Cardiac surgery in infants results in a profound inflammatory response secondary to cardiopulmonary bypass (CPB) and the need for blood products. It is not clear how this inflammatory response modulates post-operative course or whether quantification of pro-inflammatory cytokines can aid with risk stratification. In this study, we prospectively assessed a panel of candidate markers to determine the time course for inflammation and the association of specific markers with clinical outcomes defined as intensive care unit length of stay. We obtained pre-operative blood samples from 71 neonates undergoing surgery with CPB and then serially for 5 days following surgery. Numerous interleukins were assayed along with TNF-α and INF gamma. Diagnoses included transposition of the great arteries n=14, hypoplastic left heart syndrome n=15, 42, other single ventricle defects n=24, and other two ventricle defects n=18. Multivariate analysis was performed to determine if inflammatory mediators could independently predict length of stay. Compared to the pre-surgery level, there are statistically significant increases (P < 0.005) at day 1 for six markers: IL-10, IL-13, IL-8, INF gamma, TNF alpha, and IL-6. At 3 days post-op all markers had returned to pre-surgery levels except IL-6 and IL-8, which remained elevated. No marker on the first pre-operative day was independently associated with length of stay. However, IL-8 obtained on day 3 following surgery was significantly associated with a prolonged ICU length of stay (p<.001) after adjusting for other covariates. In summary, neonatal heart surgery for complex lesions elicits a broad inflammatory response. This early inflammatory response appears non-specific and does not predict clinical course. Persistence of specific inflammatory mediators such as IL-8 on the 3rd day of surgery, however, provides important prognostic information. As such, IL-8 may serve as a biomarker in this population. Whether strategies targeting specific cytokines can alter clinical course is not known.