DRUGMonitor

Brief summaries of recent drug approvals, interactions, and adverse events

Endocarditis and Cancer

Endocarditis is a strong clinical marker for occult cancer, say researchers from Aarhus University Hospital and the Danish Cancer Society, both in Denmark. But unfortunately, they add, intensive antibiotics don't reduce the long-term risk of cancer.

The researchers analyzed data from 8,445 patients with a first hospital diagnosis of endocarditis between 1978 and 2008. The median follow-up time was 3.5 years, with a maximum of 31 years. During that time, 997 cancers were observed in patients with endocarditis (620 were expected). The overall risk was slightly higher for patients with prior heart valve disease, a recent surgery, or a recent infection.

The most dangerous time for patients with endocarditis was the first few months after admission. During the first 3 months, 188 cancers were diagnosed vs 23 expected cancers. By comparison, the researchers say they observed 292 cancers during the first year, with 83 expected, and 388 during the first 2 years, with 151 expected.

Risks were substantially higher for gastrointestinal and hematologic cancers; the risks of lung, prostate, and breast cancer were lower. Among the main cancer subgroups, the 3-month risk was 24-fold for hematologic cancers and a 50 times or more increased risk for several rare cancers, including cancer of the heart, Kaposi sarcoma, and meningeal cancer.

The risks of most cancers fell markedly after the first 3 months, although the overall risk of cancer remained at approximately 1.5-fold for the next 5 years. After that, the risk was still increased, but modestly so, at 1.21. They suggest that the continued slightly increased risk attributed to endocarditis may also have been related to shared risk factors including lifestyle (eg, smoking and alcohol use) and immunosuppression. Notably, the researchers say, the risk for liver, colon, rectal, and small intestine cancers remained high—double to triple—throughout the first 2 years.

However, early cancer risk was highest in patients without other endocarditis risk factors. That finding supports a causal role for occult cancer in endocarditis development, the researchers say. Moreover, they say, bacterial pathogens causing endocarditis could also play a direct role in cancer development. They cite "increasing evidence," for instance, that *Streptococcus gallolyticus* may not only invade colorectal tumors, but also be involved in carcinogenesis, and they point to the "well-documented" link between *Helicobacter pylori* and gastric adenocarcinoma and lymphoma. They note, also, that acutely impaired cell-mediated immunity is strongly associated with both lymphomas and leukemias, and with systemic bacterial infection.

Although evidence is "sparse and conflicting" on whether antibiotic use affects the risk of cancer, the researchers sound a warning: The fact that longer-term cancer relative risks were particularly increased for endocarditis patients with predisposing risk factors supports the hypothesis that intensive antibiotic treatment increases general cancer risk, rather than decreasing it, potentially by harming intestinal microflora.

Source: Thomsen RW, Farkas DK, Friis S, et al. *Am J Med.* 2013;126(1):58-67.
doi: 10.1016/j.amjmed.2012.07.026.

Cognitive Impairment and Heart Failure

Mild cognitive impairment (CI) can be easy to miss, but it may have a disproportionately significant impact on adherence to treatment of patients with heart failure (HF). A study at the VA Loma Linda Healthcare System in California found a high prevalence of unrecognized CI among veterans and a "robust association" between the presence of CI and poor adherence. In fact, of study variables including alcohol use and older age, only CI had a statistically significant association with medication adherence.

The 251 participants, all veteran outpatients with HF, were screened for CI, depression, and the propensity to adhere to the prescribed medication regimen. The researchers used the Saint Louis University Mental Status (SLUMS) test, which has 11 questions that test recall, semantic fluency, and verbal memory, among other variables. They also used the Geriatric Depression Scale, a widely used self-report consisting of 30-simple yes/no questions suitable for the mildly cognitively impaired.

The CI screening revealed that 58% of the veterans had unrecognized CI, with verbal learning, immediate memory, and delayed verbal memory being the most often impaired. Patients with no CI had adherence rates of 78%, compared with 70% for those with mild CI and 73% for those with severe CI.

The prevalence of unrecognized CI was high but consistent with other studies in nonveteran outpatients with HF. Age was a factor, as were African American race, use of alcohol, and depression.

Adherence worsened significantly with mild CI but did not continue to worsen with severe CI. The researchers say this is particularly important to clinical practice, because mild CI is easily missed. The patient may deny needing any help with medication administration and may hide memory loss. It's also possible that patients with worse CI were getting more help from family members or others.

The researchers say both overtaking and undertaking prescribed medicines were common, although they found no statistically significant patterns. Overtaking is a potentially serious safety issue, compounded by multiple drugs prescribed by multiple health care providers. In this study, the researchers say, it was not uncommon to find patients with several bottles of the same medication, taking a tablet from each one. They also found that patients most often knew their medications by color and shape rather than by name or indication—this is important in the VA system, because generic medications are mailed to patients' homes from a centralized pharmacy. Changes in vendors used by the pharmacy often meant the medicine changed in appearance, thus patients might not recognize that the new tablet was actually the same medication.

The researchers note that current clinical practice guidelines don't recognize CI as a risk factor for poor adherence. But they point out that many cognitively impaired patients won't understand, or will forget, what the health care provider instructed them to do soon after leaving the clinic. The researchers recommend screening all patients with HF, using a tool such as the SLUMS test, which takes only 10 minutes or less. They also note that the average patient in their study was mildly depressed. They suggest it may be another easily missed diagnosis in these patients. Depression is known to affect information processing and has shown to be associated with worsened outcomes in nonveterans with HF. Here, too, they advocate screening to identify patients at risk.

Source: Hawkins LA, Kilian S, Firek A, Kashner TM, Firek CJ, Silvet H. *Heart Lung.* 2012;41(6):572-582. doi: 10.1016/j.hrtlng.2012.06.001.

Older Patients Are Major Source of Resistant Organisms

Older patients may be bringing multidrug-resistant organisms (MDROs) into the hospital with them, according to a 12-year surveillance study at Beth Israel Deaconess Medical Center in Boston, Massachusetts. Researchers found that rates of MDROs among the elderly were 2 to 3 times higher than in younger patients.

The researchers compared rates of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant gram-negative (MDRGN) bacteria from clinical cultures taken within the first 48 hours of admission. They collected an average of 7,534 positive bacterial cultures per year. The prevalence of all 3 organisms was consistently higher among older patients, who had approximately twice the prevalence of MRSA and VRE and triple the prevalence of MDRGN.

The researchers cite several probable reasons for the higher incidence among the older patients. For one, substantially higher rates of MDRO colonization and cross-transmission have been documented in long-term care facilities (LTCFs). Moreover, residents of LTCFs are frequently prescribed antimicrobials, have more comorbidities, and are hospitalized more often.

The rate of resistance was clearly on the rise from the beginning to the end of the study: In 1998, for instance, only 2.2% of isolates were multidrug resistant, compared with 14% in 2009. The rise was significantly higher in the elderly, leading the researchers to suggest that the older population will "continue to provide a constant and increasing source of MDRO." However, they also point to documented declines in MRSA infections in the last 6 or 7 years, even among the elderly. Programs targeting MRSA and better compliance with infection control efforts may be responsible.

Choosing the right antimicrobial therapy for an elderly patient can be problematic. In the last year of the study, 57% of all *S aureus* isolates recovered from older patients were resistant to methicillin, 25% of enterococcal isolates were resistant to vancomycin, and 14% of gram-negative isolates were multidrug resistant. Given those findings, the researchers suggest that older patients may benefit from empiric use of broad-spectrum antimicrobials, but, they warn, that approach also needs to take into account potential further emergence of antimicrobial resistance. ●

Source: Denkinger CM, Grant AD, Denkinger M, Gautam S, D'Agata EM. *Arch Gerontol Geriatr.* 2013;56(1):227-230. doi: 10.1016/j.archger.2012.05.006.