Capsule

Hepatitis C virus still unacceptably high risk for health care workers

A recently published study describes that the prevalence of occupational hepatitis C virus (HCV) infection is higher than the general population. This study provides insights into the risk associated with virus acquisition from other surveillance systems that quantify needle-stick and other blood and body fluid exposure incidents among the health care workforce. For decades, health care facilities have focused on preventing occupational exposure to blood-borne pathogens using universal and standard precautions, and adhering to federal regulations. Based on occupational incident surveillance data (EPINet), it seems that this may not still be the case. As HCV infections among health care workers are still unacceptably high and occupational incident data confirm that exposures are still occurring and can be prevented, this article provides evidence for suggesting that policies at the national, local, and facility level need to be improved in order to decrease transmission of blood-borne pathogens.

http://infectioncontrol.tips/2016/01/01/hepatitis-c-virus-still-unacceptably-high-risk-for-healthcare-workers/

Eitan Israeli

Capsule

Azithromycin versus doxycycline for urogenital *Chlamydia trachomatis* infection

Urogenital *Chlamydia trachomatis* infection remains prevalent and causes substantial reproductive morbidity. Recent studies have raised concern about the efficacy of azithromycin for the treatment of *Chlamydia* infection. Geisler and team conducted a randomized trial comparing oral azithromycin with doxycycline for the treatment of urogenital *Chlamydia* infection among adolescents in youth correctional facilities, to evaluate the non-inferiority of azithromycin (1 g in one dose) to doxycycline (100 mg twice daily for 7 days). The treatment was directly observed. The primary endpoint was treatment failure at 28 days after treatment initiation, with treatment failure determined on the basis of nucleic acid amplification testing, sexual history, and outer membrane protein A (OmpA) genotyping of *C. trachomatis* strains. Among the 567 participants enrolled, 284 were randomly assigned to receive azithromycin and 283 to doxycycline. A total of 155 participants in each treatment group (65% male) comprised the per-protocol population. There were no treatment failures in the doxycycline group. In the azithromycin group, treatment failure occurred in 5 participants (3.2%, 95% confidence interval 0.4–7.4%). The observed difference in failure rates between the treatment groups was 3.2 percentage points, with an upper boundary of the 90% confidence interval of 5.9 percentage points, which exceeded the prespecified absolute 5-percentage point cutoff for establishing the non-inferiority of azithromycin. In the context of a closed population receiving directly observed treatment for urogenital *Chlamydia* infection, the efficacy of azithromycin and of doxycycline was 97% and 100% respectively. The non-inferiority of azithromycin was not established in this setting.

N Engl J Med 2015; 373: 2512

Eitan Israeli

Capsule

Friendly fire from organ failure

These days organ transplantation may seem like a routine procedure, but rejection of the donated organ still poses a substantial risk. Autoantibodies contribute to rejection, but how these autoantibodies are generated remains unclear. Dieudé et al. found that exosome-like vesicles derived from apoptotic endothelial cells stimulated autoantibody production in mice, which increased graft rejection. These vesicles contained active 20S proteasome core complexes; proteasome inhibition decreased both vesicle immunogenicity and graft rejection in transplanted mice. Circulating exosome-like vesicles and increased anti-autoantibody titers were also observed in mouse models of vascular injury, suggesting that the same organ failure that necessitates the transplant might increase the risk of rejection.

Sci Transl Med 2015; 7: 318ra200

Eitan Israeli

Capsule

Tolerance is established in polyclonal CD4+ T cells by distinct mechanisms, according to self-peptide expression patterns

Studies of repertoires of mouse monoclonal CD4+ T cells have revealed several mechanisms of self-tolerance; however, which mechanisms operate in normal repertoires is unclear. Malhotra et al. studied polyclonal CD4+ T cells specific for green fluorescent protein expressed in various organs, which allowed us to determine the effects of specific expression patterns on the same epitope-specific T cells. Peptides presented uniformly by thymic antigen-presenting cells were tolerated by clonal deletion, whereas peptides excluded from the thymus were ignored. Peptides with limited thymic expression induced partial clonal deletion and impaired effector T cell potential but enhanced regulatory T cell potential. These mechanisms were also active for T cell populations specific for endogenously expressed self antigens. Thus, the immunotolerance of polyclonal CD4+ T cells was maintained by distinct mechanisms, according to self-peptide expression patterns.

Nature Immunol 2016; 17: 187

Eitan Israeli

Capsule

Phosphorylation and linear ubiquitin direct A20 inhibition of inflammation

Inactivation of the TNFAIP3 gene, encoding the A20 protein, is associated with critical inflammatory diseases including multiple sclerosis, rheumatoid arthritis and Crohn's disease. However, the role of A20 in attenuating inflammatory signaling is unclear owing to paradoxical in vitro and in vivo findings. Wertz et al. utilized genetically engineered mice bearing mutations in the A20 ovarian tumor (OTU)-type deubiquitinase domain or in the zinc finger-4 (ZnF4) ubiquitin-binding motif to investigate these discrepancies. The authors found that phosphorylation of A20 promotes cleavage of Lys63-linked polyubiquitin chains by the OTU domain and enhances ZnF4-mediated substrate ubiquitination. Additionally, levels of linear ubiquitination dictate whether A20-deficient cells die in response to tumor necrosis factor. Mechanistically, linear ubiquitin chains preserve the architecture of the TNFR1 signaling complex by blocking A20-mediated disassembly of Lys63-linked polyubiquitin scaffolds. Collectively, their studies reveal molecular mechanisms whereby A20 deubiquitinase activity and ubiquitin binding, linear ubiquitination, and cellular kinases cooperate to regulate inflammation and cell death.

Nature 2015; 28: 370

Eitan Israeli

Capsule

Low mutation rate okay for T cells

Cancers that tend to have high numbers of mutations, such as melanoma and smoking-induced lung cancer, respond well to immunotherapies, whereas those with fewer mutations, such as pancreatic cancer, do not. Tran and collaborators searched for tumor mutation-reactive T cells in 10 patients with metastatic gastrointestinal cancers, which have relatively low mutation burdens, and discovered that 9 out of 10 harbored such cells. T cells from one patient recognized a mutation common to many types of cancers. Engineering T cells to express this particular mutation-reactive T cell receptor may extend adoptive cell immunotherapy to a larger pool of patients than previously anticipated.

Science 2015; 350: 1387

Eitan Israeli

Capsule

Hypothermia for intracranial hypertension after traumatic brain injury

In patients with traumatic brain injury, hypothermia can reduce intracranial hypertension. The benefit of hypothermia on functional outcome is unclear. Andrews et al. randomly assigned adults with an intracranial pressure of more than 20 mmHg despite stage 1 treatments (including mechanical ventilation and sedation management) to standard care (control group) or hypothermia (32–35°C) plus standard care. In the control group, stage 2 treatments (e.g., osmotherapy) were added as needed to control intracranial pressure. In the hypothermia group, stage 2 treatments were added only if hypothermia failed to control intracranial pressure. In both groups, stage 3 treatments (barbiturates and decompressive craniectomy) were used if all stage 2 treatments failed to control intracranial pressure. The authors enrolled 387 patients at 47 centers in 18 countries from November 2009 through October 2014, at which time recruitment was suspended owing to safety concerns. Stage 3 treatments were required to control intracranial pressure in 54% of the patients in the control group and in 44% of the patients in the hypothermia group. The adjusted common odds ratio for the GOS-E score was 1.53 (95%CI 1.02–2.30, $P = 0.04$), indicating a worse outcome in the hypothermia group than in the control group. A favorable outcome (GOS-E score of 5–8, indicating moderate disability or good recovery) occurred in 26% of the patients in the hypothermia group and in 37% of the patients in the control group ($P = 0.03$). The authors conclude that in patients with an intracranial pressure › 20 mmHg after traumatic brain injury, therapeutic hypothermia plus standard care to reduce intracranial pressure did not result in outcomes better than those with standard care alone.

N Engl J Med 2015; 373: 2403

Eitan Israeli

Capsule

Monocytes block tumor access to the lung

Metastatic cancer is especially hard to treat. In order to find potential new therapeutic targets, scientists are trying to understand the cellular events that promote or prevent metastasis. Hanna and co-authors report a role for patrolling monocytes in blocking tumor metastasis to the lungs in mice. Tumors in mice engineered to lack patrolling monocytes showed increased metastasis to the lung but not to other tissues. Patrolling monocytes resided in the microvasculature of the lung, where they engulfed tumor material, which may explain how these cells prevent tumors from colonizing the lung.

Science 2015; 350: 985

Eitan Israeli

Capsule

Getting all stressed out by vitamin C

Few experimental cancer therapies have incited as much debate as vitamin C. Yet the mechanistic effect of vitamin C on cancer cells is still poorly understood. Yun and team studied human colorectal cancer cells with KRAS or BRAF mutations and found that they "handle" vitamin C in a different way than other cells, ultimately to their detriment. Because a certain receptor is upregulated in the mutant cells, they take up the oxidized form of vitamin C (dehydroascorbate). This leads to oxidative stress, inactivation of a glycolytic enzyme required by the mutant cells for growth, and finally cell death. Whether the selective toxicity of vitamin C to these mutant cells can be exploited therapeutically remains unclear.

Science 2015; 350: 1391

Eitan Israeli

Capsule

Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma

Survivors of Hodgkin's lymphoma are at increased risk for treatment-related subsequent malignant neoplasms. The effect of less toxic treatments, introduced in the late 1980s, on the long-term risk of a second cancer remains unknown. Schaapveld and fellow researchers enrolled 3905 persons in the Netherlands who had survived for at least 5 years after the initiation of treatment for Hodgkin's lymphoma. Patients had received treatment between 1965 and 2000, when they were 15 to 50 years of age. The authors compared the risk of a second cancer among these patients with the risk that was expected on the basis of cancer incidence in the general population. Treatment-specific risks were compared within the cohort. With a median follow-up of 19.1 years, 1055 second cancers were diagnosed in 908 patients, resulting in a standardized incidence ratio (SIR) of 4.6 (95%CI 4.3–4.9) in the study cohort as compared with the general population. The risk was still elevated 35 years or more after treatment (SIR 3.9, 95%CI 2.8–5.4), and the cumulative incidence of a second cancer in the study cohort at 40 years was 48.5% (95%CI 45.4–51.5). The cumulative incidence of second solid cancers did not differ according to study period (1965–1976, 1977–1988, or 1989–2000) ($P = 0.71$ for heterogeneity). Although the risk of breast cancer was lower among patients who were treated with supradiaphragmatic-field radiotherapy not including the axilla than among those who were exposed to mantle-field irradiation (hazard ratio 0.37, 95%CI 0.19–0.72), the risk of breast cancer was not lower among patients treated in the 1989–2000 study period than among those treated in the two earlier periods. A cumulative procarbazine dose of 4.3 g per square meter of body surface area (which has been associated with premature menopause) was associated with a significantly lower risk of breast cancer (hazard ratio for the comparison with no chemotherapy (HR 0.57, 95%CI 0.39– 0.84) but a higher risk of gastrointestinal cancer (HR 2.70, 95%CI 1.69–4.30). The risk of second solid cancers did not appear to be lower among patients treated in the most recent calendar period studied (1989–2000) than among those treated in earlier periods. The awareness of an increased risk of second cancer remains crucial for survivors of Hodgkin's lymphoma.

N Engl J Med 2015; 373: 2499

Eitan Israeli

Capsule

A virus linked to shrinking newborns' brains is spreading rapidly beyond Brazil

Until 2014, Brazil had no more than 200 cases of microcephaly, a debilitating neurological disorder where newborns have an abnormally small brain. In 2015, the country recorded nearly 3000 cases. Some of the worst affected areas have declared a state of emergency. Many born with microcephaly die young. Those who survive have life-long cognitive impairment. To understand the sudden rise, in November the country's health ministry drew a link to an epidemic of Zika virus that began in early 2015. Zika virus is transmitted by mosquitoes, and it was first detected in Uganda in the 1940s. After spreading through Africa and parts of Asia, it has made its way to Latin America. There is no known vaccine to prevent or medicine to treat the disease caused by the virus. Since May 2015, the Brazilian government estimates that some 1.5 million people have been infected with the virus. In children and adults, the infection is mostly benign: some suffer from fever and red rashes, while others may be symptomless. However, after finding the virus in the placenta of children born with microcephaly, Brazilian doctors have been warning women to delay their pregnancy if at all possible. "Most" mothers of microcephalic children, according to CNN, had Zika-like symptoms early in their pregnancy. There is no known physiological basis for how Zika virus can cause microcephaly, and previous epidemics do not help make the case. A 2007 outbreak on Yap Islands in Micronesia is estimated to have affected nearly 75% of the population of some 12,000 people, and a 2013 outbreak in French Polynesia affected nearly 28,000 of 270,000 residents. Neither epidemic caused a spike in microcephaly. An explanation for the link may be that a new strain of the virus is spreading through Brazil, according to Alain Kohl, a virologist at the University of Glasgow who studies Zika. Still, even for the fastest evolving organism on the planet, acquiring completely new powers of devastation is rare. A more likely explanation is that the link has simply gone unnoticed so far. It may be that Zika-induced microcephaly occurs only in a small proportion of pregnant women, and none of the previous epidemics have affected a large enough population to raise an alarm.

http://qz.com/585140/a-virus-linked-to-shrinking-newborns-brains-is-spreading-rapidly-beyond-brazil/

Eitan Israeli

Capsule

Limiting inflammation in obesity

Obese individuals have increased circulating levels of inflammatory cytokines produced by adipose tissue macrophages. Velmurugan et al.found that adipose tissue macrophages from obese mice had decreased levels of the gasotransmitter H2S, increased calcium signaling, and increased production of pro-inflammatory cytokines. H2S inhibited a calcium channel, which resulted in reduced calcium entry into macrophages. Thus, inflammatory stimuli lead to the depletion of H2S in adipose tissue, which exacerbates inflammatory responses by resident adipose tissue macrophages.

Sci Signal 2015; 8: ra128

Eitan Israeli