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

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Abstract

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.

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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) 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 non-comparable 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, resulting in 4 regression models. The significance level was considered $P < .05$.

All UDPIC codes were assigned to a syndromic category based on the type of syndrome to which the coded illness was likely related (Table I). The UDPIC ICD-10 codes that fell into syndromic categories other than “Cardiac,” “Gastrointestinal,” “Neurologic,” “Respiratory,” or “Sepsis” were classified in the “Other” category. Less than 5% (75 cases) had codes assigned that were in >1 syndromic category. These cases were assigned to multiple UDPIC categories, resulting in summed syndromic category totals greater than the total number of cases as some records were counted more than once. SAS 9.3 (SAS Institute, Cary, North Carolina) was used to perform all analyses.

Results

For 2006, the weighted number of infant deaths with a UDPIC after excluding deaths with contributing causes was 3570, accounting for 12.5% of all US infant deaths. UDPIC in infants accounted for 83.7 deaths per 100 000 US live births (95% CI, 81.0-86.5). The UDPIC rate for male infants (93.5 per 100 000; 95% CI, 89.5-97.6) was statistically higher than the rate for female infants (73.3; 95% CI, 69.7-77.1, $P < .0001$). The lowest UDPIC rates were found in white (66.5; 95% CI, 63.7-69.3) and Asian/Pacific Islander (57.4; 95% CI, 47.9-67.0) infants. The highest UDPIC rate was among black infants (175.2; 95% CI, 165.1-185.2), although the rate in American Indian/Alaska Native infants was comparable (130.2; 95% CI, 99.6-166.6). Additional rate-related data are available from the authors.

Unweighted counts and proportions for selected characteristics by case-control status and birth weight category are presented in Table III. The proportion of black infants with UDPIC is higher than both control groups with no such difference found for the other race

categories. The proportion of married mothers is about 25% lower in mothers of infants with UDPIC than in both control groups. Among infants with UDPIC, there are many characteristics more common in LBW infants, including multiple birth, mother ≥30 years of age, first live birth, and black race, compared with NBW infants.

UDPIC Infants versus Nonsurviving Control Infants

Multiple birth status, live birth order, sex, and the interaction between maternal age and race each was significantly associated with UDPIC in this LBW model (Table IV). Males and first live birth infants were at increased odds for UDPIC. Married mothers ≥20 years old had lower odds of UDPIC compared with unmarried women in the same age groups. Black LBW infants had significantly increased odds for UDPIC regardless of maternal age, and as maternal age increased, the odds for UDPIC among black infants increased. Of births performed via cesarean delivery, only white infants were at increased odds for UDPIC.

Comparing UDPIC with nonsurviving controls in NBW infants in Model 2, race, pregnancy-associated hypertension, cesarean delivery, and the interaction of maternal age with marital status and Hispanic ethnicity were significantly associated with a UDPIC-type outcome (Table IV). Relative to white infants, increased odds for UDPIC were found for both black infants and infants of other races. Further, Hispanic infants are at decreased odds for UDPIC, although this is only true for infants of mothers ≥20 years of age. This model showed decreased odds of UDPIC in NBW infants of married mothers ≥20 years of age compared with unmarried women in the same age groups.

UDPIC Infants versus Surviving Control Infants

Comparing LBW UDPIC infant cases with surviving control infants, single births had increased odds for UDPIC. Black infants had the highest odds of UDPIC, and infants of other races had statistically similar odds for UDPIC compared with white infants. Males had higher odds of UDPIC than females. Cesarean births had increased odds for UDPIC compared with vaginal births. First live births to women ≥30 years of age had increased odds for UDPIC compared with subsequent births, a finding not significant for younger mothers in this model.

Last, among NBW UDPIC cases compared with NBW surviving control infants, black infants, male infants, infants of cesarean births, and infants of mothers <20 years of age had increased odds for UDPIC. In contrast, infants at lower odds for UDPIC included first live births, Hispanic infants, infants of married mothers, and infants of mothers ≥30 years of age.

Confirmed ID

Death records met the definition of a confirmed ID-related death for 260 infant deaths. In general, UDPIC cases were not statistically different from these infants with a few notable differences (data available from the authors). Compared with those with UPDIC, infants with death attributed to confirmed ID were more likely to be a first live birth (OR 1.4; 95% CI, 1.1-1.8) and have an older gestational age (>32 weeks; OR 1.5; 95% CI, 1.1-1.9) and were more likely to undergo an autopsy (OR 1.6; 95% CI, 1.2-2.1), based on univariate analyses.

Autopsy

In 2006, 1665 (53.0%) infants with UDPIC underwent autopsies compared with 744 (23.7%) nonsurviving controls ($P < .0001$). Overall, infants with UDPIC were more likely to undergo autopsies if the UDPIC ICD-10 code was related to possible respiratory infections (OR 3.8; 95% CI, 2.8-5.1) or was classified in the "Other" syndromic category (OR 7.9; 95% CI, 6.7-9.3). Conversely, infants with UDPIC classified as sepsis had the lowest odds of undergoing an autopsy (OR 0.09; 95% CI, 0.07-0.10). Infants with UDPIC related to gastrointestinal, cardiac, or neurologic disease were not significantly more or less likely to undergo autopsy. For all infants with UDPIC, those with NBW had significantly greater odds of undergoing autopsy, regardless of syndromic category, compared with LBW infants (OR 14.9; 95% CI, 12.3-18.1).

Discussion

This study examined factors associated with US infant deaths classified as UDPIC on the death certificate. Using UDPIC ICD-10 code definitions, 1 in 8 infant deaths can be classified as a UDPIC. This result is similar to the finding that 14% of all hospital and emergency department deaths, approximately 1 in 7, are attributed to UDPIC in persons aged 1-49 years.[1]

Infants of black race are more likely to have UDPIC recorded as a cause of death compared with other race categories in both control groups and both birth weight categories. This is analogous to higher rates of UDPIC in black adults in populations examined in previously published work.[1] Findings parallel data showing that non-Hispanic blacks have the highest infant all-cause infant mortality rate as well as the highest mortality rate among LBW infants in the United States.[6] Lack of appropriate prenatal care in black mothers may increase the risk of congenital infections that contribute to high UDPIC rates.[12,13] Although the percentages of black infants of LBW and very LBW are about twice those of white infants[12] and a link between LBW and impaired immunity in infants has been shown,[14] the regression models still showed that black infants have worse outcomes regardless of birth weight category. Furthermore, differences in UDPIC rates in black infants cannot be attributed to differences in the proportion of infants who undergo an autopsy (45% in black infants), which is similar to white infants (48%), corresponding to a previous finding that race was not a factor in the decision to consent to neonatal autopsy.[15]

In both NBW groups, odds of UDPIC are lower in Hispanics compared with non-Hispanics. This finding is consistent with other literature, suggesting a curious paradox relating to the health of US Hispanics,[16,17] including Hispanic infants,[18] who have lower rates of mortality despite socioeconomic data, which would suggest higher mortality rates in other US populations. This finding was only applicable in NBW infants; Hispanic ethnicity was not significant in either LBW model. This may suggest that factors other than ethnicity may be more closely associated with UDPIC in LBW infants.

Infants of unmarried mothers are at increased odds of UDPIC compared with infants of married mothers for all groups except for married mothers younger than 20 years of age in models using nonsurviving controls. The results of these models may suggest that increased

maternal age at birth can be a protective factor against UDPIC. However, the relationship of maternal age and UDPIC may be confounded by marital status and Hispanic ethnicity for some populations. Previous work suggests that marital status may be related to increased socioeconomic status, which can translate into better prenatal care and better pregnancy outcomes,[19,20] although these studies do not specifically focus on the relationship between marital status and outcomes associated with ID.

Based on the results of the regression models, the birth weight status of an infant modifies the relationship between UDPIC status and other birth-related and maternal characteristics. LBW might make an infant more susceptible to infection.[14] Future research should examine why some characteristics are more affected by birth weight in infants with UDPIC.

In this study, NBW infants are shown to have higher odds of undergoing an autopsy than LBW infants regardless of the syndromic category of illness. This analysis is not able to inform differences in autopsy rates between these birth weight groups. It is possible that LBW infants did not undergo an autopsy because their deaths were more likely to be attended or be under the care of a physician for a condition that can reasonably be recognized to cause death without benefit of postmortem examination. However, it may be just as important to perform autopsies on LBW infants due to the number of UDPIC deaths in LBW infants. If a susceptibility to infection exists, autopsy results can help contribute to the knowledge of and extent to which the infection contributed to death.

The analysis shows few statistically significant differences between UDPIC and IDs. These results may suggest UDPIC could serve as a proxy for IDs and an additional means to collect ID mortality data in infants for surveillance efforts, but this cannot be confirmed with this analysis. If UDPIC is a true proxy for ID-related deaths in infants, it would suggest the need to more fully examine infant deaths with prodromes of infection. The increased odds of infants with UDPIC undergoing an autopsy compared with ID deaths may indicate increased access to health care, which may lead to a diagnosis of illness before death and reduce the perceived need for postmortem examination.

Despite the number of infants with no autopsy performed in the face of an ID prodrome, the present analysis does not provide information as to why an autopsy was not performed. Published literature has suggested that many factors may contribute to lack of autopsy procurement.[21] Despite the fact that many UDPIC cases did undergo an autopsy, no infection-related cause of death was assigned. This may point to the presence of pathogens for which testing procedures are not readily available at the test facility, do not have high diagnostic value (eg, poor sensitivity), or do not exist or the determination that the prodrome-type symptom did not warrant further testing though it was ultimately recorded on the death certificate. The possibility also exists that death certificates may have been completed before autopsy results could inform alternative causes of death, or a limited autopsy was performed and no significant conclusions were made.

This analysis has important strengths. The data analyzed represent nearly all US infant deaths, with their corresponding birth and death certificate information. Additionally, because of the high level of linkage between the infant birth and death records (98.7% of

infant death records), characteristics related to pregnancy, birth, and death can be analyzed for nearly every infant death in 2006. However, because of our decision to stratify by birth weight, we are limited in our ability to directly assess the impact of birth weight in the models. In addition, the UDPIC definition and the excluded conditions presume that the prodrome conditions are possibly due to infectious causes. Several of the ICD-10 codes used as part of the UDPIC definition can be the result of a non-ID process, which would preclude a case from being defined as UDPIC, although the nature of the data makes that distinction impossible.

Because multiple cause-of-death data are used in the present study, the presence of a UDPIC code on a death record does not indicate that the condition is the underlying cause of death. Rather, it is possible that the cause of death is determined ultimately to be a non-UDPIC condition, but the presence of the UDPIC-related condition indicates that it may have contributed to death. Moreover, possible inaccuracy related to completion of the death certificate may contribute to increased UDPIC-related deaths if ID organisms were identified at the time of death but were not translated onto the death certificate. This situation results in a death certificate that lacks specificity as to a detailed cause of death as many UDPIC codes represent infectious conditions with an unspecified organism. More complete autopsy procedures and additional testing may reduce the number of UDPIC-related deaths because confirmed (ie, specified) IDs are not part of the UDPIC definition. This also could increase the value of surveillance for ID mortality. Additionally, it is not known if a full or partial postmortem examination was completed as both procedures qualify as a completed autopsy for purposes of US death certificate data. It is possible that diagnostic assays (eg, polymerase chain reaction testing) that can identify infectious agents are not available to the coroners and medical examiners who perform autopsies. Likewise, it is possible that potential ID agents were not identified because of diagnostic limitations such as culture growth limitations or limited access to methods for identifying emerging pathogens.[22]

These findings suggest that there may be a large number of US infants with symptoms suggestive of an infection that remains undiagnosed at death. Although these data cannot address if or how this possible infection may have contributed to infant death, the analyses suggest that more research should be done to further examine possible infection related deaths in US infants. Additional analysis is needed in this area to determine whether these possible infections contribute to death and to understand the issues related to causes of death in infants due to IDs in a first-world nation, as well as factors associated with autopsy procurement in infants, specifically infants with UDPIC.

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Glossary

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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Table I

Codes selected from ICD-10 used to characterize inclusion criteria for UDPIC in infants with syndromic category

ICD-10 code	Syndromic category	Syndromic category
A04.9	G	Bacterial intestinal infection, unspecified
A05.9	G	Bacterial foodborne intoxication, unspecified
A07.9	G	Protozoal intestinal disease, unspecified
A08.4	G	Viral intestinal infection, unspecified
A09	G	Diarrhea and gastroenteritis of presumed infectious origin
A28.9	O	Zoonotic bacterial disease, unspecified
A41.9	S	Septicemia, unspecified
A49.8	O	Other bacterial infection of unspecified site
A49.9	O	Bacterial infection, unspecified
A64	O	Unspecified sexually transmitted disease
A68.9	O	Relapsing fever, unspecified
A81.9	N	Atypical virus infection of central nervous system, unspecified
A83.9	N	Mosquito-borne viral encephalitis, unspecified
A84.9	N	Tick-borne viral encephalitis, unspecified
A85.2	N	Arthropod-borne viral encephalitis, unspecified
A86	N	Unspecified viral encephalitis
A87.9	N	Viral meningitis, unspecified
A89	N	Unspecified viral infection of central nervous system
A92.9	N	Mosquito-borne viral fever, unspecified
A94	N	Unspecified arthropod-borne viral fever
A99	O	Unspecified viral hemorrhagic fever
B09	O	Unspecified viral infection characterized by skin and mucous membrane lesions
B19.0	G	Unspecified viral hepatitis with hepatic coma
B19.9	G	Unspecified viral hepatitis without hepatic coma
B30.9	N	Viral conjunctivitis, unspecified
B34.9	O	Viral infection, unspecified
B36.9	O	Superficial mycosis, unspecified
B49	O	Unspecified mycosis
B64	O	Unspecified protozoal disease
B82.0	G	Intestinal helminthiasis, unspecified
B82.9	G	Intestinal parasitism, unspecified
B83.9	O	Helminthiasis, unspecified
B88.9	O	Infestation, unspecified
B89	O	Unspecified parasitic disease
B94.9	O	Sequelae of unspecified infectious or parasitic disease
B99	O	Other and unspecified infectious diseases
D59.4	C	Other non-autoimmune hemolytic anemias
D59.9	C	Acquired hemolytic anemia, unspecified

ICD-10 code	Syndromic category	Syndromic category
D61.9	C	Aplastic anemia, unspecified
D64.9	C	Anemia, unspecified
D69.6	C	Thrombocytopenia, unspecified
D72.9	O	Disorder of white blood cells, unspecified
D73.3	O	Abscess of spleen
E06.9	O	Thyroiditis, unspecified
G00.9	N	Bacterial meningitis, unspecified
G03.9	N	Meningitis, unspecified
G04.9	N	Encephalitis, myelitis and encephalomyelitis, unspecified
G06.2	N	Extradural and subdural abscess, unspecified
H01.9	N	Inflammation of eyelid, unspecified
H10.9	N	Conjunctivitis, unspecified
H16.9	O	Keratitis, unspecified
H20.9	O	Iridocyclitis, unspecified
H60.9	O	Otitis externa, unspecified
H66.4	O	Suppurative otitis media, unspecified
H66.9	O	Otitis media, unspecified
H70.9	O	Mastoiditis, unspecified
I01.9	C	Acute rheumatic heart disease, unspecified
I30.9	C	Acute pericarditis, unspecified
I33.9	C	Acute endocarditis, unspecified
I40.9	C	Acute myocarditis, unspecified
I42.8	C	Other cardiomyopathies
I42.9	C	Cardiomyopathy, unspecified
I51.4	C	Myocarditis, unspecified
I77.6	C	Arteritis, unspecified
I88.9	O	Nonspecific lymphadenitis, unspecified
J01.9	R	Acute sinusitis, unspecified
J02.9	R	Acute pharyngitis, unspecified
J03.9	R	Acute tonsillitis, unspecified
J06.9	R	Acute upper respiratory infection, unspecified
J12.9	R	Viral pneumonia, unspecified
J15.9	R	Bacterial pneumonia, unspecified
J18.0	R	Bronchopneumonia, unspecified
J18.1	R	Lobar pneumonia, unspecified
J18.2	R	Hypostatic pneumonia, unspecified
J18.8	R	Other pneumonia, organism unspecified
J18.9	R	Pneumonia, unspecified
J20.9	R	Acute bronchitis, unspecified
J21.9	R	Acute bronchiolitis, unspecified
J22	R	Unspecified acute lower respiratory infection
K29.7	G	Gastritis, unspecified

ICD-10 code	Syndromic category	Syndromic category
K29.9	G	Gastroduodenitis, unspecified
K37	G	Unspecified appendicitis
K51.9	G	Ulcerative colitis, unspecified
K65.9	G	Peritonitis, unspecified
K75.9	G	Inflammatory liver disease, unspecified
K81.9	G	Cholecystitis, unspecified
K85.9	G	Acute pancreatitis, unspecified
L02.9	O	Cutaneous abscess, furuncle and carbuncle, unspecified
L03.9	O	Cellulitis, unspecified
L04.9	O	Acute lymphadenitis, unspecified
L08.9	O	Local infection of skin and subcutaneous tissue, unspecified
L95.9	C	Vasculitis limited to skin, unspecified
M00.9	O	Pyogenic arthritis, unspecified
M13.9	O	Arthritis, unspecified
M60.0	O	Infective myositis
M60.9	O	Myositis, unspecified
N10.9	O	Acute tubulointerstitial nephritis
N41.9	O	Inflammatory disease of prostate, unspecified
O98.9	O	Unspecified maternal infectious or parasitic disease
P35.9	O	Congenital viral disease, unspecified
P36.9	S	Bacterial sepsis of newborn, unspecified
P37.9	O	Congenital infectious and parasitic disease, unspecified
R04.9	R	Hemorrhage from respiratory passages, unspecified
R11	G	Nausea and vomiting
R16.0	G	Hepatomegaly, not elsewhere classified
R16.1	G	Splenomegaly, not elsewhere classified
R16.2	G	Hepatomegaly, with splenomegaly, not elsewhere classified
R21	O	Rash and other nonspecific skin eruption
R29.8	N	Other and symptoms and signs involving the nervous and musculoskeletal systems
R40.2	N	Coma, unspecified
R50.9	O	Fever, unspecified
R56.0	O	Febrile convulsions
R57.9	S	Shock, unspecified
R59.9	O	Enlarged lymph nodes, unspecified
R69	O	Unknown and unspecified causes of morbidity
R74.0	O	Abnormal levels of LDH
R74.8	O	Abnormal levels of other serum enzymes
R74.9	O	Abnormal levels of unspecified serum enzyme
R76.9	O	Abnormal immunological finding in serum, unspecified
R77.9	O	Abnormality of plasma protein, unspecified
R83.5	N	Abnormal microbiological findings in cerebrospinal fluid, Positive culture findings

ICD-10 code	Syndromic category	Syndromic category
R83.6	N	Abnormal cytological findings in cerebrospinal fluid, abnormal Papanicolaou smear
R83.7	N	Abnormal histological findings in cerebrospinal fluid
R84.5	R	Abnormal microbiological findings in specimens from organs and thorax, positive culture findings
R84.6	R	Abnormal cytological findings in specimens from organs and thorax, abnormal Papanicolaou smear
R84.7	R	Abnormal histological findings in specimens from organs and thorax
R85.5	G	Abnormal microbiological findings in specimens from digestive organs and abdominal cavity, Positive culture findings
R85.6	G	Abnormal cytological findings in specimens from digestive organs and abdominal cavity, abnormal Papanicolaou smear
R85.7	G	Abnormal histological findings in specimens from digestive organs and abdominal cavity
R89.5	O	Abnormal microbiological findings in specimens from other organs, systems, and tissues, positive culture findings
R89.6	O	Abnormal cytological findings in specimens from other organs, systems, and tissues, abnormal Papanicolaou smear
R89.7	O	Abnormal histological findings in specimens from other organs, systems, and tissues
R96.0	O	Instantaneous death
R96.1	O	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	O	Unattended death
R99	O	Other ill-defined and unspecified causes of mortality

C, cardiac; *G*, gastrointestinal; *LDH*, lactic acid dehydrogenase; *N*, neurologic; *O*, other; *R*, respiratory; *S*, sepsis.

Table II

Codes selected from ICD-10 used to characterize exclusion criteria for UDPIC in infants

ICD-10 code	Code description
A00-B99, F02.4, R75	Infectious and parasitic diseases (excluding UDPIC inclusion criteria codes in Table I)
C00-D48	Neoplasms
D73	Diseases of the spleen (excluding D73.3)
D80-D89	Disorders involving the immune mechanism
E10-E14	Diabetes mellitus
Q00-Q99	Congenital malformations, deformations, and chromosomal abnormalities
R95	SIDS
S00-T98	Injury, poisonings, and certain consequences of external causes
V01-Y34, Y40-Y84	External causes of morbidity and mortality

SIDS, Sudden infant death syndrome.

Table III

Frequencies of selected characteristics for UDPIC in infants and control groups by birth weight—US, 2006

Characteristic	UDPIC infants, n (%)		Nonsurviving control infants, n (%)		Surviving control infants, n (%)	
	<2500 g	≥2500 g	<2500 g	≥2500 g	<2500 g	≥2500 g
Sample size	2112 (100.0)	1407 (100.0)	2112 (100.0)	1407 (100.0)	2112 (100.0)	1407 (100.0)
Multiple birth status						
Multiple birth	466 (22.1)	21 (1.5)	251 (11.9)*	26 (1.9)	532 (25.2)*	24 (1.7)
Singleton	1646 (77.9)	1386 (98.5)	1861 (88.1)	1381 (98.2)	1580 (74.8)	1383 (98.3)
Maternal age, y						
<20	314 (14.9)	287 (20.4)	242 (11.5)*	155 (11.0)*	266 (12.6)*	126 (9.0)*
20-29	1113 (52.7)	830 (59.0)	1050 (49.7)	747 (53.1)	1054 (49.9)	768 (54.6)
≥30	685 (32.4)	290 (20.6)	820 (38.8)	505 (35.9)	792 (37.5)	513 (36.5)
Maternal race						
White	1213 (57.4)	954 (67.8)	1543 (73.1)*	1098 (78.0)*	1431 (67.8)*	1106 (78.6)*
Black	802 (38.0)	353 (25.1)	451 (21.4)	231 (16.4)	534 (25.3)	189 (13.4)
Other	97 (4.6)	100 (7.1)	118 (5.6)	78 (5.5)	147 (7.0)	112 (8.0)
Maternal ethnicity						
Non-Hispanic	1660 (79.6)	1109 (79.1)	1585 (76.1)*	1036 (74.0)*	1659 (79.0)	1041 (74.4)*
Hispanic	425 (20.4)	293 (20.9)	498 (23.9)	364 (26.0)	441 (21.0)	358 (25.6)
Marriage status						
Yes	950 (45.0)	569 (40.4)	1247 (59.0)*	807 (57.4)*	1131 (53.6)*	882 (62.7)*
No	1162 (55.0)	838 (59.6)	865 (41.0)	600 (42.6)	981 (46.5)	525 (37.3)
Sex						
Male	1189 (56.3)	824 (58.6)	1059 (50.1)*	832 (59.1)*	981 (46.6)*	714 (50.8)*
Female	923 (43.7)	583 (41.4)	1053 (49.9)	575 (40.9)	1131 (53.5)	693 (49.3)
Live birth order						
First live birth	906 (43.5)	455 (32.6)	729 (35.0)*	470 (33.6)*	859 (41.0)*	579 (41.3)*
Subsequent live birth	1175 (56.5)	943 (67.5)	1355 (65.0)	927 (66.4)	1236 (59.0)	822 (58.7)
Pregnancy-associated hypertension						
Yes	137 (6.6)	57 (4.1)	106 (5.1)*	39 (2.8)*	233 (11.1)*	51 (3.6)*
No	1953 (93.4)	1345 (95.9)	1982 (94.9)	1357 (97.2)	1871 (88.9)	1349 (96.4)
Delivery method						
Vaginal	917 (43.5)	947 (67.6)	1001 (47.5)*	782 (55.8)*	1038 (49.3)*	988 (70.6)*
Cesarean	1190 (56.5)	455 (32.5)	1107 (52.5)	619 (44.2)	1069 (50.7)	412 (29.4)

*$P < .05$. The P value reflects significance of χ^2 testing for differences between UDPIC and control infants within birth weight category.

Table IV

Multivariate logistic regression analysis of demographic, maternal, and birth-related characteristics for UDPIC in infants and nonsurviving and surviving controls by birth weight—US, 2006

		OR (95% CI)			
		UDPIC cases vs nonsurviving controls		UDPIC cases vs surviving controls	
Characteristic	Referent group	Model 1: birth weight <2500 g	Model 2: birth weight ≥2500g	Model 3: birth weight <2500 g	Model 4: birth weight ≥2500 g
Standard variables					
Single birth	Multiple birth	0.4 (0.3-0.5)*	†	1.2 (1.0-1.4)*	†
First live birth	Subsequent live birth	1.5 (1.3-1.8)*	†	†	0.5 (0.4-0.5)*
Male sex	Female sex	1.3 (1.1-1.5)*	†	1.5 (1.3-1.7)*	1.4 (1.2-1.7)*
Maternal race					
Black	White	†	1.4 (1.1-1.7)*	1.7 (1.5-2.0)*	1.4 (1.2-1.8)*
Other	White		1.5 (1.1-2.1)*	0.8 (0.6-1.0)	1.2 (0.9-1.6)
Hispanic ethnicity	Non-Hispanic	†	†	†	0.7 (0.6-0.8)*
Married mother	Unmarried	†	†	0.9 (0.8-1.0)*	0.5 (0.4-0.6)*
Maternal age, y					
<20	20-29 y	†	†	†	2.4 (1.8-3.1)*
≥30	20-29 y				0.5 (0.4-0.6)*
Pregnancy-associated hypertension	No pregnancy-associated hypertension	†	1.7 (1.1-2.7)*	†	†
Cesarean delivery	Vaginal delivery	†	0.6 (0.6-0.8)*	1.4 (1.2-1.6)*	1.3 (1.1-1.6)*
Interaction terms					
Race × delivery method					
White, cesarean delivery	White, vaginal delivery	1.3 (1.1-1.5)*	†	†	†
Black, cesarean delivery	Black, vaginal delivery	0.9 (0.7-1.1)			
Other, cesarean delivery	Other, vaginal delivery	0.9 (0.5-1.6)			
Maternal age × race					
<20 y, black	<20 y, white	1.5 (1.0-2.2)*	†	†	†
<20 y, other	<20 y, white	0.3 (0.1-1.3)			
20-29 y, black	20-29 y, white	2.7 (2.1-3.4)*			
20-29 y, other	20-29 y, white	1.2 (0.7-2.1)			
≥30 y, black	≥30 y, white	3.0 (2.2-4.1)*			
≥30 y, other	≥30 y, white	1.7 (1.0-2.9)			
Maternal age × marital status					
<20 y, married	<20 y, unmarried	1.1 (0.7-1.9)	0.8 (0.5-1.3)	†	†
20-29 y, married	20-29 y, unmarried	0.7 (0.6-0.8)*	0.7 (0.6-0.9)*		

Characteristic	Referent group	OR (95% CI)			
		UDPIC cases vs nonsurviving controls		UDPIC cases vs surviving controls	
		Model 1: birth weight <2500 g	Model 2: birth weight ≥2500g	Model 3: birth weight <2500 g	Model 4: birth weight ≥2500 g
≥30 y, married	≥30 y, unmarried	0.6 (0.5-0.8)*	0.4 (0.3-0.6)*		
Maternal age × Hispanic ethnicity					
<20 y, Hispanic	<20 y, non-Hispanic	†	1.2 (0.8-1.9)	†	†
20-29 y, Hispanic	20-29 y, non-Hispanic		0.7 (0.5-0.9)*		
≥30 y, Hispanic	≥30 y, non-Hispanic		0.6 (0.4-0.9)*		
Maternal age × live birth order					
<20 y, first live birth	<20 y, subsequent live birth	†	†	0.7 (0.5-1.1)	†
20-29 y, first live birth	20-29 y, subsequent live birth			1.0 (0.9-1.2)	
≥30 y, first live birth	≥30 y, subsequent live birth			1.3 (1.1-1.7)*	

*P < .05.

†Variable/interaction term not included in the model.