced traumatic brain injury in 118 mice using a controlled cortical impact injury, after which they received either ketamine or vehicle systemically for 1 week. They used immunohistochemical assays to evaluate neuronal, astrogial, and microglial cell proliferation and survival at 3 days, 2 weeks, and 6-week post-intervention. The Morris Water maze resulted in a normal task was used to assess cognitive recovery. The results showed that ketamine dramatically increased microglial proliferation in the granule cell layer of the hippocampus 3 days after injury. Ketamine also prevented the production of astrocytes 2 weeks after injury. Independent of injury, ketamine administration improved performance in the Morris Water maze reversal test after injury, but had no effect on performance in sham-treated mice. The investigators concluded that ketamine alters hippocampal cell proliferation after traumatic brain injury. Surprisingly, these changes were associated with ketamine-induced pyroptosis in the hippocampus.

Next is an investigation of asepis. We know that no molecular-targeted treatments for sepsis have proved successful in humans. Additionally, the role of sphingosine-1-phosphate receptor 2 signaling in sepsis is unclear. Fang Song and colleagues at the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, tested the hypothesis that sphingosine-1-phosphate receptor signaling would increase caspase-11-dependent macrophage pyroptosis and worsen gram-negative sepsis outcome. The investigators used intraperitoneal injection of E. coli to induce a gram-negative sepsis model. They isolated primary peritoneal macrophages from wild-type, sphingosine phosphate receptor-deficient mice or mice deficient for a functional TLR4/LD-1 signaling. The investigators performed a systemic lipopolysaccharide (LPS) and RhoA/GTP levels were assessed in these cells. In an accompanying clinical investigation, in 11 patients with gram-negative sepsis, monocyte caspase-4 expression and its correlation with sphingosine phosphate receptor expression were determined. The investigators estimated that genetic deficiency of sphingosine-1-phosphate receptor significantly improved survival rate: 7/10 sphingosine phosphate receptor deficient mice survived, compared to only 2/10 wild-type mice. Decreased caspase-11 activation in sphingosine phosphate receptor signaling deficient cells contributed to reduced mortality. RhoA inhibitor abrogated the amplified caspase-11 activation in wild type or sphingosine phosphate receptor overexpressing cells. In patients with gram-negative sepsis, caspase-4 increased significantly in monocytes compared to non-infected controls. The investigators measured that sphingosine-1-phosphate receptors and caspase-2 and caspase-11 may be potential new targets for sepsis treatment.

Our Clinical Focus Review this month looks at a practical approach to presumed β-lactam allergy and cross-reactivity in the peripерoperative setting. Dr. Jeroen Hermansides and colleagues at Academic Medical Center, Amsterdam, The Netherlands, note that β-lactam allergy is the most common suspected in-hospital drug allergy. It has an incidence of 5-17% in hospitalized patients and up to 35% in the surgical population at the preoperative assessment clinic. β-lactam antibiotics are frequently avoided as surgical prophylaxis due to the possibility of cross-reactivity, and the risk of serious adverse reactions. However, long-term consequences can include overuse of these alternative antibiotics, leading to resistance and an increase in serious hospital infections. The authors show that a careful history is necessary to distinguish between serious reactions, after which all β-lactams should be avoided, and non-serious reactions, for which an alternative antibiotic is prescribed. However, in cases of cross-reactivity, knowledge of the possible mechanisms behind cross reactivity between the different β-lactams may guide antibiotic choices. Physicians must also take into account the antimicrobial spectrum of the antibiotic, and monitor the patient closely. Hermansides et al. suggest avoiding all β-lactams in case of a suspected previous serious allergic reaction. When there is a history of a suspected non-serious reaction with skin rash only, an alternative β-lactam antibiotic can be selected based on cross-reactivity patterns. This approach may reduce the likelihood of a peripерoperative anaphylaxis.

Finally, our Review Article this month, by Dr. Ru-Rong Ji and colleagues at Duke University Medical Center examines the role of neuroinflammation and central sensitization in chronic pain. Chronic pain is in part maintained by central sensitization, a phenomenon of synaptic plasticity and increased neuronal responsiveness in central pain pathways. Accumulating evidence suggests that central sensitization is also driven by neuroinflammation in the peripheral and central nervous system. A characteristic feature of neuroinflammation is the activation of glial cells, such as microglia and astrocytes, in the spinal cord and brain, leading to the release of proinflammatory cytokines and chemokines. Recent studies suggest that central cytokines and chemokines are powerful neuroendocrinal modulators and play a sufficient role in inducing hyperalgesia and allodynia after central nervous system administration. The expression of peripheral cytokines and chemokines in the central nervous system also promotes chronic widespread pain that affects multiple body sites. Thus, neuroinflammation drives widespread chronic pain via chronic pain sensitization. The authors focus on recent evidence on specific drug targets that could slow neuroinflammation and pain control the progression of neurological and psychiatric diseases in aged as well as younger populations. Increasing the precision with which drugs can target neuroinflammation in the central nervous system, by increasing access to the spinal cord and brain, and monitoring and measuring outcomes is crucial. The role of the peripheral and central nervous system will be of great importance. By developing specific neuroinflammation profiles, their creation may also reveal novel biomarkers and means to identify chronic pain states.