Nailing Down the Debate on Antibiotic Resistance in Post-Transplant Patients

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Following hematopoietic cell transplantion (HCT), the extreme neutropenia (decrease of neutrophil number) and the impairment of the immune response make the body more susceptible to bacterial infections. Gram-negative rod (GNR) bacteremias affect 5-10% of HCT patients and are associated with a higher mortality rate than gram-positive infections. To reduce the probability of such infections, the use of prophylactic antibiotics have been recommended by international guidelines. Among available antibiotic treatments, fluoroquinolones have been shown to reduce the rate of post-transplant infections and mortality rates. Although these agents were thought to be less prone to resistance due to their unique molecular structure, excessive use in medicine and agriculture has led to increasing resistance throughout the world.

Studies from investigators at the Fred Hutch Vaccine and Infectious Disease Division (VIDD) suggested an increase in gram-negative bacteremia events in allogeneic HCT recipients in recent years, raising the question of whether this increase was related to increased resistance to fluoroquinolones. In order to address this question, Epidemiology PhD student Arianna Miles-Jay from Dr. Steven Pergam's group in VIDD analyzed GNR bacteremia data from patients undergoing HCT at Seattle Cancer Care Alliance (SCCA). The group conducted a longitudinal retrospective study on data from patients that underwent HCT during an era in which levofloxacin (a member of the fluoroquinolone family) prophylaxis was standard practice for HCT recipients: January 2003 to December 2012. Results from the study were published in December in Biology of Blood and Marrow Transplantation.

The study had two main purposes: first, to look at trends over time in the incidence of all GNR and FQ-resistant GNR bacteremia events in the first 100 days after HCT; and second, to compare the mortality rates following infection with FQ-sensitive versus resistant strains. "While antibiotics are a lifesaving necessity, especially in this high risk population, their widespread use does not come without consequences. Evaluating the local epidemiology of GNR infections, including antibiotic susceptibilities, is important for optimizing the standard of care for SCCA patients." said researcher Miles-Jay to introduce the reason for her interest. The study includes data from 2306 patients that underwent allogeneic HCT, of whom 12.1% experienced GNR bacteremia following transplantation.

The bacteremias increased in the period of time between 2003 and 2009, and then declined in the following years. Although the study was not set to explain why such patterns occurred, the authors speculated that several infection control interventions implemented at SCCA between 2009 and 2010 played a role in the post-2009 decrease. The incidence rate of FQ-resistant GNR followed a similar trend as total GNR, implying that the increased rate of GNR bacteremias were not due major increases in resistant strains. However, survival analyses showed that patients with a FQ resistant GNR bacteriemia had a significantly higher post-event cumulative mortality than patients experiencing a FQ-sensitive event, a finding that persisted after adjusting the analyses for various parameters, such as underlying illness, age at transplantation and conditioning regimen. This higher rate could be possibly be explained by delays in appropriate antibiotic therapy or that the bacteria most likely to acquire a resistant phenotype were ones known to be associated with higher mortality.

Even though this study was a retrospective analysis, the large sample size and the fact that it was conducted from the center's robust long term longitudinal data make this publication an important step in addressing evidence-based decisions on the use of fluoroquinolones prophylaxis at the center.

Arianna Miles-Jay concludes: "Since there is no evidence of overall increasing rates of fluoroquinolone resistance among gram-negative bacteremia events, levofloxacin is still appears to be a viable option for neutropenic prophylaxis for HCT recipients at the SCCA. However, the mortality difference we observed between FQ-resistant and sensitive infections highlights the importance of continued vigilance when it comes to antibiotic resistant infections."

Miles-Jay A, Butler-Wu S, Rowhani-Rahbar A, Pergam SA. 2014. Incidence rate of fluoroquinolone resistant gram-negative rod bacteremia among allogeneic hematopoietic cell transplant patients during an era of levofloxacin prophylaxis. *Biol Blood Marrow Transplant*. S1083-8791(14):01399-8.

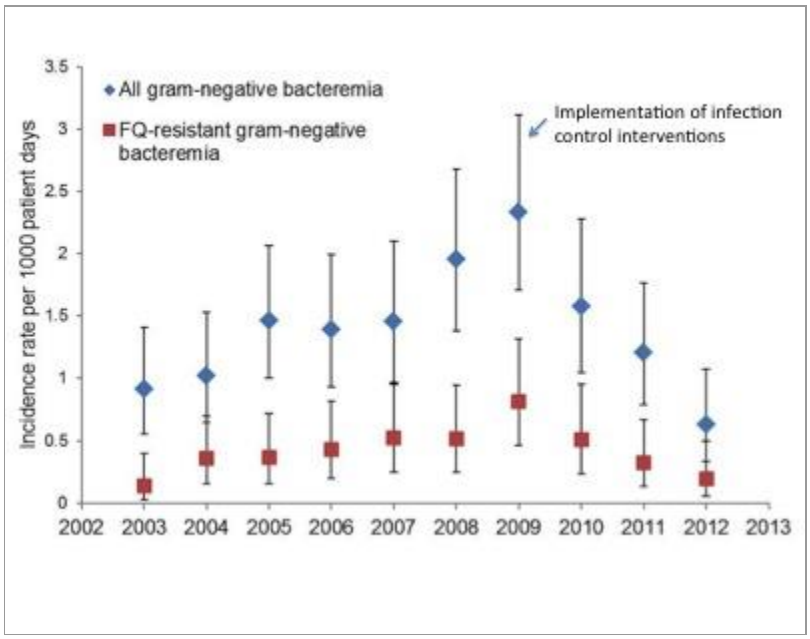

Image provided by Arianna Miles-Jay

Incidence rate of first gram-negative bacteremia event by transplant year, 2003-2012.