AN OUTBREAK OF ENDOTOXIN-LIKE REACTIONS ASSOCIATED WITH SINGLE DAILY DOSED INTRAVENOUS GENTAMICIN--LOS ANGELES, 1998

On July 30, 1998, the hospital epidemiology department at a large, private acute care hospital in Los Angeles notified the Los Angeles County (LAC) Department of Health Service's, Acute Communicable Disease Control unit (ACDC) about several patients who had severe chills following the receipt of intravenous (IV) gentamicin. Chills developed within three hours after IV gentamicin infusion and were variably accompanied by fever, tachycardia, and/or a decrease of $\geq$20 mm Hg systolic blood pressure (BP). This type of reaction has been previously reported from outbreaks as a complication of hemodialysis, or in experimental studies, and has been attributed to the effect of endotoxins.

When a preliminary investigation identified 20 patients with reactions between April 30 and July 26, 1998, the Hospital Infections Program, Centers for Disease Control and Prevention (CDC), was invited to assist in the investigation. The investigation was initiated to describe the demographic and clinical characteristics of patients with gentamicin-associated reactions, to assess the risk factors for gentamicin-associated reactions, and to determine the cause of these reactions.

A case-patient was defined as any patient at this hospital aged $\geq$28 days who had documented chills, rigors or shivering within three hours after the start of intravenous gentamicin from December 1, 1997 through August 25, 1998. Three retrospective cohort studies, and assays of gentamicin vials for bacterial growth and endotoxin levels were conducted.

Our analysis included 220 gentamicin-treated patients: 152 in the epidemic period, 20 in the post-epidemic period, and 48 in the pre-epidemic period. Gentamicin administered in the pre-epidemic and epidemic period was manufactured by Fujisawa Pharmaceuticals, Inc., and in the post-epidemic period by Schein Pharmaceuticals, Inc. Patients received gentamicin in a multiple daily dosed (MDD; N=79) or single daily dosed (SDD; N=141) regimen. Twenty-four (11%) of the 220 patients met the case definition: 22 in the epidemic period, none in the post-epidemic period, and 2 in the pre-epidemic period. The median age of case-patients was 37 years (range: 18-69), and 17 (71%) were women. From April 30 until June 15, 1998 (i.e., epidemic period), reactions among SDD patients (20/73 [27%]) were more likely than among MDD patients (2/79 [3%]; relative risk =10.8; 95% confidence interval=2.6-44.7). Furthermore, attack rates (AR) among SDD-treated patients (20/73 [27%]) in the epidemic period (when Fujisawa-manufactured gentamicin was used) were significantly higher ($p<0.01$) compared to SDD patients in the post-epidemic period (0/20 [0%]; i.e., when Schein-manufactured gentamicin was used) and the pre-epidemic period (2/48 [4%]; i.e., when Fujisawa-manufactured gentamicin used was from different lots than

in the epidemic period). Case-patients treated with SDD gentamicin received a median dosage of 6.2 mg gentamicin/kg body weight (BW). Eighteen Fujisawa-manufactured gentamicin vials from lots used during the epidemic period were tested and contained a median of 0.49 endotoxin units (EU)/mg gentamicin (range 0.1-1.01 EU/mg). We estimated that patients receiving 6.2 mg gentamicin/kg BW would receive between 0.6 and 6.3 EU/kg BW. Doses above 5 EU/kg BW would exceed the experimentally derived human threshold for endotoxin.

We concluded that this outbreak of endotoxin-like reactions was caused by the lots of Fujisawa-manufactured gentamicin administered during the epidemic period. The calculated endotoxin load of SDD case-patients is consistent with endotoxin-mediated reactions. Use of SDD medications may place patients at greater risk of receiving doses of endotoxin above the threshold for humans. While endotoxin levels in the vials did not exceed U.S. Pharmacopeia limits (1.7 EU/mg gentamicin based on MDD dosing), this limit may need to be reassessed since use of SDD gentamicin is likely to become increasingly popular.