Unexplained Death due to Possible Infectious Diseases in Infants—United States, 2006

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Objectives To quantify and examine factors related to unexplained death due to possible infectious causes (UDPIC) in infants and to analyze the associations between these factors in unexplained deaths and infants with fatal and nonfatal outcomes.

Study design Infant deaths meeting the *International Classification of Diseases, Tenth Revision* code inclusion and exclusion criteria for UDPIC were selected from the 2006 US Linked Birth and Infant Death data set. Two control groups of surviving and nonsurviving infants were selected and compared with the infants with UDPIC using a case-control study design with multivariate logistic regression models stratified by birth weight category. Comparisons with infants with identified infectious causes of death were also made.

Results During 2006, 3570 infant deaths (12.5% of all US infant deaths) were categorized as a UDPIC. The highest rates for these unexplained infants deaths were found in blacks and American Indians/Alaska Natives. Infants of black mothers were more likely to experience UDPIC. Birth weight was a significant effect modifier in these models.

Conclusions Many factors may contribute to an infant's death being classified as a UDPIC, including race and marital status. Other factors, such as Hispanic ethnicity and maternal age, also may play a role. Infant characteristics, such as birth weight, may be related to factors that influence the decision not to conduct a postmortem examination in infant death cases. Additional research is needed to determine the true extent of infectious disease and its relationship to UDPIC in infants. *(J Pediatr 2013;162:195-201)*.

Death in which premortem signs and symptoms suggest an infectious cause but in which no definitive infection-related cause of death is reported on the death certificate can be classified as an unexplained death due to possible infectious causes (UDPIC).[1] Although suggestive of infection, these deaths are not attributed to a confirmed infectious agent. Therefore, the reported cause of death is often vague or nonspecific, frequently reported with known prodromes of infectious disease (ID) as contributing factors. Published work on UDPIC includes deaths in previously healthy persons 1-49 years of age chosen for simulating surveillance of emerging infections in selected US communities.[1,2] Infants (<1 year of age) are excluded from UDPIC analyses despite the fact they may be especially susceptible to infectious agents because of the naiveté and immaturity of their neonatal immune system.[3]

Determining a definitive cause of death in infants can be a complicated task. Because infants cannot verbalize internal symptoms of pain and discomfort, it can be difficult for coroners and medical examiners to fully understand the extent of both symptoms and disease in postmortem investigations, which rely heavily on objective observation of clinical signs provided by caregivers and health care providers. Furthermore, even though infant and adult anatomy are similar, infant postmortem examinations are notably different, requiring the use of specially sized instruments and modified procedures.[4] Despite these barriers, it is important to study UDPIC in infants to define the burden of UDPIC in this population and to understand if there are any clinical or epidemiologic characteristics that are associated with these poorly defined, possible infection-related causes of death not attributed to a confirmed infectious agent on the death certificate.

The specific aims of the present study are to (1) quantify the number of infants with UDPIC-type outcomes in the US; (2) describe epidemiologic characteristics relating to UDPIC in infants; (3) compare characteristics of infants whose death was the result of a noninfectious condition; (4) characterize infants who survived the first year of life with infants with UDPIC; and (5)

ICD-10	*International Classification of Diseases, Tenth Revision*
ID	Infectious disease
LBW	Low birth weight
NBW	Normal birth weight
UDPIC	Unexplained death due to possible infectious causes

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examine similarities between infants with UDPIC and those with deaths attributed to confirmed IDs.

Methods

Publicly available national Linked Birth and Infant Death data for 2006, compiled by the National Center for Health Statistics, Centers for Disease Control and Prevention, were used for this case-control study. Data from 2006 were used as it was the latest year for which linked data were available at the time of analysis. These linked data, released annually, include birth certificate data spanning 1 calendar year (2006) for all US births, regardless of outcome, as well as birth-linked death certificate data for deaths occurring in these infants before 1 year of age.[5] Only infants reported as US residents were included in this analysis; infants born in US territories were excluded. For 2006, the total number of linked records was 28 509, accounting for 0.7% of 4 265 593 total US births.[6] A small proportion of deaths (1.3%) were excluded from the analysis because their death records could not be linked to corresponding birth certificates.[6]

For this analysis, a UDPIC case was defined as an infant death with possible ID prodromes indicated by the presence of select codes (**Table I**; available at www.jpeds.com) from the *International Classification of Diseases, Tenth Revision* (ICD-10)[7] listed anywhere on the death record without indication of a significant underlying or contributing factor (**Table II**; available at www.jpeds.com). These UDPIC inclusion and exclusion criteria differed from the original UDPIC definitions set forth by Perkins et al that used earlier mortality data with *International Classification of Disease, Ninth Revision* codes and did not exclude death records with specific birth- and infant-related conditions because of the focus on older children and adults.[1] Both these new criteria and the prior criteria allow the focus of UDPIC analysis to be on deaths in which IDs may be the underlying cause of death rather than just a complication of underlying disease.

Infant mortality rates were calculated as the weighted number of deaths per 100 000 live births.[5] Weighting was applied to adjust for unlinked infant death certificate data.[5,6] Rates and 95% CIs were calculated overall, by sex, maternal race, ethnicity, and age group.

For comparison with the infants with UDPIC, 2 control groups were identified. The first control group (nonsurviving controls) was randomly selected using a 1:1 case-control ratio. Nonsurviving controls were defined as infants who did not survive to 1 year of age and had a cause of death listed anywhere on the death certificate that included codes for neoplasms, diseases of the spleen, disorders involving immune mechanism, diabetes mellitus, and congenital malformations as defined by ICD-10 codes (**Table II**). Nonsurviving control death records that contained ICD-10 codes related to injury and poisonings (S00-T98), external causes (V01-Y34, Y40-Y84), ID (A00-B99), or UDPIC (**Table I**) were excluded from the nonsurviving control group. The second control group (surviving controls) was randomly selected using a 1:1 case-control ratio from infants with a birth certificate in the linked data but no matched death certificate data indicating that the infant survived the first year of life. Deaths attributed to confirmed ID also were examined. These deaths were defined as infants with an ID ICD-10 code (A00-B99) listed anywhere on the death certificate excluding those meeting the UDPIC case definition.

Maternal and infant characteristics were selected from the linked data, based on the literature and comparability between 1989 and 2003 birth certificate revisions. In 2006, the 1989 revision was used by 31 states, and 19 states and Puerto Rico used the 2003 revision.[5] Some characteristics are considered by the National Center for Health Statistics to be noncomparable between the 1989 and 2003 revisions of the US Standard Certificate of Live Birth, including maternal education, trimester prenatal care began, maternal smoking, congenital anomaly, and abnormal newborn condition.[5,6] Only variables comparable between both revisions of the birth certificate were included in the present analysis.

Infant characteristics examined included sex, live birth order (first and second or more), 5-minute Apgar score (0-3, 4-7, and 8-10), birth weight (<2500 g, low birth weight [LBW]; ≥2500 g, normal birth weight [NBW]), and gestational age (<37 and ≥37 weeks). Maternal characteristics examined included race (white, black, and other), Hispanic ethnicity, age (<20, 20-29, and ≥30 years), weight gain, method of delivery (vaginal or cesarean), marital status (married and unmarried), and preexisting pregnancy conditions. Apgar score was missing for 13.5% of infants; 20.6% were missing maternal weight gain. No other variables were missing for >1% of the records. Maternal race and ethnicity as reported on the birth certificate were used because they are generally considered to be more reliable than race and ethnicity information reported for the infant on the death certificate.[5] For this study, the race and ethnicity of the infant and mother are considered the same.

Because of the large number of infants missing Apgar score data, due in large part because California birth certificates did not collect Apgar score data in 2006,[8] 2 multivariate logistic regression models were fit. One model included Apgar score and kept all infants with Apgar score reported; the second excluded Apgar score to include infants with missing Apgar score data. Statistical models including Apgar score were ultimately not used because these models were ill-fitting.[9] Univariate logistic regression analysis for both models was conducted, and ORs with corresponding 95% CIs were calculated. Infant and maternal characteristics considered significant in the univariate analysis ($P < .10$) and interaction terms were tested for association with UDPIC using hierarchical multivariate logistic regression modeling.[10] Gestational age was excluded from the multivariate model because the measure is unreliable and has a high correlation with birth weight.[11] Initial multivariate logistic regression models indicated that several of the variables had statistical interaction with infant birth weight. The final models presented were stratified by birth weight categories of LBW and NBW,