Saint Luke's REGIONAL LABORATORIES

Clinical Laboratory News

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Chikungunya and Dengue in the Americas

Chikungunya and dengue are both zoonotic viruses, transmitted by two species of Aedes mosquito, *A. aegypti* and *A. albopticus*. At onset, both viruses cause similar symptoms of fever, headache, myalgia, & rash. Chikungunya is often initially mis-diagnosed as dengue based on symptomatology.

Dengue became widely distributed geographically after World War II, when virus-carrying mosquitoes were carried worldwide due to increasing international trade. Even so, dengue infections were not widely documented in the Americas until 1981. Currently, an estimated 50-100 million infections occur annually, making dengue the most prolific mosquito-borne virus worldwide. Epidemics occur regularly in South America and the Caribbean. Dengue is caused by a flavivirus, and has 4 antigenically distinct serotypes. Most infections are subclinical, but the disease spectrum includes hemorrhagic shock and overall mortality is 10%.

In contrast, chikungunya is caused by a togavirus. Incubation period averages 3-7 days with the majority of those infected developing symptoms. A distinguishing clinical feature from dengue is prominent severe arthralgia commonly involving multiple joints in hands and feet that may persist for months after infection. Chikungunya virus was first isolated in Tanzania in the early 1950's and most outbreaks have occurred in Africa and the Indian subcontinent at 40-50 year intervals. In late 2013, the first locally transmitted chikungunya infection in the Americas was confirmed in the Caribbean islands. The virus has been identified in 44 countries in the Western hemisphere since then. In the United States, local transmission has emerged in Puerto Rico, the Virgin Islands and Florida. Mortality from chikungunya is less than 1%.

Despite the similarities, distinctive clinical features of these two viral syndromes were recognized in the 19th century prior to modern virus-detection methods. Indeed chikungunya is believed to have visited the Americas previously in the 1820's, causing an outbreak in the Virgin Islands and possibly New Orleans. That epidemic is believed to have originated in Zanzibar, at which time the disease was named kidenga pepo, Swahili for 'sudden cramp-like seizure caused by an evil spirit'.

Laboratory findings include lymphopenia most commonly in chikungunya, while neutropenia and thrombocytopenia are reported more often with dengue. Transaminitis is found with both infections. CDC advises that chikungunya should be considered in patients with acute onset of fever and polyarthralgia who recently returned from the Caribbean. In addition to dengue, the differential diagnosis includes malaria and parvovirus. Recommended diagnostic tests include PCR, particularly within the initial week of symptom onset, as well as serum IgM and IgG antibodies. PCR and serologic tests for both chikungunya and dengue are available through a reference laboratory.

Red Blood Cell Storage Outcomes

Red blood cells can be stored for up to 42 days, though most transfusions involve blood that is about 18 days old. During the storage of donated blood, RBCs undergo physical and biochemical changes that potentially decrease their oxygen carrying capacity.

More than 50 observational studies have been carried out during the past 30 years trying to determine if this so-called storage lesion affects clinical outcomes of transfusion recipients. Results of these studies have been mixed with 47% showing that blood stored for more than 2 or 3 weeks was associated with worse outcomes while 53% showed no difference. Recently, three large randomized clinical trials have been published that investigated clinical outcomes of fresher versus older RBC transfusions in different patient populations.

The Age of Red Blood Cells in Premature Infants (ARIPI) trial was a randomized controlled trial involving 377 very low birth weight infants in a neonatal intensive care unit (Fergusson DA, et al. JAMA 2012;308:1443-51). One hundred and eighty eight infants were transfused with fresh RBCs, having a median storage duration of 5.1 days and 189 were transfused with older RBCs stored for a median duration of 14.9 days. The primary outcome was a composite measure of neonatal morbidities including necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage, bronchopulmonary dysplasia and death. The primary outcome was met in 52.7% of neonates receiving fresher RBCs and 52.9% of neonates receiving older blood. Secondary outcomes, including infection rate and positive cultures, did not differ between the two groups. The ARIPI trial concluded that the use of fresher red cells did not improve outcomes in premature, very-low-birth-weight infants requiring a transfusion compared to those receiving standard of care. A benefit of using older blood was a reduction of total donor exposures (3.7 ± 2.7 donors versus 2.1 ± 1.6 donors).

The Red Cell Storage Duration Study (RECESS) study was a randomized controlled trial conducted at 33 medical centers in the United States that evaluated the effect of red blood cell storage time in 1481 patients aged 12 years or older undergoing complex cardiac surgery between 2010 and 2014 (Steiner ME, et al. *N Engl J Med.* 2015;doi:10.1056/NEJMoa1414219). Patients were randomized to receive either fresher units of leukocyte reduced red blood cells stored for 10 days or less or older units stored for 21 days or more. Primary outcome was the change in the multi-organ dysfunction score (MODS) through day 7. Higher scores indicated more serious organ dysfunction. Secondary end points included changes in MODS through day 28, serious adverse events and mortality at 28 days post surgery.

Of the 1096 evaluable patients who received transfusions within 96 hours following surgery, 538 patients received blood with a median of 4 units of fresher RBCs with a median storage duration of 7 days and 560 patients received a median of 3 units of older RBCs with a median storage duration of 28 days. The mean change in MODS was an increase of 8.5 points in the shorter-term storage group and 8.7 points in the longer-term storage group. This difference was not statistically significant (95% CI for the difference, –0.6 to 0.3, *P* 0.44).

Seven day mortality rates were 4.4% in the shorter-term storage group and 5.3% in the longer-term storage group (*P* = .57). There was no difference between the groups in adverse events except that the longer-term storage group was more likely to have hyperbilirubinemia. This randomized trial did not detect any significant differences in MODS, serious adverse events or mortality at day 28 between the two groups.

The Age of Transfused Blood in Critically Ill Patients (ABLE) study randomized 2430 patients admitted to intensive care units at 64 medical centers in Canada and Europe to receive fresher blood that was stored for an average duration of 6 days or standard-issue blood that was stored for an average duration of 22 days (Lacroix J, et al. N Engl J Med 2015.doi.10.1056/NEJMoa1500704).

Mortality rates were essentially the same. At 90 days, 37% of patients who received fresh blood had died, compared with 35% in the standard-issue blood group (time-to-death hazard ratio=1.1, p=0.38). The groups exhibited no differences in secondary outcomes including major illnesses; duration of respiratory, hemodynamic or renal support; length of hospital stay; and transfusion reactions. The authors concluded that fresh RBcs did not appear to be superior to standard issue RBCs in critically ill patients.

Three large randomized trials in neonates, cardiac surgery patients and ICU patients have concluded that freshly donated blood is not better than older blood when it is transfused into severely ill patients. These studies support continuation of the current inventory management practice of issuing the oldest units first to minimize outdating of blood components.

Change in Epic Virus Culture Ordering

Virus cultures are currently ordered based on specimen type, for example CSF, eye, or stool. Beginning May 6, all virus cultures should be ordered as “Virus Culture, General.” This designation should also be used in Epic personal preference lists.